Received: 9 August 2023 | Accepted: 17 December 2023

DOI: 10.1111/acer.15259

ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH ISBRA

RESEARCH ARTICLE

Neural correlates of drinking reduction during a clinical trial of cognitive behavioral therapy for alcohol use disorder

Nasir H. Naqvi[1] | A. Benjamin Srivastava[1] | Juan Sanchez-Peña[1] | Jessica K. Lee[1] | Andrew T. Drysdale[1] | John J. Mariani[1] | Kevin N. Ochsner[2] | Jon Morgenstern[3] | Gaurav H. Patel[1] | Frances R. Levin[1]

[1]Department of Psychiatry, Columbia University Irving Medical Center/New York State Psychiatric Institute, New York, New York, USA

[2]Department of Psychology, Columbia University, New York, New York, USA

[3]Department of Psychiatry, Donald and Barbara Zucker School of Medicine at Hofstra University/Northwell Health, Hempstead, New York, USA

Correspondence
A. Benjamin Srivastava, Division on Substance Use Disorders, Department of Psychiatry, Columbia University Irving Medical Center/New York State Psychiatric Institute, 1051 Riverside Drive, Unit 66, New York, NY 10032, USA.
Email: benjamin.srivastava@nyspi.columbia.edu

Funding information
National Institute on Alcohol Abuse and Alcoholism; National Institute on Drug Abuse; National Institute of Mental Health; National Institutes of Health, Grant/Award Number: R01 MH123639, R01 MH121790, T32 DA007294 and K23 AA022771

Abstract

Background: Cognitive behavioral therapy (CBT) is an effective treatment for alcohol use disorder (AUD). We hypothesized that the dorsolateral prefrontal cortex (DLPFC), a region implicated in cognitive control and goal-directed behavior, plays a role in behavior change during CBT by facilitating the regulation of craving (ROC).

Methods: Treatment-seeking participants with AUD ($N = 22$) underwent functional magnetic resonance imaging (fMRI) scanning both before and after a 12-week, single-arm trial of CBT, using an ROC task that was previously shown to engage the DLPFC.

Results: We found that both the percentage of heavy drinking days (PHDD) and the overall self-reported alcohol craving measured during the ROC task were significantly reduced from pre- to post-CBT. However, we did not find significant changes over time in either the ability to regulate craving or regulation-related activity in any brain region. We found a significant 3-way interaction between the effects of cue-induced craving, cue-induced brain activity and timepoint of assessment (pre- or post-CBT) on PHDD in the left DLPFC. Follow-up analysis showed that cue-induced craving was associated with cue-induced activity in the left DLPFC among participants who ceased heavy drinking during CBT, both at pre-CBT and post-CBT timepoints. No such associations were present at either timepoint among participants who continued to drink heavily.

Conclusions: These results suggest that patients in whom DLPFC functioning is more strongly related to cue-induced craving may preferentially respond to CBT.

KEYWORDS
alcohol use disorder, cognitive control, craving, dorsolateral prefrontal cortex, regulation of craving

INTRODUCTION

Alcohol use disorder (AUD) is associated with significant morbidity and mortality that has substantially increased since 2020 (Sacks et al., 2015; White et al., 2020, 2022; Yeo et al., 2022). Cognitive behavioral therapy (CBT) is an effective treatment for AUD that involves learning strategies for managing cravings and negative emotional states that promote heavy drinking (Longabaugh & Morgenstern, 1999; McCrady et al., 2014; Witkiewitz et al., 2019; Witkiewitz & Marlatt, 2011). Prior

Nasir H. Naqvi and A. Benjamin Srivastava contributed equally to this manuscript and are co-first authors.

Gaurav H. Patel and Frances R. Levin contributed equally to this manuscript and are co-senior authors.

research on the mechanisms of behavior change in CBT has focused on understanding the role of various psychological constructs, e.g., the self-regulation (Berking et al., 2011; Roos & Witkiewitz, 2017), self-efficacy (Kadden & Litt, 2011), and the acquisition of coping skills (Morgenstern & Longabaugh, 2000). However, attempts at studying these psychological mechanisms have yielded inconsistent results (Magill et al., 2020; Morgenstern & Longabaugh, 2000). These inconsistencies may result from the inherent complexity in these constructs, which are likely to engage multiple underlying cognitive functions. Also, behavior change may occur through processes that occur outside of conscious awareness and thus are inaccessible by self-report and exacerbated by impaired insight that is common in substance use disorders (SUDs) (Goldstein et al., 2009). Furthermore, these constructs may not directly relate to neural mechanisms underlying AUD (Naqvi & Morgenstern, 2015). Studying neural mechanisms of behavior change may help overcome these limitations, allowing for the identification of brain systems that are more specifically targeted to (1) make CBT more effective and (2) develop novel treatments.

Behavior-change constructs such as self-regulation, self-efficacy, and coping can be conceptualized as mental processes that engage cognitive control. Cognitive control involves the coordinated deployment of attention, goal representation, action selection, and the suppression of competing behaviors, all in the service of reducing automaticity and increasing flexible, goal-directed behavior (Friedman & Robbins, 2022). Cognitive control can thus be seen as a general function that subserves behavior change across multiple domains. The dorsolateral prefrontal cortex (DLPFC) is a large and heterogeneous region of prefrontal cortex that, broadly speaking, is thought to play a central role in cognitive control (Friedman & Robbins, 2022; Miller & Cohen, 2001; Turnbull et al., 2019). Both DLPFC structure/function (Beylergil et al., 2017; Li et al., 2009; Pfefferbaum et al., 1997, 1998; Zou et al., 2018) and behavioral measures of cognitive control (Naqvi et al., 2015; Wilcox et al., 2014) are negatively impacted in AUD. Thus, by facilitating cognitive control, CBT may remediate deficits in DLPFC function, increasing the capacity to regulate alcohol-seeking motivational states such as craving. We have proposed elsewhere (Naqvi et al., 2014) that treatments such as CBT, which seek to increase both the saliency of the negative consequences of drinking and the value of alternative rewards, promote a more goal-directed and less automatic mode of alcohol seeking (Tiffany & Conklin, 2000). According to this model, this goal-directed mode of alcohol seeking leads to less drinking, and whatever drinking remains is more driven by craving, a deliberative process subject to regulation (Suzuki et al., 2019). The goal-directed mode is likely more strongly dependent upon cognitive control functions mediated by the DLPFC, in coordination with higher-order affective processing and risk representation within the ventromedial prefrontal cortex and the insula (Everitt & Robbins, 2005).

While theoretical accounts highlight a potential role for the DLPFC in behavior change in CBT, research evidence is limited. Schneider et al. (2001) examined how CBT impacted neural correlates of cue-induced craving and found that treatment reduced cue-induced activity in the amygdala and hippocampus, while increasing activity in the superior temporal sulcus. However, DLPFC activity did not change during CBT. This study did not examine any cognitive control or regulation functions, and it included pharmacological interventions that were likely to have confounded CBT-related changes (Schneider et al., 2001). DeVito et al. (2012) used a cognitive control task (the Stroop task (Friedman & Robbins, 2022)) to examine the changes in brain activity over a course of CBT in individuals with a variety of substance use disorders, including AUD. They found that CBT decreased Stroop-related activity in the DLPFC, as well as in the anterior cingulate cortex and midbrain. However, this study was not focused on AUD exclusively. In cocaine use disorder, Brewer et al showed that reductions in Stroop-related DLPFC activity were associated with increased treatment retention (Brewer et al., 2008), while DeVito et al. (DeVito et al., 2017) showed that changes in Stroop-related activity in DLPFC were associated with the number of CBT sessions completed. In aggregate, these prior studies support a role for the DLPFC in behavior change during CBT for AUD. However, none examined cognitive control processes as they specifically relate to alcohol-seeking motivational states, e.g., craving, which may be more sensitive and specific to mechanisms of CBT (Magill et al., 2015). Moreover, no prior study has examined the relationship between changes in brain function and clinical drinking outcomes of CBT for AUD.

One of the core skills taught in CBT is the ability to regulate craving in high-risk situations using various cognitive strategies, including by thinking about the long-term negative consequences of drinking (Magill et al., 2015). This is a form of reappraisal-based emotion regulation, which is theorized to depend upon cognitive control (Ochsner et al., 2012). Kober and colleagues created an functional magnetic resonance imaging (fMRI) paradigm designed to assess this type of regulation, applying it across a variety of substances, including alcohol (Koban et al., 2023; Kober, Kross, et al., 2010; Kober, Mende-Siedlecki, et al., 2010; Naqvi et al., 2015; Suzuki et al., 2019). A consistent set of findings in these studies is that regulation of craving (ROC) is associated with increased activity in areas within DLPFC, superior temporal sulcus, and anterior cingulate and ventrolateral prefrontal cortices, coupled with decreased activity in the ventral striatum/nucleus accumbens and amygdala. We have previously shown this form of regulation to be impaired at the behavioral level in individuals with AUD (Naqvi et al., 2015). The ROC task may be a particularly sensitive probe for revealing the role of the DLPFC in behavior change during CBT. However, to date, this task has never been combined with a clinical treatment for AUD.

