Elucidating the Effect of a Brief Drinking Intervention Using Neuroimaging: A Preliminary Study

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Background: Brief interventions have empirical support for acutely reducing alcohol use among non–treatment-seeking heavy drinkers. Neuroimaging techniques allow for the examination of the neurobiological effect of behavioral interventions, probing brain systems putatively involved in clinical response to treatment. Few studies have prospectively evaluated whether psychosocial interventions attenuate neural cue reactivity that in turn reduces drinking in the same population. This study aimed to examine the effect of a brief intervention on drinking outcomes, neural alcohol cue reactivity, and the ability of neural alcohol cue reactivity to prospectively predict drinking outcomes.

Methods: Non–treatment-seeking heavy drinking participants were randomized to receive a brief interview intervention (n = 22) or an attention-matched control (n = 24). Immediately following the intervention or control, participants underwent a functional magnetic resonance imaging scan comprised of the alcohol taste cues paradigm. Four weeks after the intervention (or control), participants completed a follow-up visit to report on their past-month drinking. Baseline and follow-up percent heavy drinking days (PHDD) were calculated for each participant.

Results: There was no significant effect of the brief intervention on PHDD at follow-up or on modulating neural activation to alcohol relative to water taste cues. There was a significant association between neural response to alcohol taste cues and PHDD across groups ($Z > 2.3$, $p < 0.05$), such that individuals who had greater neural reactivity to alcohol taste cues in the precuneus and prefrontal cortex (PFC) had fewer PHDD at follow-up.

Conclusions: This study did not find an effect of the brief intervention on alcohol use in this sample, and the intervention was not associated with differential neural alcohol cue reactivity. Nevertheless, greater activation of the precuneus and PFC during alcohol cue exposure predicted less alcohol use prospectively suggesting that these neural substrates subserve the effects of alcohol cues on drinking behavior.

Key Words: Brief Intervention, Mechanisms of Behavior Change, fMRI, Alcohol, Precuneus.

BRIEF INTERVENTIONS HAVE empirical support for acutely reducing alcohol use among non–treatment-seeking heavy drinkers. For example, randomized clinical trials of brief interventions have found favorable results among heavy drinkers reached through primary care (Fleming et al., 1997; Saitz et al., 2003), trauma centers (Gentilello et al., 1999), and emergency departments (Bernstein et al., 2007; D'Onofrio and Degutis, 2002). Brief interventions also have shown effectiveness in reducing alcohol use in nonmedical settings among a young adult college population (Carey et al., 2006). Given this sizable evidence base, there is considerable interest in understanding the underlying mechanisms toward optimizing this approach.

Neuroimaging techniques allow for the examination of the neurobiological effects underlying behavioral interventions, probing brain systems putatively involved in clinical response to treatment. To date, 1 study has examined the effect of a motivational interviewing (MI)-based intervention on the neural substrates of alcohol reward (Feldstein Ewing et al., 2011b). In this study, neural response to alcohol cues was evaluated while individuals were exposed to change talk and counterchange talk (i.e., sustain talk), which are thought to underlie motivation changes during psychosocial intervention. The authors report activation in reward processing areas following counterchange talk, which was not present following exposure to change talk (Feldstein Ewing et al., 2011b). Feldstein Ewing and colleagues (2014) have also probed the nature of the origin of change talk in order to better understand the neural underpinnings of change language. In this study, binge drinkers were presented with self-generated and experimenter-selected change and sustain talk. Self-generated change talk and sustain talk resulted in greater activation in regions associated with introspection, including the interior frontal gyrus and insula, compared to

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experimenter-elicited client language (Feldstein Ewing et al., 2014). These studies employed an active ingredient of MI within the structure of the functional magnetic resonance imaging (fMRI) task, thus allowing for a more proximal test of treatment effects.

Neuroimaging has also been used to explore the effect of psychological interventions on changes in brain activation that are specifically focused on alcohol motivation. For example, cue-exposure extinction training, a treatment designed to prevent return to use by decreasing conditioned responses to alcohol cue stimuli through repeated exposure to cues without paired reward, has also been evaluated using neuroimaging (Vollstadt-Klein et al., 2011). Alcohol-dependent patients who underwent cue-exposure extinction training had larger decreases in neural alcohol cue reactivity in mesocorticolimbic reward circuitry than patients who had standard clinic treatment. Cognitive bias modification training, which similarly trains individuals to reduce attentional bias toward alcohol cues, resulted in decreased neural alcohol cue reactivity in the amygdala (Wiers et al., 2015b) and reduced medial prefrontal cortex (mPFC) activation when approaching alcohol cues (Wiers et al., 2015a). These studies suggest that fMRI tasks may be sensitive to treatment response.

Further, neurobiological circuits identified using fMRI can be used to predict treatment and drinking outcomes, providing unique information beyond that of self-report and behavior. Individuals with alcohol use disorder (AUD) who return to use demonstrate increased activation in the mPFC to alcohol cues compared to individuals with AUD who remain abstinent (Beck et al., 2012; Grusser et al., 2004). Moreover, the degree that the mPFC was activated was associated with the amount of subsequent alcohol intake, but not alcohol craving (Grusser et al., 2004). Activation in the dorsolateral PFC to alcohol visual cues has been associated with higher percent heavy drinking days (PHDD) in treatment-seeking alcohol-dependent individuals (Schacht et al., 2013b). Increased activation in the mPFC, orbitofrontal cortex, and caudate in response to alcohol cues has also been associated with the escalation of drinking in young adults (Dager et al., 2014). Mixed findings have been reported for the direction of the association between cue-induced striatal activation and return to use. Increases (Bach et al., 2015; Grusser et al., 2004; Reinhard et al., 2015) and decreases (Beck et al., 2012) in ventral and dorsal striatal activation to alcohol cues have been associated with subsequent return to use. Utilizing a different paradigm, Seo and colleagues (2013) found that increased mPFC, ventral striatal, and precuneus activation to individually tailored neutral imagery scripts predicted subsequent return to use in treatment-seeking individuals with AUD. Interestingly, brain activity during individually tailored alcohol and stress imagery scripts was not associated with return to use (Seo et al., 2013).

While initial evidence indicates that psychological interventions are effective at reducing mesocorticolimbic response to alcohol-associated cues, few studies have prospectively evaluated if psychosocial interventions attenuate neural cue reactivity that in turn reduces drinking in the same population. Furthermore, no previous studies have used neural reactivity to alcohol cues to understand the mechanisms of brief interventions. Therefore, this study aimed to examine the effect of a brief intervention on drinking outcomes, neural alcohol cue reactivity, and the ability of neural alcohol cue reactivity to predict drinking outcomes. Specifically, this study investigated: (i) if the brief intervention would reduce PHDD or drinks per week in non–treatment-seeking heavy drinkers in the month following the intervention; and (ii) if the brief intervention would attenuate neural alcohol cue reactivity. In the first case, we predicted significant effects on drinking based on the existing clinical literature, and in the second case, we predicted decrements in alcohol's motivational salience based on the feedback about the participant's drinking levels relative to clinical recommendations and their personal negative consequences of drinking. The effects of neural cue reactivity on subsequent drinking outcomes were tested in order to elucidate patterns of neural cue reactivity that predict drinking behavior prospectively.

MATERIALS AND METHODS

Participants and Screening Procedures

Participants were recruited between November 2015 and February 2017 from the greater Los Angeles metropolitan area. Study advertisements described a research study investigating the effects of a brief health education session on beliefs about the risks and benefits of alcohol use. Inclusion criteria were as follows: (i) engaged in regular heavy drinking, as indicated by consuming 5 or more drinks per occasion for men or 4 or more drinks per occasion for women at least 4 times in the month prior to enrollment (as indicated on the Timeline Follow-back [TLFB]); or (ii) a score of ≥8 on the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993). Exclusion criteria included the following: (i) under the age of 21; (ii) currently receiving treatment for alcohol problems, history of treatment in the 30 days before enrollment, or currently seeking treatment; (iii) a positive urine toxicology screen for any drug other than cannabis; (iv) a lifetime history of schizophrenia, bipolar disorder, or other psychotic disorder; (v) serious alcohol withdrawal symptoms as indicated by a score of ≥10 on the Clinical Institute Withdrawal Assessment for Alcohol—Revised (Sullivan et al., 1989); (vi) history of epilepsy, seizures, or severe head trauma; (vii) nonremovable ferromagnetic objects in body; (viii) claustrophobia; or (ix) pregnancy.

Initial assessment of the eligibility criteria was conducted through a telephone interview. Eligible participants were invited to the laboratory for additional screening. Upon arrival, participants read and signed an informed consent form. Participants then completed a series of individual differences measures and interviews, including a demographics questionnaire and the TLFB to assess for quantity and frequency of drinking over the past 30 days. All participants were required to test negative on a urine drug test (except for marijuana, which was allowed to be positive). A total of 120 participants were screened in the laboratory, 38 did not meet inclusion criteria, and 22 decided not to participate in the trial, leaving 60 participants who enrolled and were randomized. Of the 60 individuals randomized, 46 completed the entire study. See Fig. 1 for a CONSORT diagram for this trial.