In this study, we used fMRI to examine how brain function related to regulation of cue-induced alcohol craving changes over the course of CBT for AUD and how these changes are related to drinking outcomes. We recruited treatment-seeking participants with AUD who were drinking heavily at the baseline. They then completed the ROC task both before and after undergoing approximately 12 weeks of manualized CBT for AUD. In this task, participants are shown alcohol cues that are known to elicit

cravings while being instructed to focus on long-term negative consequences of drinking vs. immediate pleasurable consequences, using food cues as control stimuli, while brain activation and self-reported craving are measured. We chose reduction in the percentage of drinking days as the primary clinical outcome since it is a clinically meaningful outcome that has been used in prior treatment studies (Bogenschutz et al., 2022; Falk et al., 2019; Hagman et al., 2022) and is more attainable than total abstinence. We also explored how the relevant variables (cue induced brain activity, cue induced craving, and timepoint) may be related to each other as well as heavy drinking. We hypothesized that (a) CBT will increase the ability to regulate cue-induced alcohol craving; (b) this improved ability to regulate craving during CBT will be associated with an increase in DLPFC activity; and (c) increased DLPFC activity will in turn be related to reductions in heavy drinking days.

PATIENTS AND METHODS

Participants

The details of participant recruitment, including the inclusion/exclusion criteria, study structure, and data collection are published elsewhere (Srivastava et al., 2021). Briefly, men and women of ages 21–65 seeking treatment for alcohol-related problems were recruited from the New York City Area. In total, we consented 38 participants (24 men and 14 women) aged 26–64. All participants met the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition, criteria for AUD, as confirmed by the MINI (Sheehan et al., 1998). Participants were excluded from the study for neurological or medical illnesses that would interfere with magnetic resonance imaging (MRI) scanning, other moderate or severe substance use disorders besides tobacco or caffeine use disorder, significant psychiatric illness, or a significant alcohol withdrawal history. The study was approved by the New York State Psychiatric Institute (NYSPI) Institutional Review Board. All participants provided informed consent.

Clinical outcome and analysis

The primary clinical outcome was percentage of heavy drinking days (PHDD), defined as the percentage of days over the previous 28 days on which participants consumed ≥4 standard drinks/day for women and ≥5 drinks/day for men, as assessed using the 28 Day Timeline Followback (TLFB) procedure (Sobell & Sobell, 1995). The PHDD was calculated for both pre-CBT and post-CBT timepoints, approximately 12 weeks (the study duration) apart. The PHDD was measured at the pre-CBT and post-CBT behavioral assessments and was contrasted using a paired *t*-test. To consider the role of dropout, we performed a last observation carried forward (LOCF) analysis in which the pre-CBT PHDD for each participant who dropped out was imputed as its post-CBT PHDD.

CBT sessions

Participants received up to 12 sessions of CBT, administered by a master's- or doctoral-level clinician with experience delivering CBT, adhering to the Project Match CBT Manual (Kadden et al., 2003). Each session lasted 1 h and included the following modules: (1) Introduction to Coping Skills; (2) Coping with Craving and Urges to Drink; (3) Managing Thoughts About Alcohol and Drinking; (4) Problem-Solving; (5) Drink Refusal Skills; (6) Planning for Emergencies and Coping with Lapses; (7) Seemingly Irrelevant Decisions; and (8) up to five elective modules on various topics as relevant. Additionally, sessions included the assessments of drinking levels and psychiatric symptoms. Only participants who completed a minimum of six sessions were included in the analyses.

The ROC task and analysis

At both the pre- and post-CBT timepoints, each participant performed the ROC task while fMRI data were collected. The task was programmed in E-Prime version 2.0 (Psychology Software Tools, Sharpsburg, PA) and displayed to the participants using a back projection mirror. Prior to performing the ROC task in the scanner, participants completed eight practice trials outside the scanner. The structure of the ROC task is as follows (Figure S1): Participants were shown an instructional word for 2 s, directing them to focus on either the immediate, pleasurable consequences of consuming the depicted item ("LOOK") or the long-term, negative consequences ("NEGATIVE") of repeatedly consuming the depicted item. They were then immediately shown a picture cue for 6 s: either an image of an alcoholic beverage or an image of a high-calorie food, followed by a fixation cross during an interstimulus interval randomly jittered between 1 and 7.5 s. They were then shown a visual instruction to rate the desire to consume the depicted item (craving) on a 1–5 point Likert scale, during which they made rating responses with their right hand using a five-finger button-response unit. They were given up to 3 s to make their response. Once the response was made (or after 3 s, which ever came first), participants were then shown a fixation point during the inter-trial interval, which was randomly jittered between 1 and 7.5 s; this was then followed by the next trial. The cue images (alcohol and food) were previously validated as eliciting moderate cravings in participants with AUD [35]. The order of instructions was counterbalanced across alcohol and food cues. The food ($n = 40$) and alcohol ($n = 40$) cues were presented in pseudorandom order, and different cue images were used for the pre- and post-CBT scans. Participants performed 4 runs of the task with 20 trials per run. We examined how self-report response data (craving scores) varied as a function of cue (food vs alcohol cues), instruction (LOOK vs. NEGATIVE), and treatment timepoint (pre-CBT vs. post-CBT) with a repeated measures ANOVA. Post hoc comparisons for this and subsequent ANOVAs were assessed using paired *t*-tests with a threshold of $p < 0.05$.

ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH ISBRA

MRI acquisition and preprocessing

The scanning procedures for both pre- and post-treatment MRI scanning sessions were the same. Participants first completed a 7-day TLFB (Sobell & Sobell, 1995) to quantify recent drinking and reported the time since the last drink. They were then administered a breath alcohol test, vital signs, the Clinical Institute Withdrawal Assessment of Alcohol Scale-Revised (CIWA-Ar) (Sullivan et al., 1989), and a urine drug screen. This was followed by ROC task practice trials outside the scanner, followed by fMRI scanning during ROC task during, followed by a 10-min resting state scan. The results of the resting-state scans are published elsewhere (Srivastava et al., 2021, 2022).

MRI data were collected on a 3T MR750 GE Scanner. Details of the image acquisition protocol are described elsewhere (Srivastava et al., 2021). Pre-processing procedures were performed using fMRIPrep version 1.5.10, including alignment to individual's anatomical data, movement correction, distortion correction, and atlas alignment into MNI volume space (Esteban et al., 2019). We then used Ciftify version 2.3.3 to adapt these data, in which T2w anatomical images and field maps were not acquired, to Human Connectome Project Pipelines (Dickie et al., 2019). Specifically, Ciftify performs surface-based extraction and surface atlas alignment of gray matter voxels to improve the co-registration of functional maps between individuals and with standard surface atlases (Dickie et al., 2019; Glasser et al., 2016).

ROI selections for parcel-based analyses

We used a surface-based parcel-wise analysis, which has been shown to improve alignment across both subjects and studies and provides more reliable anatomical specificity of brain function than voxel-based approaches (Coalson et al., 2018; Glasser et al., 2013). Cortical areas were defined using a multimodal parcellation from Glasser et al. (2016). Subcortical parcellations were defined using separate atlases containing dorsal and ventral striatal structures (Tyszka & Pauli, 2016), amygdala (Pauli et al., 2018), and bed nucleus of the stria terminalis (BNST) (Theiss et al., 2017).