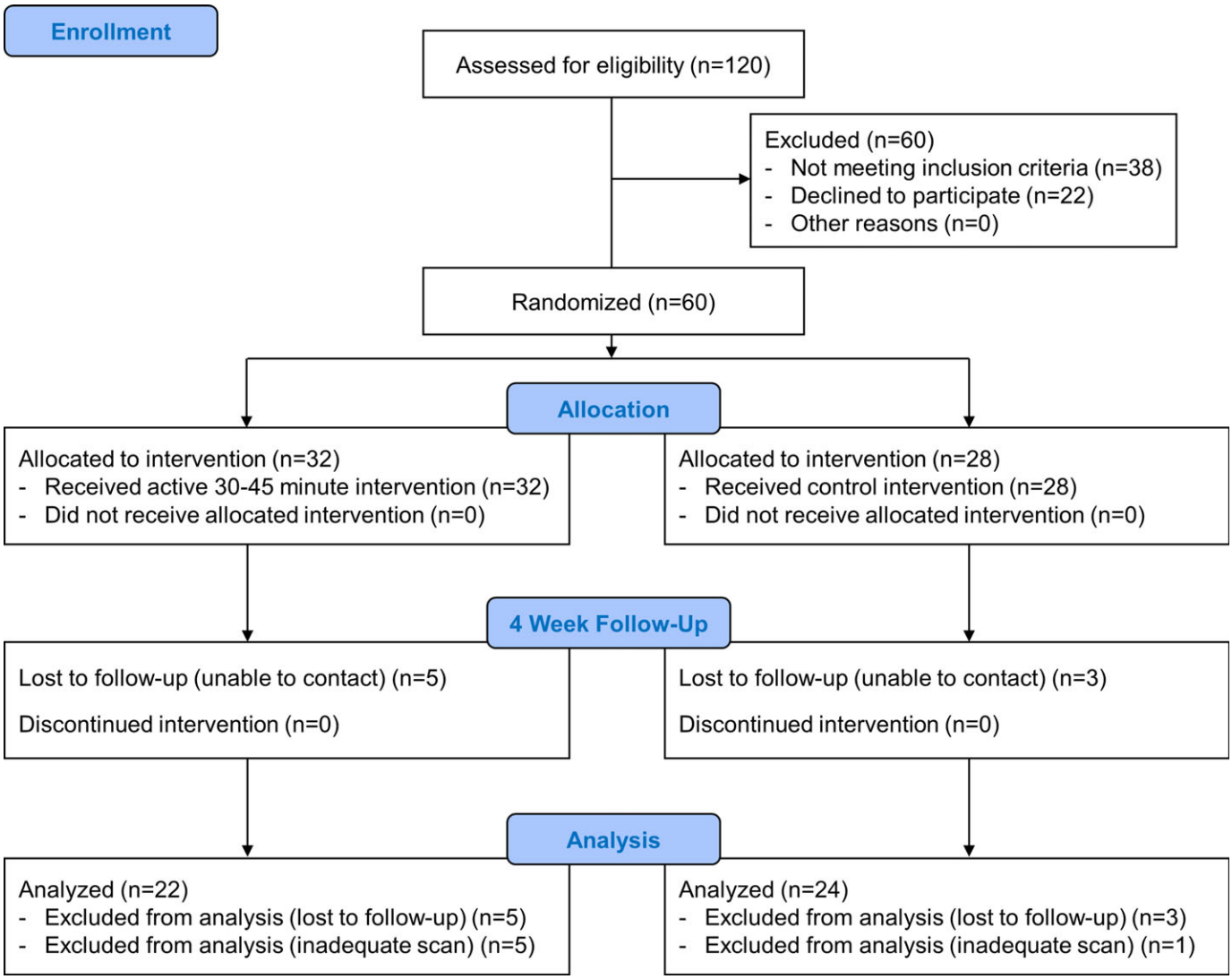

Fig. 1. CONSORT diagram for the trial.

Study Design

The study was a randomized controlled trial. Participants were assessed at baseline for study eligibility, and eligible participants returned for the randomization visit up to 2 weeks later. During their second visit, participants completed assessments and then were randomly assigned to receive a 1-session brief intervention or to an attention-matched control condition. Immediately after the conclusion of the session, participants completed an fMRI scan to assess brain activity during exposure to alcohol cues and completed additional assessments. Participants were followed up 4 weeks later to assess alcohol use since the intervention (or control) through the 30-day TLFB interview. Participants who completed all study measures were compensated $160.

The brief intervention consisted of a 30- to 45-minute individual face-to-face session based on the principles of MI (Miller and Rollnick, 2002; Miller and Rose, 2009). The intervention adhered to the FRAMES model, which includes personalized feedback (F), emphasizing personal responsibility (R), providing brief advice (A), offering a menu (M) of change options, conveying empathy (E), and encouraging self-efficacy (S). In accordance with MI principles, the intervention was nonconfrontational and emphasized participants' autonomy. The content of the intervention mirrored brief interventions to reduce alcohol use that have been studied with non–treatment-seeking heavy drinkers (e.g., Borsari and Carey, 2000; Longabaugh et al., 2001; Saitz et al., 2007). The intervention included the following specific components: (i) giving normative feedback about frequency of drinking and of heavy drinking; (ii) AUDIT score and associated risk level (Saunders et al., 1993); (iii) potential health risks associated with alcohol use; (iv) placing the responsibility for change on the individual; (v) discussing the reasons for drinking and downsides of drinking; and (vi) setting a goal and change plan if the participant was receptive (see Fig. S1). The aim of the intervention was to help participants understand their level of risk and to help them initiate changes in their alcohol use. Sessions were delivered by master's level therapists who received training in MI techniques, including the use of open-ended questions, reflective listening, summarizing, and eliciting change talk, and in the content of the intervention. All sessions were audiotaped and rated by author MPK for fidelity and for quality of MI interventions using the Global Rating of Motivational Interviewing Therapists (Moyers, 2004). On the 7-point scale, session scores

ranged from 5.87 to 6.93 with an average rating of 6.61 ± 0.23, which indicates that the MI techniques used in the intervention were delivered with good quality. Supervision and feedback were provided to therapists by author MPK following each intervention session. The treatment manual is available from the last author upon request.

Participants randomized to the attention-matched control condition viewed a 30-minute video about astronomy. In the control condition, there was no mention of alcohol or drug use beyond completion of research assessments. Both the intervention and attention-matched control sessions took place within the UCLA Center for Cognitive Neuroscience in separate rooms from the neuroimaging suite.

Individual Difference Measures

The following individual questionnaires and interviews were administered during the study: (i) the 30-day TLFB was administered in interview format to capture daily alcohol and marijuana use over the 30 days prior to the visit by trained research assistants (Sobell et al., 1988); (ii) the self-report AUDIT was administered in order to assess for drinking severity (Saunders et al., 1993); and (iii) the Penn Alcohol Craving Scale (PACS) was administered to measure alcohol craving over the past week (Flannery et al., 1999). Participants also completed the Fagerstrom Test for Nicotine Dependence (Heatherton et al., 1991). Last, participants completed a demographics questionnaire reporting, among other variables, age, sex, and level of education.

fMRI Paradigm

The Alcohol Cues Task involves the delivery of oral alcohol or control (water) tastes to elicit physiological reward responses and subjective urges to drink (Filbey et al., 2008a,b). During the task, each trial began with the presentation of a visual cue (alcohol or water; 2 seconds) such that the words Alcohol Taste and Control Taste were visually presented to participants. This was followed by a fixation cross (jittered for an average of 3 seconds), delivery of the taste (1 ml alcohol or water; 5 seconds), and a fixation cross (jittered using an exponential distribution with a mean of 3 seconds and a range of 0.5 to 6 seconds). Alcohol and water tastes were delivered through Teflon tubing using a computer-controlled delivery system (Infinity Controller; J-KEM Scientific Inc., St. Louis, MO) as described by Filbey and colleagues (2008a). Participants were instructed to press a button on a response box placed in their right hand upon swallowing. Alcohol tastes consisted of participants' preferred alcoholic beverage (wine or liquor). Beer could not be administered due to incompatibility of the alcohol administration device with carbonated liquids. The presentation of visual stimuli and response collection was programmed using MATLAB (MathWorks, Natick, MA) and the Psychtoolbox (www.psychtoolbox.org) on an Apple MacBook running Mac OS X (Apple Computers, Cupertino, CA), and visual stimuli were presented using MRI-compatible goggles (Resonance Technologies, Van Nuys, CA). The alcohol cues task was administered over the course of 2 runs with 50 trials/run.

fMRI Protocol

At the start of the scanning visit, participants were required to have a BrAC of 0.00 g/dl and a urine toxicology screen negative for all drugs (excluding tetrahydrocannabinol [THC]). Additionally, female participants were required to have a negative pregnancy test.