Analysis of brain activation during the ROC task

A parcel-wise generalalized linear model (GLM) was used to estimate the BOLD response at each parcel for each cue-instruction event type (LOOK/alcohol, NEGATIVE/alcohol, LOOK/food, NEGATIVE/food). Following previous studies using the ROC task (Kober, Mende-Siedlecki, et al., 2010; Suzuki et al., 2019), the instruction and picture cue events were combined into a single 8-s event. The self-report response interval was modeled separately. Each event type was modeled as a separate boxcar regressor that was then convolved with the hemodynamic response function (Grinband et al., 2008). These were entered into the first level GLM analyses as predictors of the measured BOLD response, resulting in a parameter estimate (β-weight) for each of the four cue-instruction event conditions, at each parcel, in each participant, at each timepoint. For each brain parcel, we then examined how cue-instruction event-evoked brain activity varied as a function of cue (food vs alcohol cues), instruction (LOOK vs NEGATIVE), and measurement timepoint (pre-CBT vs. post-CBT) using a repeated-measures ANOVA. A false discovery rate (FDR) correction (adjusted $p < 0.05$) using the Benjamini–Hochberg procedure (Benjamini & Hochberg, 1995) was performed for each factor to correct for the multiple comparisons across the 396 parcels. Post-hoc *t*-tests were Bonferroni corrected for multiple comparisons. To allow for more direct comparison between our results and those of previous studies (Kober, Mende-Siedlecki, et al., 2010), we also performed supplemental analyses that more closely resembled those earlier studies, specifically: (1) a whole-brain grayordinate analysis examining the main effect of regulation and (2) an ROI-based ANOVA analysis examining how activity in the in areas shown to be implicated in ROC in prior studies (Kober, Mende-Siedlecki, et al., 2010) varied as a function of cue-type, instruction and timepoint (i.e., how regulation-related brain activity may change with CBT). See the Appendix S1 for detailed methods and results.

Analysis of the relationships between whole-brain activity, craving and heavy drinking, at pre-CBT to post-CBT timepoints

For exploratory analyses, we used a linear mixed effects model to examine how PHDD varied as a function of pre- vs. post-CBT timepoint, cue-induced alcohol craving, and alcohol cue-induced brain activity, as well as their interaction. Analyses were performed on each parcel. Following prior cue-reactivity imaging studies, we defined alcohol cue-induced brain activity as the average BOLD response (β-weight) in that parcel during alcohol trials minus the average BOLD response during nonalcohol (food) trials (Ekhtiari et al., 2022; Schacht et al., 2013; Zeng et al., 2021), while we defined cue-induced alcohol craving as the average Likert scale rating for alcohol cues only (Fryer et al., 2013; MacNiven et al., 2019). For both alcohol cue-induced brain activity and the self-reported cue-induced alcohol craving, trials were averaged without regard to LOOK vs. NEGATIVE instruction (i.e., regulation was not included as a factor in this regression analysis). Time between scans was also entered as an independent variable. Continuous variables were *z*-scored. The individual participants were modeled as a random effect. We restricted this analysis to parcels in the DLPFC, selecting 26 DLPFC parcels (13 in each hemisphere), as defined by Glasser et al. (Figure S3). In a supplemental analysis, the same regression was performed across the whole brain using grayordinates, to allow for closer comparison to the results of earlier studies using whole-brain voxel-based approaches (see the Appendix S1 for detailed methods). All statistical analyses were performed in Matlab v 2022a and HCP Workbench v 1.5. Power analyses were performed with G*Power v. 3.1.

RESULTS

Demographics

For the CONSORT diagram, see Figure 1. Table 1 describes demographic characteristics of the 22 participants who were included in the analyses. For detailed demographic data, see the Appendix S1.

Heavy drinking outcomes and self-reported craving in the ROC task

Percentage of heavy drinking days (PHDD) was significantly reduced over the course of CBT ($t(21) = 15.69$; $p < 0.0001$), with 10/22 participants ceasing heavy drinking (PHDD = 0) at the post-CBT timepoint. LOCF analyses similarly showed a significant reduction in PHDD ($t(34) = 6.84$; $p < 0.0001$). We found significant main effects of regulation instruction ($F(1,21) = 10.69$; $p = 0.004$) and time ($F(1,21) = 13.40$; $p = 0.0015$) as well as a significant interaction effect of cue type and time ($F(1,21) = 16.16$; $p = 0.0006$) on self-reported craving. We did not find a significant main effect of cue, significant interaction effects of instruction and cue, significant interaction effects of instruction and time, or significant 3-way interaction effects of instruction, cue, and time. Post-hoc testing showed that the self-reported craving was (1) significantly greater in LOOK than in NEGATIVE conditions ($t(87) = 4.86$; $p < 0.0001$), (2) significantly greater at the pre-CBT timepoint than post-CBT timepoint ($t(87) = 5.35$; $p < 0.0001$), and (3) significantly lower for alcohol cues at the post-CBT timepoint compared with the pre-CBT timepoint ($t(43) = 6.80$; $p < 0.0001$) but not for food cues ($t(43) = 1.23$; $p = 0.22$) (Figure 2).

Brain activation during the ROC task

There was a significant main effect of cue-type in multiple parcels within bilateral posterior occipital, temporal and parietal cortices, ventral anterior cingulate and ventromedial prefrontal cortices, and posterior insular cortices (Figure 3A, Table S1). We found a significant main effect of regulation instruction on brain activity in parcels corresponding to the left ventral superior temporal sulcus, bilateral dorsal superior temporal sulcus, the left ventrolateral prefrontal cortex/frontal operculum, and left lateral parietal lobe (Figure 3B, Table S1). We also found a significant

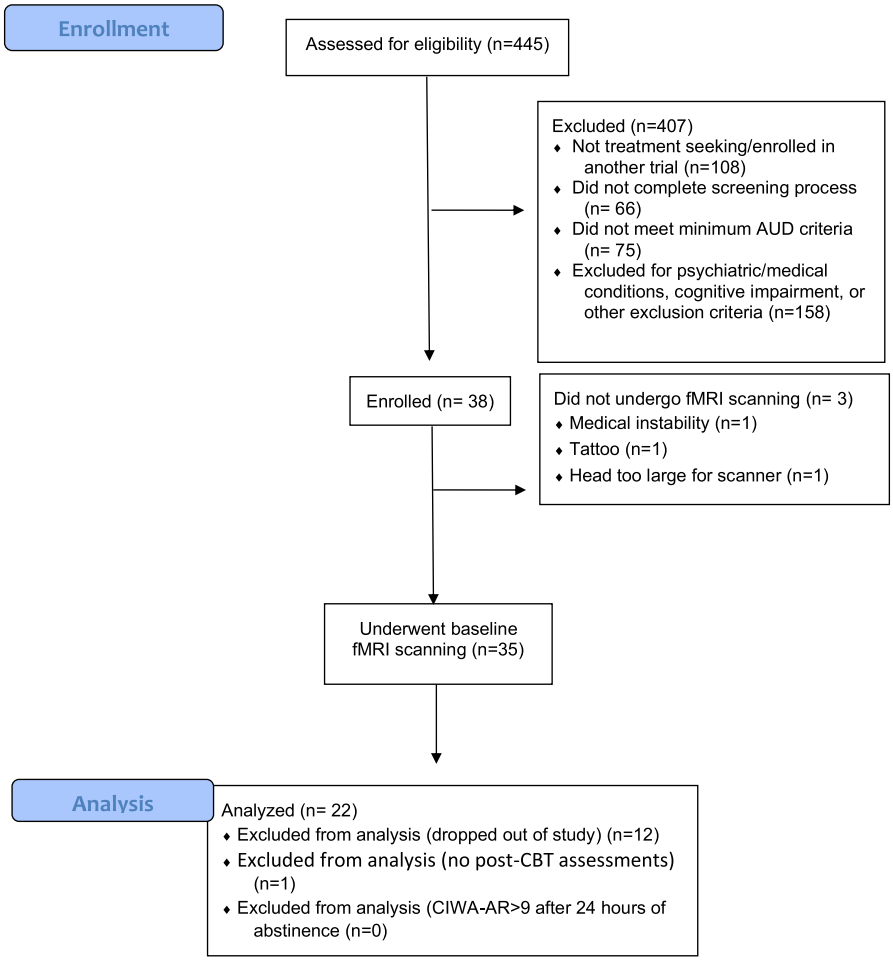


FIGURE 1 CONSORT diagram of study.

ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH ISBRA

TABLE 1 Subject characteristics.

	Initially consented ($n=35$)		Included in the analyses ($n=22$)	
	Mean ± SD	*n* (%)	Mean ± SD	*n* (%)
Age	45.9 ± 11.6		46.68 ± 12.4	
Female		14 (40)		8 (36.4)
Hispanic		9 (25.7)		4 (18.2)
Race				
White		24 (68.6)		17 (77.3)
Black		5 (14.3)		3 (13.6)
Asian		1 (2.9)		1 (4.6)
Multi-racial		1 (2.9)		0 (0.0)
Other		4 (11.4)		1 (4.6)
DSM-5 Diagnoses				
MDD		11 (31.4)		6 (27.2)
GAD		2 (5.7)		0 (0.0)
Panic disorder		1 (2.9)		0 (0.0)
Anorexia nervosa		1 (2.9)		1 (4.6)
Cannabis use disorder (mild)		1 (2.9)		1 (4.6)
Cocaine use disorder (past)		1 (2.9)		1 (4.6)
Baseline Utox[a]		7 (20)		4 (18)
Baseline ADS	14.4 ± 6.49		13.6 ± 6.74	
Baseline PHDD	81.1 ± 16.3		81.5 ± 15.3	
Baseline CIWA-Ar	1.14 ± 1.42		0.68 ± 0.89	
Number of CBT sessions completed	7.46 ± 3.98		10 ± 1.69	

Abbreviations: ADS, Alcohol Dependence Scale; CBT, Cognitive behavioral therapy; CIWA, Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised; GAD, Generalized anxiety disorder; MDD, Major depressive disorder; PHDD, Percentage of heavy drinking days; Utox, Urine toxicology (for drugs other than alcohol).

[a]All participants who tested positive were positive for tetrohydrocannabinol (THC). One of these participants (who completed the study) additionally tested positive for benzodiazepines.

interaction between instruction and cue in a parcel located within the right lateral occipital cortex. We did not find significant interaction effects of instruction and time or instruction, cue, and time in any parcel. Supplemental grayordiante analyses showed broad patterns of activation across the prefrontal cortex in the NEGATIVE-LOOK contrast, aligning with peak prefrontal cortex (PFC) activations from prior ROC studies examining this same contrast (Kober, Mende-Siedlecki, et al., 2010; Suzuki et al., 2019) (Figure S3). However, we did not find significant interaction effects of instruction and time, cue and time, or instruction, cue, and time in any of these areas (Appendix S1). Sensitivity analyses demonstrated that the study was powered to detect effect sizes larger than Cohen's $F=0.57$ (large effect size).

Neural and self-report correlates of heavy drinking

We found significant ($p<0.05$) 3-way interaction between effects of cue-induced alcohol craving, pre-/post CBT timepoint, and cue-induced brain activity on heavy drinking in 10/26 DLPFC parcels. These included three DLPFC parcels in the right hemisphere and seven DLPFC parcels in the left hemisphere. This interaction was not significant in the BA 8 parcel that had been identified as playing a role in ROC in prior studies (Figure 4; Appendix S1).

Follow-up analyses of the relationships between cue-induced craving, cue-induced DLPFC activity and heavy drinking at pre- and post-CBT timepoints

To further clarify the role of the DLPFC in reductions in craving and heavy drinking during CBT, we performed a set of follow-up regression analyses focused on the average activity in a composite DLPFC ROI comprising seven left-sided DLPFC parcels that showed a significant 3-way interaction effect in the linear mixed effects model described above. Given that our previous work in this same dataset (Srivastava et al., 2021, 2022) demonstrated that an increase over the course of CBT in resting state functional connectivity (RSFC) between the left anterior insula and left DLPFC area 9/46 was associated with a reduction in heavy drinking, we focused further analyses on the left DLPFC parcels. The average parameter estimates

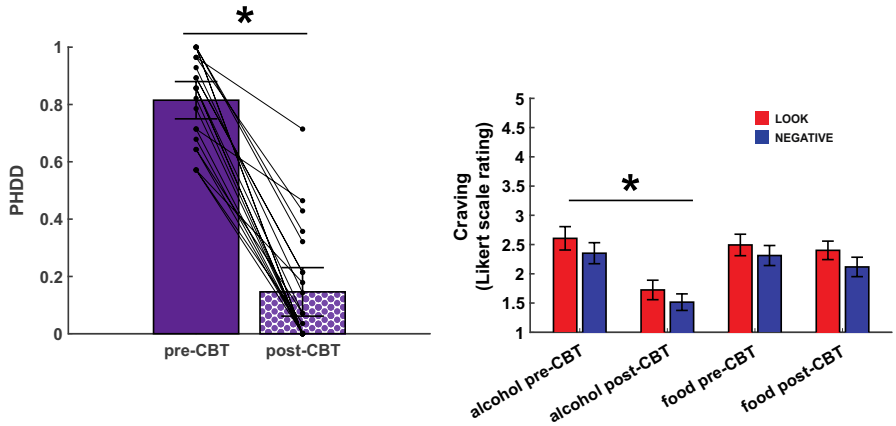


FIGURE 2 Plots of heavy drinking (left) and craving (right) before and after CBT. Heavy drinking is represented by percentage of heavy drinking days (PHDD). Craving is represented as Likert scale ratings (1–5) reported by participants as a function of cue type (alcohol/food), instruction type (LOOK/NEGATIVE). Overall, heavy drinking was significantly reduced from pre-CBT to post-CBT. Significant main effects were present for instruction and time, and a significant interaction effect between cue type and time was found. Post-hoc testing using paired *t*-tests showed that craving for alcohol cues was significantly lower at the post-CBT time point when compared to the pre-CBT timepoint. Significance is noted for both the difference in NHDD (left) and cue x time interaction (right) at $^*p < 0.0001$. Error bars represent 95% confidence intervals.

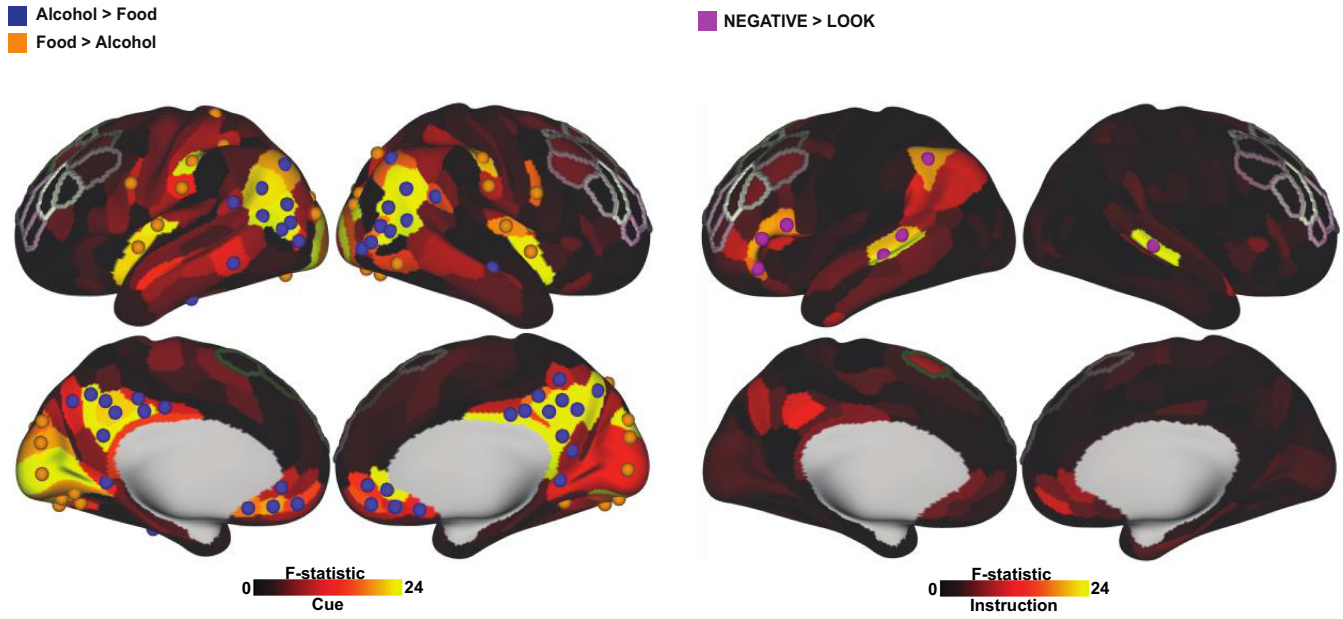


FIGURE 3 Main effects of cue type (left) and instruction (right) on the whole brain activity. Overall, significant main effects of cue type were found in parcels within the posterior occipital, temporal, and parietal lobes bilaterally as well as in the left nucleus accumbens. Main effects of instruction were found in parcels in the superior temporal sulcui (STS) bilaterally, left frontal operculum/VLPFC, left lateral parietal lobe, and right amygdala. Post-hoc *t*-tests revealed that areas where BOLD response to alcohol cues was greater than food cues in parietal and temporal areas as well as the nucleus accumbens (blue dots), whereas the BOLD response was greater for food than alcohol cues in the occipital lobe (orange dots). For instruction, BOLD response in the STS bilaterally, frontal operculum/VLPFC, and lateral parietal lobe was greater for the NEGATIVE compared with the LOOK condition (purple dots), whereas BOLD response was greater in the LOOK compared with the NEGATIVE in the right amygdala (green dot). DLPFC borders from Glasser et al. are shown for reference. See the Appendix S1 for parcel labels and detailed statistics.

of alcohol cue-induced brain activation were calculated within this composite DLPFC ROI for each subject and then subjected to four pairs of follow-up regression analyses (Figure 5). Cue-induced alcohol craving was significantly associated with PHDD at the post-CBT ($r = 0.42$, $p = 0.049$), but not the pre-CBT timepoint (Figure 5A). There was no relationship between cue-induced DLPFC activity and PHDD at either the pre-CBT or post-CBT timepoints (Figure 5B). While DLPFC activity was not associated with cue-induced alcohol craving at either timepoint in participants who continued drinking heavily after CBT (Figure 5C), DLPFC activity did correlate with

cue-induced alcohol craving in participants who stopped drinking heavily at both pre-CBT ($r=0.65$, $p=0.041$) and post-CBT ($r=0.72$, $p=0.02$) timepoints (Figure 5D). Neither the baseline alcohol severity nor baseline alcohol cue-induced differed between the two groups, and trial-by-trial, within-subject variations in the DLPFC response to alcohol cues were not associated cue-induced alcohol craving in either group (see the Appendix S1 for more details).