Scanning took place immediately following the brief intervention or attention-matched control at the UCLA Center for Cognitive Neuroscience on a 3.0T Siemens Prisma scanner (Siemens Medical Solutions USA, Inc., Malvern, PA). A T2-weighted, high-resolution matched-bandwidth (MBW) anatomical scan (time to repetition (TR) = 5,000 ms, time to echo (TE) = 34 ms, flip angle = 90°, voxel size: 1.5 mm × 1.5 × 4 mm, field of view (FOV) = 192 mm^2, 34 slices, ~1.5 minutes) and a T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TR = 2,530 ms, TE = 1.74 ms, time to inversion = 1,260 ms, flip angle = 7°, voxel size: 1 mm^3, FOV = 256 mm^2, ~6.2 minutes) were acquired for coregistration to the functional data. A T2*-weighted echo planar imaging scan (TR = 2,000 ms, TE = 30 ms, voxel size: 3 mm × 3 mm × 4 mm, FOV = 192 mm^2, 325 TRs, ~10.83 min/run) was acquired to examine the blood oxygen level–dependent signal during 2 runs of the alcohol cues task (total time: ~22 minutes).

Preprocessing of data followed conventional procedures implemented in FMRIB Software Library (FSL 5.0) (www.fmrib.ox.ac.uk/fsl). This included motion correction (Motion Correction Linear Image Registration Tool ([McFLIRT], version 5.0), high-pass temporal filtering (100-second cutoff) using FSL's FMRI Expert Analysis Tool (FEAT; version 5.63), and smoothing with a 5-mm full-width half-maximum Gaussian kernel. FSL's Brain Extract Tool was used to remove skull and nonbrain tissue from both the structural and functional scans. Data were denoised using ICA-AROMA (Pruim et al., 2015) to reduce motion artifacts associated with swallowing. Six subjects (5 in the intervention group and 1 in the control group) were excluded from further analysis due to excessive motion (exceeding 3 mm of translation) or incomplete scan data.

Data Analysis

For the intervention effect on drinking, linear mixed model analyses were conducted to test for the main effect of the intervention on the average number of drinks per week and percent of heavy drinking days in the 4 weeks postintervention. One model was run for each dependent variable. The intercept was a random effect. The models accounted for sex, smoking status, and age as covariates. The intervention effect was evaluated by testing the time (baseline and follow-up)-by-condition interaction. Comparative effect size estimates for the effect of intervention on drinking outcomes were calculated based on adjusted models using $d = B_{\text{condition*time}}/\text{SD}_{\text{pooled baseline}}$. In addition, the effects of neural cue reactivity on drinking outcomes were also examined.

For the analysis of the cues task, all first-level analyses of imaging data were conducted within the context of the general linear model (FSL's FEAT), modeling the combination of the cue and taste delivery periods convolved with a double-gamma hemodynamic response function (HRF), and accounting for temporal shifts in the HRF by including the temporal derivative. Alcohol and water taste cues were modeled as separate event types. The onset of each event was set at the cue period (visual cue indicating trial type) with a duration of 11 seconds. Six motion regressors representing translational and rotational head movement were also entered as regressors of no interest. Data for each subject were registered to the MBW, followed by the MPRAGE using affine linear transformations, and then normalized to the Montreal Neurological Institute (MNI avg152) template. Registration was further refined using FSL's nonlinear registration tool.

The alcohol taste > water taste contrast was specified in the first-level models. Higher-level analyses combined these contrast images within subjects (across the 2 task runs) and between subjects (within study conditions and across study conditions). Age, sex, cigarette smoking status, and positive urine THC were included as covariates. Additional analyses evaluated if neural response to alcohol taste cues was predictive of drinking outcomes. Two models were run, evaluating PHDD and the average number of drinks per week in the 4 weeks following the intervention or matched control. Both models were controlled for age, sex, cigarette smoking status, positive urine THC, and baseline PHDD or average drinks per week

depending on the drinking outcome model. *Z*-statistic images were thresholded with cluster-based corrections for multiple comparisons based on the theory of Gaussian random fields with a cluster-forming threshold of $Z > 2.3$ and a corrected cluster-probability threshold of $p < 0.05$ (Worsley, 2001).

RESULTS

Demographics Info

Forty-six individuals (intervention group = 22; control group = 24) successfully completed the scan and follow-up visits. The intervention and control groups were well-matched on demographic measures including age, sex, years of education, smoking status, and cannabis use. The groups did not differ on baseline alcohol use characteristics including total AUDIT score, alcohol craving (PACS), average number of drinks consumed per week, or PHDD (see Table 1).