DISCUSSION

Here we showed that in participants seeking treatment for AUD, receiving CBT is associated with (1) significant reductions in drinking, indicative of a clinical effect for the purposes of a mechanistic translational study, (2) a decrease in overall cue-induced alcohol craving, but (3) no change in the ability to regulate craving as measured in the ROC paradigm. Furthermore, in patients who ceased heavy drinking, we found a strong relationship between cue-induced craving and cue-induced DLPFC activation at both pre- and post-CBT timepoints. These results are consistent with a model in which CBT is more effective for individuals in whom baseline subjective craving elicited by alcohol cues may be more strongly tied to the baseline DLPFC response to these cues. The results suggest that behavior change during CBT may depend on how the DLPFC processes the incentive salience of alcohol cues during treatment, and CBT may not change the ability to regulate craving using cognitive strategies. The DLPFC region of interest where we found relationships between cue-induced activity, cue-induced craving and reductions in heavy drinking during CBT was a relatively large and heterogeneous area that included parcels spanning areas 9, 9/46, and the anterior portions of area 8 in the left hemisphere, which have previously been shown to play a role in multiple forms of cognitive control (Assem et al., 2020), as well as a role in emotion regulation (Ochsner & Gross, 2005). We previously showed, in the same participants as in the present study, at a trend level, that reduction in the number of heavy drinking days

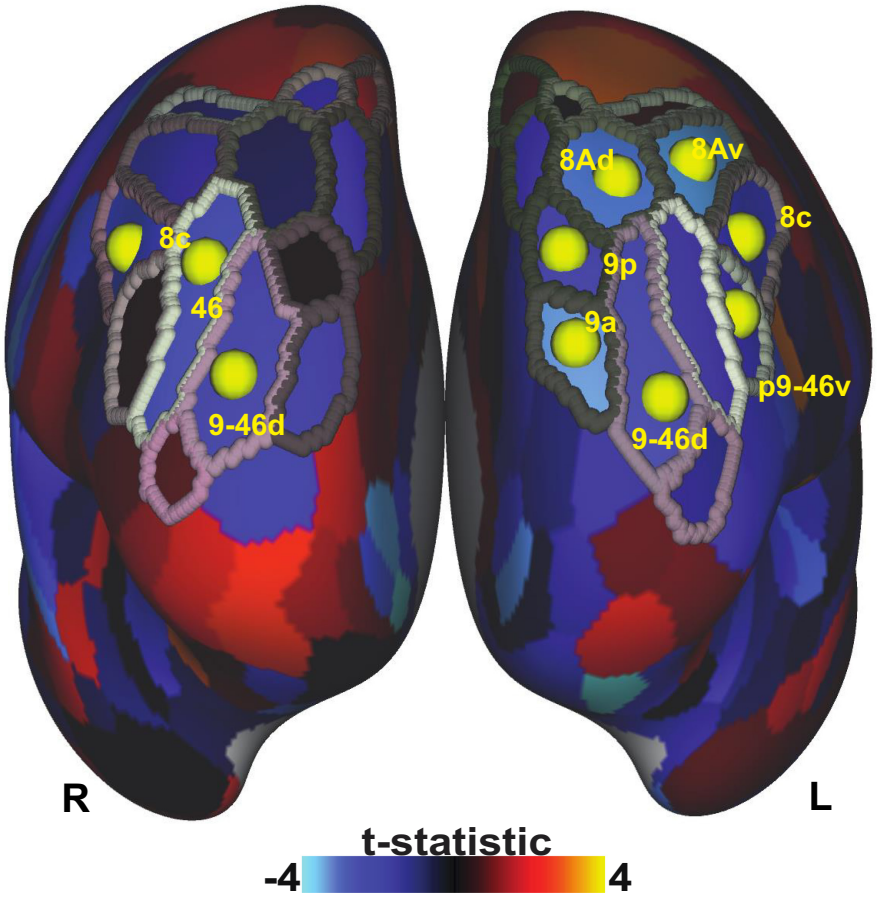
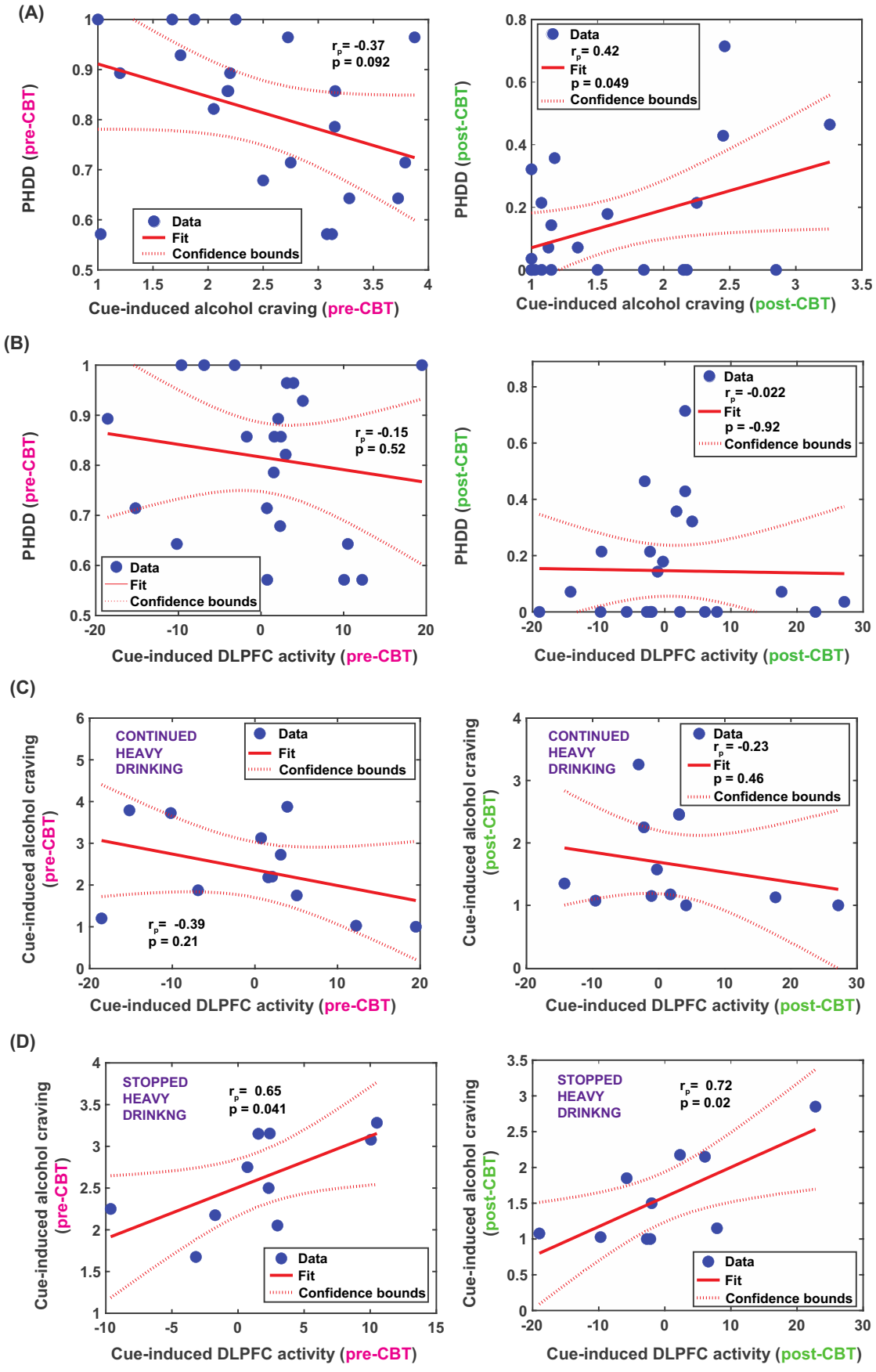


FIGURE 4 Parcellated map of 3-way interaction (cue induced alcohol craving x alcohol cue-induced brain activity x pre-CBT/post-CBT timepoint) on PHDD. DLPFC parcels are outlined. DLPFC parcels significant at $p<0.05$ are in this 3-way interaction are noted and include right DLPFC parcels 8C (b = −0.49; 95% CI −0.90 to −0.08; p = 0.020), 46 ($\beta=-0.29$; 95% CI −0.52 to −0.06; $p=0.014$), and 9–46d (b = −0.26; 95% CI −0.51 to −0.02; p = 0.035) as well as left DLPFC parcels 8C (b = −0.27; 95% CI −0.51 to −0.02; p = 0.033), 8Av ($\beta=-0.38$; 95% CI: −0.61 to −0.15; $p=0.002$), 9p (b = −0.23; 95% CI −0.43 to −0.02; p =0.032), 9a ($\beta=-0.30$; 95% CI: −0.48 to −0.11; $p=0.003$), 8Ad ($\beta=-0.25$; 95% CI −0.41 to −0.09; $p=0.004$), p9–46v (b = −0.22; 95% CI −0.43 to −0.002; p = 0.048), and 9–46d ($\beta=-0.21$; 95% CI: −0.38 to −0.03; $p=0.023$). See the Appendix S1 for detailed statistics of all DLPFC areas.



ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH ISBRA

FIGURE 5 Follow-regression analyses focused on left DLPFC. Shown are the regression lines for (A) the relationships between cue-induced alcohol craving and PHDD at pre-CBT and post-CBT timepoints (B), the relationships between alcohol-cue induced DLPFC activation at pre-CBT and post-CBT timepoints (C), and the relationship between baseline alcohol-cue induced DLPFC activation and baseline cue-induced alcohol craving in participants with PHDD >0 post-CBT (C) and with PHDD = 0 post-CBT (D).

was also associated with increased resting state functional connectivity (RSFC) between left area 9/46 and left anterior insula (Srivastava et al., 2021, 2022), a region that plays an important role in craving (Naqvi et al., 2014). Together, this suggests that pre-treatment DLPFC functional integrity may play a role in reduction of craving and heavy drinking during CBT.

We initially hypothesized that CBT works to reduce drinking through affecting the DLPFC's role in cognitive ROC, as assessed by the ROC paradigm. However, while we found that overall craving for alcohol decreased over the course of CBT, there was no change in the ability to regulate this craving at the behavioral level. We did observe regulation-related activity in the same DLPFC region where it was reported in previous studies (the caudal aspect of area 8). However, we did not find regulation-related activity changed over time (i.e., there were no interaction effects of instruction and time or instruction, cue, and time) in this area or any other PFC region. This suggests that PFC regions involved in cognitive regulation of alcohol craving, as assessed by the ROC paradigm, may not be the principal brain regions targeted by CBT. The task demands of the ROC paradigm resemble the coping skills that are taught in CBT modules 2 (Coping with Craving and Urges to Drink) and 3 (Managing Thoughts About Alcohol and Drinking). Our results suggest that behavior change that results from CBT may not be directly tied to an increased ability to utilize these specific coping skills, at least as indexed by the ROC task. Furthermore, the lack of an interaction effect of cue and time in any DLPFC parcel, juxtaposed with a significant interaction effect of cue and time on self-reported craving, suggests that changes in craving over time may not be a singular process specifically related to regulation.

Because we found no effects of CBT on regulation at the behavioral level, we then explored how changes in cue-induced craving and brain activity, irrespective of regulation status, may relate to both each other and to heavy drinking. We found an interaction between the effects of cue-induced brain activity, cue-induced craving and treatment timepoint on heavy drinking within a DLPFC region comprising contiguous Glasser parcels 8, 9, and 9/46, which is rostral to the region previously shown to play a role in cognitive ROC. This discrepancy may be explained by the possibility that there are at least two different forms of craving regulation involving different DLPFC regions. One form may involve more explicit/controlled processes and is engaged during the ROC task through activity in the DLPFC (BA 8) (Buhle et al., 2013; Ochsner et al., 2012), while the other form is more implicit/automatic (Dosenbach et al., 2006, 2008) that develops over time during CBT, if the baseline DLPFC (broadly corresponding to Glasser areas 8, 9, and 9/46) functioning is intact. This latter form may play a stronger role in drinking reduction during treatment.

Conclusions from this study should be drawn carefully given its limitations. First, our study included neither a control intervention nor a nontreatment seeking group. Thus, we do not know whether changes in alcohol craving or the lack of change in regulation-related DLPFC activity over time were due to specific effects of CBT, non-specific effects of treatment, nontreatment-related behavior change processes, the physiological effects of drinking reduction, or the mere passage of time. Second, the sample size was small, limiting the ability to interpret findings. Specifically, while our study ruled out any large effect-size changes in regulation-related DLPFC functioning, small to medium effect size changes remain possible. The small sample size also limits the interpretability of the 3-way interaction given the small degrees of freedom. Additionally, the baseline craving scores were low, raising the possibility that DLPFC activity changes related to changes in craving may not have been detectable. Notably, craving scores were lower than those in previous studies using this paradigm (Naqvi et al., 2015; Suzuki et al., 2019), which were conducted in nontreatment seeking individuals with AUD. This difference may suggest that the baseline group difference (treatment-seeking vs. not) may dictate whether the ROC task is useful for elucidating mechanisms of behavior change in CBT. However, it would be problematic at an ethical level to deliver a treatment intervention to individuals with AUD who are not seeking treatment. Next, the ROC task may not resemble the craving regulation strategies used by patients in their real lives, which may be much more implicit/automatic, limiting ecological and clinical validity. Furthermore, even though the measures that we defined for overall cue-induced alcohol craving and brain activity did not take into account task regulation effects, they may nonetheless have been influenced by regulation, given that half of the trials were under the NEGATIVE (high regulation) instruction; this leads to a degree of uncertainty about the relationship between cue-induced craving, ROC, brain activity and heavy drinking. In addition, heavy drinking may be driven in part by covert motivational processes that are not indexed by craving self-reports, such as attentional bias toward alcohol cues, automatic action tendencies, and psychophysiological responses (Field et al., 2010; Tiffany & Conklin, 2000). Nevertheless, cue-induced craving has been shown to be a strong predictor substance use and relapse (Vafaie & Kober, 2022).

CBT involves bringing to awareness the triggers and consequences of craving and heavy drinking, promoting alternative goals, and teaching the patient to engage in self-regulatory strategies aimed at managing craving, negative emotions, and impulsivity (Longabaugh & Morgenstern, 1999; Morgenstern & Longabaugh, 2000; Witkiewitz et al., 2013). We have proposed that treatments such as CBT depend upon a goal-directed mode of alcohol seeking, in which drinking is subject to deliberation and self-regulation, is strongly tied to craving, and dependent

on cognitive control functions of the DLPFC (Naqvi et al., 2014). This model is supported by the finding that patients who cease heavy drinking, who are presumably in a goal-directed state, exhibit a stronger relationship between craving and DLPFC activity both prior to and after treatment, compared to patients who continue heavy drinking. The clinical implications of the results, which will be examined in future research, are that individuals with AUD who have more intact DLPFC function pre-treatment should benefit more from CBT, and biological interventions that facilitate DLPFC function, such as repetitive transcranial magnetic stimulation (rTMS) should increase the efficacy of CBT for AUD (Hu et al., 2022).

FUNDING INFORMATION

This work was supported by the National Institutes of Health grants K23 AA022771 (Naqvi), T32 DA007294 (Levin), R01 MH121790 (Patel), and R01 MH123639 (Patel). The funding sources had no role in the design of this study or in its execution, analyses, interpretation of the data, or decision to submit the results for publication.

CONFLICT OF INTEREST STATEMENT

Dr. Levin receives grant support from the NIDA, NCATS, SAMHSA, US World Meds, and research support from Aelis Pharmaceuticals. She also receives medication from Indivior for research and royalties from APA publishing. In addition, Dr. Levin served as a nonpaid member of a Scientific Advisory Board for Alkermes, Indivior, Novartis, Teva, and US WorldMeds and is a consultant to Major League Baseball. Dr. Mariani has served as a consultant to Indivior. Dr. Naqvi has served as a paid consultant to Google and Regeneron, Inc. Dr. Patel receives income through Pfizer, Inc. through family. Dr. Drysdale, Dr. Lee, Dr. Morgenstern, Dr. Ochsner, Juan Sanchez-Peña, and Dr. Srivastava report no competing interests.

DATA AVAILABILITY STATEMENT

All data are available upon written request.