Effect of Intervention on Drinking Outcomes

Overall, there was no statistically significant effect of the brief intervention on drinking outcomes as measured by the TLFB. Results from the analyses did not support an effect of the intervention relative to the control condition on changes in the frequency of heavy drinking days ($p > 0.4$) or on the average weekly number of drinks consumed ($p > 0.3$). Estimated marginal means indicated a pattern that favored of the intervention in that there was a 53.3% reduction in heavy drinking days from baseline to follow-up among participants in the intervention condition versus a 37.4% reduction among participants in the control condition. In terms of drinks per week, the model estimated a mean reduction of 37.7% in the intervention condition versus 26.1% in the control conditions. The comparative effect size estimates for the change in alcohol use over time in the intervention versus control condition were $d = -0.182$ for PHDD and $d = -0.203$ for average drinks per week.

Intervention Group: Neural Alcohol Cue Reactivity

The intervention group showed increased activation to alcohol taste cues compared to water taste cues in 2 large clusters: the first consisting of the thalamus, insula, and the putamen, and the second containing the paracingulate and middle frontal gyrus (see Table 2; Fig. 2*A*).

Control Group: Neural Alcohol Cue Reactivity

The control group also showed increased activation in response to alcohol compared to water taste cues. The control group had increased activation in regions including the superior frontal gyrus, middle frontal gyrus, ventral tegmental area, thalamus, and insula (see Table 2; Fig. 2*B*).

Effect of Intervention on Neural Alcohol Cue Reactivity

Across groups, exposure to alcohol taste resulted in increased activation in frontal and limbic regions, compared to water taste (see Table 2; Fig. 2*C*). There was no significant effect of the brief interview intervention on neural alcohol cue reactivity.

Effect of Neural Cue Reactivity on Drinking Outcomes

Across groups, activation to alcohol tastes in the precuneus and medial frontal gyrus was negatively associated with PHDD (see Table 3; Fig. 3). In other words, individuals who had lower PHDD in the weeks following the fMRI visit had greater neural reactivity to alcohol taste in the precuneus and PFC.

Table 1. Demographic Characteristics of Participants

Characteristic	Intervention group ($n = 22$)	Control group ($n = 24$)	Statistic	*p*-Value
Age	36.41 ± 13.56	32.29 ± 9.89	$t = 1.18$	0.24
Sex (m/f)	13/9	15/9	$\chi^2 = 0.06$	0.81
Smokers (*n*)	11	12	$\chi^2 = 0.00$	1
Education (years)	15.45 ± 2.13	15.04 ± 1.78	$t = 0.72$	0.48
AUDIT total score	17.68 ± 6.49	17.17 ± 7.61	$t = 0.25$	0.81
PACS score	19.32 ± 6.94	18.79 ± 7.15	$t = 0.25$	0.80
Baseline				
Average number of drinks/wk (ATLFB)	24.40 ± 17.62	20.77 ± 11.52	$t = 0.83$	0.41
PHDD (ATLFB)	37.73 ± 27.15	35.00 ± 22.93	$t = 0.37$	0.71
THC positive (*n*)	6	6	$\chi^2 = 0.04$	0.86
THC total number days used (MTLFB)	3.50 ± 7.04	1.79 ± 3.46	$t = 1.03$	0.31
Follow-up				
Average number of drinks/wk (ATLFB)	15.48 ± 12.11	14.84 ± 9.83	$t = 0.56$	0.84
PHDD (ATLFB)	18.56 ± 19.30	21.61 ± 21.58	$t = 0.50$	0.62
THC positive (*n*)	1	3	$\chi^2 = 0.92$	0.34
THC total number days used (MTLFB)	1.32 ± 4.81	2.92 ± 6.44	$t = 0.93$	0.36

ATLFB, Alcohol Timeline Follow-back; AUDIT, Alcohol Use Disorders Identification Test; MTLFB, Marijuana Timeline Follow-back; PACS, Penn Alcohol Craving Scale; PHDD, percent heavy drinking days; THC, tetrahydrocannabinol.