CLINICAL TRIAL REGISTRATION

This study is registered under ClinicalTrials.gov, identifier NCT02316574.

ORCID

A. Benjamin Srivastava https://orcid.org/0000-0001-9358-7506

REFERENCES

Assem, M., Glasser, M.F., Essen, D.C.V. & Duncan, J. (2020) A domain-general cognitive core defined in multimodally parcellated human cortex. *Cerebral Cortex*, 30, 4361–4380.

Benjamini, Y. & Hochberg, Y. (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society, Series B (Statistical Methodology)*, 57, 289–300.

Berking, M., Margraf, M., Ebert, D., Wupperman, P., Hofmann, S.G. & Junghanns, K. (2011) Deficits in emotion-regulation skills predict alcohol use during and after cognitive–behavioral therapy for alcohol dependence. *Journal of Consulting and Clinical Psychology*, 79, 307–318.

Beylergil, S.B., Beck, A., Deserno, L., Lorenz, R.C., Rapp, M.A., Schlagenhauf, F. et al. (2017) Dorsolateral prefrontal cortex contributes to the impaired behavioral adaptation in alcohol dependence. *NeuroImage: Clinical*, 15, 80–94.

Bogenschutz, M.P., Ross, S., Bhatt, S., Baron, T., Forcehimes, A.A., Laska, E. et al. (2022) Percentage of heavy drinking days following psilocybin-assisted psychotherapy vs placebo in the treatment of adult patients with alcohol use disorder. *JAMA Psychiatry*, 79, 953–962.

Brewer, J.A., Worhunsky, P.D., Carroll, K.M., Rounsaville, B.J. & Potenza, M.N. (2008) Pretreatment brain activation during Stroop task is associated with outcomes in cocaine-dependent patients. *Biological Psychiatry*, 64, 998–1004.

Buhle, J.T., Silvers, J.A., Wager, T.D., Lopez, R., Onyemekwu, C., Kober, H. et al. (2013) Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. *Cerebral Cortex*, 24, 2981–2990.

Coalson, T.S., Essen, D.C.V. & Glasser, M.F. (2018) The impact of traditional neuroimaging methods on the spatial localization of cortical areas. *Proceedings of the National Academy of Sciences of the United States of America*, 115, E6356–E6365.

DeVito, E.E., Dong, G., Kober, H., Xu, J., Carroll, K.M. & Potenza, M.N. (2017) Functional neural changes following behavioral therapies and disulfiram for cocaine dependence. *Psychology of Addictive Behaviors*, 31, 534–547.

DeVito, E.E., Worhunsky, P.D., Carroll, K.M., Rounsaville, B.J., Kober, H. & Potenza, M.N. (2012) A preliminary study of the neural effects of behavioral therapy for substance use disorders. *Drug and Alcohol Dependence*, 122, 228–235.

Dickie, E.W., Anticevic, A., Smith, D.E., Coalson, T.S., Manogaran, M., Calarco, N. et al. (2019) Ciftify: a framework for surface-based analysis of legacy MR acquisitions. *NeuroImage*, 197, 818–826.

Dosenbach, N.U.F., Fair, D.A., Cohen, A.L., Schlaggar, B.L. & Petersen, S.E. (2008) A dual-networks architecture of top-down control. *Trends in Cognitive Sciences*, 12, 99–105.

Dosenbach, N.U.F., Visscher, K.M., Palmer, E.D., Miezin, F.M., Wenger, K.K., Kang, H.C. et al. (2006) A Core system for the implementation of task sets. *Neuron*, 50, 799–812.

Ekhtiari, H., Zare-Bidoky, M., Sangchooli, A., Janes, A.C., Kaufman, M.J., Oliver, J.A. et al. (2022) A methodological checklist for fMRI drug cue reactivity studies: development and expert consensus. *Nature Protocols*, 17, 567–595.

Esteban, O., Markiewicz, C.J., Blair, R.W., Moodie, C.A., Isik, A.I., Erramuzpe, A. et al. (2019) fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nature Methods*, 16, 111–116.

Everitt, B.J. & Robbins, T.W. (2005) Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nature Neuroscience*, 8, 1481–1489.

Falk, D.E., O'Malley, S.S., Witkiewitz, K., Anton, R.F., Litten, R.Z., Slater, M. et al. (2019) Evaluation of drinking risk levels as outcomes in alcohol pharmacotherapy trials. *JAMA Psychiatry*, 76, 374–381.

Field, M., Wiers, R.W., Christiansen, P., Fillmore, M.T. & Verster, J.C. (2010) Acute alcohol effects on inhibitory control and implicit cognition: implications for loss of control over drinking. *Alcoholism, Clinical and Experimental Research*, 34, 1346–1352.

Friedman, N.P. & Robbins, T.W. (2022) The role of prefrontal cortex in cognitive control and executive function. *Neuropsychopharmacology*, 47, 72–89.

Fryer, S.L., Jorgensen, K.W., Yetter, E.J., Daurignac, E.C., Watson, T.D., Shanbhag, H. et al. (2013) Differential brain response to alcohol cue distractors across stages of alcohol dependence. *Biological Psychology*, 92, 282–291.

Glasser, M.F., Coalson, T.S., Robinson, E.C., Hacker, C.D., Harwell, J., Yacoub, E. et al. (2016) A multi-modal parcellation of human cerebral cortex. *Nature*, 536, 171–178.

Glasser, M.F., Sotiropoulos, S.N., Wilson, A.J., Coalson, T.S., Fischl, B., Andersson, J.L. et al. (2013) The minimal preprocessing pipelines for the human connectome project. *NeuroImage*, 15(80), 105–124.

Goldstein, R.Z., Craig, A.D., Bechara, A., Garavan, H., Childress, A.R., Paulus, M.P. et al. (2009) The Neurocircuitry of impaired insight in drug addiction. *Trends in Cognitive Sciences*, 13, 372–380.

Grinband, J., Wager, T.D., Lindquist, M., Ferrera, V.P. & Hirsch, J. (2008) Detection of time-varying signals in event-related fMRI designs. *NeuroImage*, 43, 509–520.

Hagman, B.T., Falk, D., Litten, R. & Koob, G.F. (2022) Defining recovery from alcohol use disorder: development of an NIAAA research definition. *The American Journal of Psychiatry*, 179, 807–813.

Hu, X., Zhang, T., Ma, H., Zhou, X., Wang, H., Wang, X. et al. (2022) Repetitive transcranial magnetic stimulation combined with cognitive behavioral therapy treatment in alcohol-dependent patients: a randomized, double-blind sham-controlled multicenter clinical trial. *Frontiers in Psychiatry*, 13, 935491.

Kadden, R., Carroll, K., Donovan, D., Cooney, N., Monti, P., Abrams, D. et al. (2003) *Cognitive-behavioral coping skills therapy manual: a clinical research guide for therapists treating individuals with alcohol abuse and dependence in: National Institute on Alcohol Abuse and Alcoholism project MATCH monograph series*. Rockville, MD: U.S. Department of Health and Human Services Public Health Service National Institutes of Health National Institute on Alcohol Abuse and Alcoholism.

Kadden, R.M. & Litt, M.D. (2011) The role of self-efficacy in the treatment of substance use disorders. *Addictive Behaviors*, 36, 1120–1126.

Koban, L., Wager, T.D. & Kober, H. (2023) A neuromarker for drug and food craving distinguishes drug users from non-users. *Nature Neuroscience*, 26, 316–325.

Kober, H., Kross, E.F., Mischel, W., Hart, C.L. & Ochsner, K.N. (2010) Regulation of craving by cognitive strategies in cigarette smokers. *Drug and Alcohol Dependence*, 106, 52–55.

Kober, H., Mende-Siedlecki, P., Kross, E.F., Weber, J., Mischel, W., Hart, C.L. et al. (2010) Prefrontal–striatal pathway underlies cognitive regulation of craving. *Proceedings of the National Academy of Sciences of the United States of America*, 107, 14811–14816.

Li, C.R., Luo, X., Yan, P., Bergquist, K. & Sinha, R. (2009) Altered impulse control in alcohol dependence: neural measures of stop signal performance. *Alcoholism, Clinical and Experimental Research*, 33, 740–750.

Longabaugh, R. & Morgenstern, J. (1999) Cognitive-behavioral coping-skills therapy for alcohol dependence. Current status and future directions. *Alcohol Research & Health*, 23, 78–85.

MacNiven, K.H., Jensen, E.L., Borg, N., Padula, C.B., Humphreys, K. & Knutson, B. (2019) Association of Neural Responses to drug cues with subsequent relapse to stimulant use. *JAMA Network Open*, 1, e186466.

Magill, M., Kiluk, B.D., McCrady, B.S., Tonigan, J.S. & Longabaugh, R. (2015) Active ingredients of treatment and client mechanisms of change in behavioral treatments for alcohol use disorders: Progress 10 years later. *Alcoholism, Clinical and Experimental Research*, 39, 1852–1862.

Magill, M., Tonigan, J.S., Kiluk, B., Ray, L., Walthers, J. & Carroll, K. (2020) The search for mechanisms of cognitive behavioral therapy for alcohol or other drug use disorders: a systematic review. *Behaviour Research and Therapy*, 131, 103648.

McCrady, B.S., Owens, M.D., Borders, A.Z. & Brovko, J.M. (2014) Psychosocial approaches to alcohol use disorders since 1940: a review. *Journal of Studies on Alcohol and Drugs. Supplement*, 75, 68–78.

Miller, E.K. & Cohen, J.D. (2001) An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, 24, 167–202.

Morgenstern, J. & Longabaugh, R. (2000) Cognitive–behavioral treatment for alcohol dependence: a review of evidence for its hypothesized mechanisms of action. *Addiction*, 95, 1475–1490.

Naqvi, N.H., Gaznick, N., Tranel, D. & Bechara, A. (2014) The insula: a critical neural substrate for craving and drug seeking under conflict and risk. *Annals of the New York Academy of Sciences*, 1316, 53–70.

Naqvi, N.H. & Morgenstern, J. (2015) Cognitive neuroscience approaches to understanding behavior change in alcohol use disorder treatments. *Alcohol Research: Current Reviews*, 37, 29–38.

Naqvi, N.H., Ochsner, K.N., Kober, H., Kuerbis, A., Feng, T., Wall, M. et al. (2015) Cognitive regulation of craving in alcohol-dependent and social drinkers. *Alcoholism, Clinical and Experimental Research*, 39, 343–349.

Ochsner, K.N. & Gross, J.J. (2005) The cognitive control of emotion. *Trends in Cognitive Sciences*, 9, 242–249.

Ochsner, K.N., Silvers, J.A. & Buhle, J.T. (2012) Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Annals of the New York Academy of Sciences*, 1251, E1–E24.

Pauli, W.M., Nili, A.N. & Tyszka, M.J. (2018) A high-resolution probabilistic in vivo atlas of human subcortical brain nuclei. *Scientific Data*, 5, 180063.

Pfefferbaum, A., Sullivan, E.V., Mathalon, D.H. & Lim, K.O. (1997) Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. *Alcoholism, Clinical and Experimental Research*, 21, 521–529.

Pfefferbaum, A., Sullivan, E.V., Rosenbloom, M.J., Mathalon, D.H. & Lim, K.O. (1998) A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. *Archives of General Psychiatry*, 55, 905–912.

Roos, C.R. & Witkiewitz, K. (2017) A contextual model of self-regulation change mechanisms among individuals with addictive disorders. *Clinical Psychology Review*, 57, 117–128.

Sacks, J.J., Gonzales, K.R., Bouchery, E.E., Tomedi, L.E. & Brewer, R.D. (2015) 2010 national and state costs of excessive alcohol consumption. *American Journal of Preventive Medicine*, 49, e73–e79.

Schacht, J.P., Anton, R.F. & Myrick, H. (2013) Functional neuroimaging studies of alcohol cue reactivity: a quantitative meta-analysis and systematic review. *Addiction Biology*, 18, 121–133.

Schneider, F., Habel, U., Wagner, M., Franke, P., Salloum, J.B., Shah, N.J. et al. (2001) Subcortical correlates of craving in recently abstinent alcoholic patients. *The American Journal of Psychiatry*, 158, 1075–1083.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E. et al. (1998) The Mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry*, 59(Suppl 20), 22–33;quiz 34–57.

Sobell, L.C. & Sobell, M.B. (1995) *Alcohol timeline followback users' manual*. Madison, WI: Addiction Research Foundation.

Srivastava, A.B., Sanchez-Peña, J., Levin, F.R., Mariani, J.J., Patel, G.H. & Naqvi, N.H. (2021) Drinking reduction during cognitive behavioral therapy for alcohol use disorder is associated with a reduction in anterior insula-bed nucleus of the stria terminalis resting-state functional connectivity. *Alcoholism, Clinical and Experimental Research*, 45, 1596–1606.

Srivastava, A.B., Sanchez-Peña, J., Levin, F.R., Mariani, J.J., Patel, G.H. & Naqvi, N.H. (2022) Corrigendum to "drinking reduction during a clinical trial of cognitive behavioral therapy for alcohol use disorder is associated with reduction in anterior insula-bed nucleus of the stria terminalis resting state functional connectivity". *Alcoholism, Clinical and Experimental Research*, 47, 1423–1424. Erratum for: Alcoholism, Clinical and Experimental Research 45: 1596–1606.

Sullivan, J.T., Sykora, K., Schneiderman, J., Naranjo, C.A. & Sellers, E.M. (1989) Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *British Journal of Addiction*, 84, 1353–1357.

Suzuki, S., Mell, M.M., O'Malley, S.S., Krystal, J.H., Anticevic, A. & Kober, H. (2019) Regulation of craving and negative emotion in alcohol use disorder. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 5, 239–250.

Theiss, J.D., Ridgewell, C., McHugo, M., Heckers, S. & Blackford, J. (2017) Manual segmentation of the human bed nucleus of the stria terminalis using 3T MRI. *NeuroImage*, 146, 288–292.

Tiffany, S.T. & Conklin, C.A. (2000) A cognitive processing model of alcohol craving and compulsive alcohol use. *Addiction*, 95, 145–153.

Turnbull, A., Wang, H.T., Murphy, C., Ho, N.S.P., Wang, X., Sormaz, M. et al. (2019) Left dorsolateral prefrontal cortex supports context-dependent prioritisation of off-task thought. *Nature Communications*, 10, 3816.

Tyszka, M.J. & Pauli, W.M. (2016) In vivo delineation of subdivisions of the human amygdaloid complex in a high-resolution group template. *Human Brain Mapping*, 37, 3979–3998.

Vafaie, N. & Kober, H. (2022) Association of drug cues and craving with drug use and relapse. *JAMA Psychiatry*, 79, 641–650.

White, A.M., Castle, I.-J.P., Powell, P.A., Hingson, R.W. & Koob, G.F. (2022) Alcohol-related deaths during the COVID-19 pandemic. *JAMA*, 327, 1704–1706.

White, A.M., Castle, I.P., Hingson, R.W. & Powell, P.A. (2020) Using death certificates to explore changes in alcohol-related mortality in the United States, 1999 to 2017. *Alcoholism, Clinical and Experimental Research*, 44, 178–187.

Wilcox, C.E., Dekonenko, C.J., Mayer, A.R., Bogenschutz, M.P. & Turner, J.A. (2014) Cognitive control in alcohol use disorder: deficits and clinical relevance. *Reviews in the Neurosciences*, 25, 1–24.

Witkiewitz, K., Litten, R.Z. & Leggio, L. (2019) Advances in the science and treatment of alcohol use disorder. *Science Advances*, 5, eaax4043.

Witkiewitz, K., Lustyk, M.K.B. & Bowen, S. (2013) Retraining the addicted brain: a review of hypothesized neurobiological mechanisms of mindfulness-based relapse prevention. *Psychology of Addictive Behaviors*, 27, 351–365.

Witkiewitz, K. & Marlatt, A. (2011) Behavioral therapy across the spectrum. *Alcohol Research & Health*, 33, 313–319.

Yeo, Y.H., He, X., Ting, P.-S., Zu, J., Almario, C.V., Spiegel, B.M.R. et al. (2022) Evaluation of trends in alcohol use disorder–related mortality in the US before and during the COVID-19 pandemic. *JAMA Network Open*, 5, e2210259.

Zeng, J., Yu, S., Cao, H., Su, Y., Dong, Z. & Yang, X. (2021) Neurobiological correlates of cue-reactivity in alcohol-use disorders: a voxel-wise meta-analysis of fMRI studies. *Neuroscience and Biobehavioral Reviews*, 128, 294–310.

Zou, X., Durazzo, T.C. & Meyerhoff, D.J. (2018) Regional brain volume changes in alcohol-dependent individuals during short-term and long-term abstinence. *Alcoholism, Clinical and Experimental Research*, 42, 1062–1072.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Naqvi, N.H., Srivastava, A.B., Sanchez-Peña, J., Lee, J.K., Drysdale, A.T., Mariani, J.J. et al. (2024) Neural correlates of drinking reduction during a clinical trial of cognitive behavioral therapy for alcohol use disorder. *Alcohol: Clinical and Experimental Research*, 48, 260–272. Available from: https://doi.org/10.1111/acer.15259