Table 2. Whole-Brain Activation to Alcohol Taste Cues Versus Water Taste Cues by Group

	Alcohol taste > water taste				
Brain region	Cluster voxels	Max. *Z*	*x*	*y*	*z*
Intervention group					
R Thalamus	1,700	4.18	20	−20	−4
R Middle temporal gyrus		3.27	62	−18	−18
R Parahippocampal gyrus		2.80	20	−14	−26
R Hippocampus		2.71	32	−26	−8
R Putamen		2.65	34	−6	−10
R Insula		2.61	42	6	−6
R/L Paracingulate gyrus	1,199	3.95	0	36	32
L Middle frontal gyrus		3.15	−38	26	42
Control group					
L Superior frontal gyrus	3,395	4.17	−14	8	62
R/L Paracingulate gyrus		3.18	0	36	32
L Middle frontal gyrus		3.13	−54	14	32
R/L Ventral tegmental area	1,497	3.93	0	−20	−20
R/L Thalamus		2.97	0	−18	8
R Parahippocampal gyrus		2.78	28	−30	−16
R Insula	1,436	4.74	44	−20	0
R Middle temporal gyrus		3.54	60	−4	−16
R Hippocampus		2.52	28	−16	−14
Combined intervention and control group					
L Superior frontal gyrus	3,691	4.51	−14	10	58
R/L Paracingulate gyrus		3.26	−2	36	34
L Precentral gyrus		3.02	−42	−2	58
L Middle frontal gyrus		2.91	−48	14	34
R Thalamus	3,380	4.16	20	−26	−2
R Middle temporal gyrus		3.62	62	−18	−18
R/L Ventral tegmental area		3.28	0	−16	−14
R Parahippocampal gyrus		3.08	16	−14	−24
R Insula		3.04	40	−16	4
R Pallidum		2.91	24	−12	−6
R Hippocampus		2.79	30	−14	−14
Intervention > control group					
N/A					
Control > intervention group					
N/A					

L, left; R, right.

Similarly, across groups, activation to alcohol tastes in the precuneus was negatively associated with average drinks per week (see Fig. S2, Table S1). That is, greater neural activity in the precuneus in response to alcohol cues was associated fewer average drinks per week at follow-up.

DISCUSSION

This study examined the effect of a brief intervention on drinking outcomes, neural alcohol cue reactivity, and the ability of neural alcohol cue reactivity to predict drinking outcomes. Results did not find an effect of the brief intervention on alcohol use in this sample, and the intervention was not associated with differential neural alcohol cue reactivity. Exploratory secondary analyses revealed inverse relationships between differential neural activity in the precuneus and medial frontal gyrus in relation to alcohol-related outcomes, but these relationships were across conditions.

The lack of main effect of intervention on either drinking outcomes or on neural alcohol cue reactivity is contrary to the study hypothesis; whereby, individuals assigned to the brief intervention condition were expected to show greater reductions in alcohol use compared to a no-intervention control condition (Elzerbi et al., 2015; Samson and Tanner-Smith, 2015; Tanner-Smith and Risser, 2016). In the present study, reductions in alcohol use were observed for both conditions and it appears that simply participating in an alcohol research study at an academic medical center prompted notable behavioral changes. Reductions in drinking following study participation may be attributable to assessment reactivity, in which participants curb drinking after completing alcohol-related assessments and interviews (Epstein et al., 2005). This phenomenon has been well-documented across several assessment modalities (Epstein et al., 2005; Helzer et al., 2002; Kypri et al., 2007), including the AUDIT and TLFB interviews, which were used in the present study. In addition, recent studies have highlighted the fact that single session interventions, while efficacious in relatively large randomized controlled trials, have modest effect sizes (Huh et al., 2015; Samson and Tanner-Smith, 2015). As such, the present study may have been underpowered to detect small effects sizes, which may account for the null findings regarding intervention effects on drinking outcomes. Future studies are encouraged to recruit larger samples of non–treatment-seeking participants to better detect small effects. Furthermore, this finding should be considered in light of the sample, which was comprised of nontreatment seekers from the community, which is not the typical sample evaluated in brief intervention research. However, non–treatment-seeking individuals with similar alcohol use characteristics are open to participating in brief interventions (Bacio et al., 2014). Also of note, the drinking outcomes in this study were evaluated using variables derived from the TLFB as the primary outcome measure. There is some evidence that some individuals under report substance use when the TLFB is administered by an interviewer rather than a computer (Delker et al., 2016), potentially due to a social desirability bias in which participants wish to appear favorably to the interviewer. In the present study, the TLFB assessment was conducted by a trained research assistant and not the clinician who delivered the brief intervention in order to reduce this bias. However, the TLFB is a retrospective self-report measure and as such is subject to limitations including inaccuracies in participant recall. Alcohol use was also not biologically verified in this study.

In light of the null findings regarding intervention effects on drinking in this study, it is perhaps not surprising that intervention condition was not associated with differences in neural cue reactivity in this sample. While it has been argued that neuroimaging techniques may be sensitive to mechanisms of behavior change (Feldstein Ewing and Chung, 2013; Feldstein Ewing et al., 2011a), in the present study, neural processing of alcohol taste cues was no more sensitive to intervention effects than traditional measures of drinking outcomes. It should be noted, however, that the alcohol taste cues task used in this study was abbreviated from its original

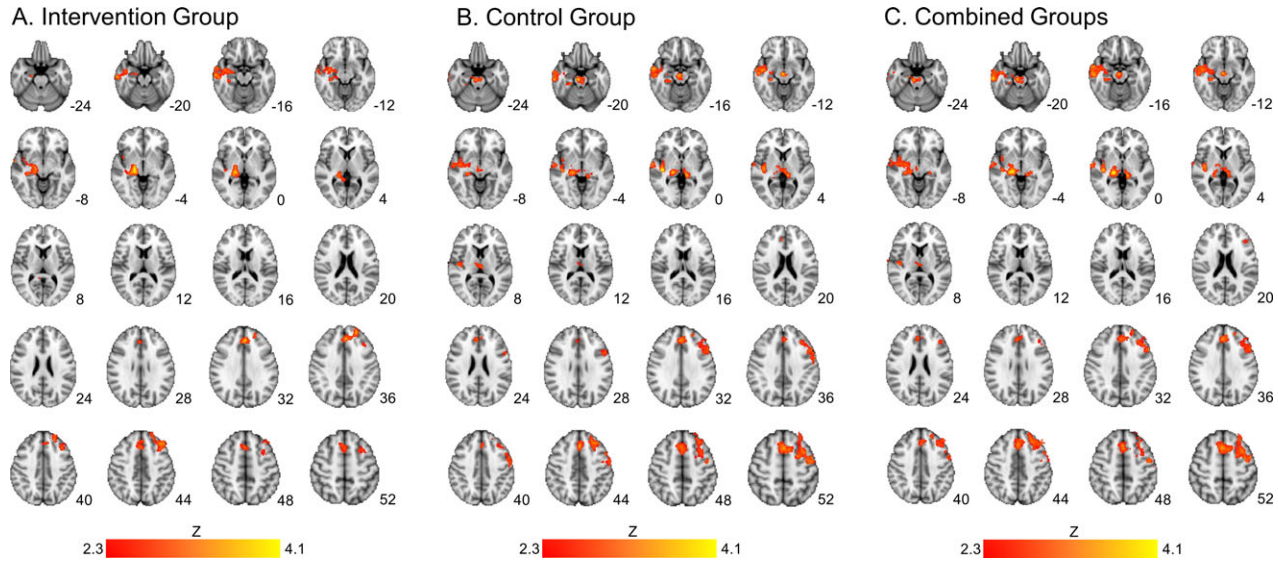

Fig. 2. Brain activation to alcohol taste compared to water taste cues. (**A**) The intervention group showed increased activation to alcohol taste cues in limbic and frontal regions. (**B**) The control group also displayed increased activation to alcohol taste cues in frontal, limbic, and insula regions. (**C**) Across groups, there was increased brain activation in frontal, limbic, and insula regions during alcohol taste cues compared to water taste cues. See Table 2 for full list of regions activated in this contrast. *Z*-statistic maps are whole-brain cluster corrected, $Z > 2.3$, $p = 0.05$. Coordinates are in MNI space. Brain is displayed in radiological convention (L = R).

Table 3. Whole-Brain Activation to Alcohol Taste Cues Negatively Correlated with PHDD Across Groups

Brain region	Cluster voxels	Max. *Z*	*x*	*y*	*z*
R/L Precuneus	2,281	3.85	14	−56	−26
L Posterior cingulate gyrus		3.05	−2	−48	8
L Medial frontal gyrus	1,417	3.87	−6	52	−2
R/L Anterior cingulate gyrus		3.15	0	42	0
R Superior frontal gyrus		3.03	10	52	22

L, left; R, right.

version (Filbey et al., 2008a) in order to increase the number of trials without substantially increasing scan duration. Additionally, the current version of the task used water as a control condition, while the original version (Filbey et al., 2008a) employed an appetitive control condition in the form of litchi juice. While the present version was recently validated in a separate sample (Cservenka et al., 2017), it may not have recruited the reward circuitry in response to alcohol cues as robustly as its previous iteration. Importantly, it should be noted that across both conditions, exposure to alcohol taste resulted in increased activation in frontal and limbic regions, compared to water taste, suggesting the task was fundamentally internally valid. Nevertheless, the magnitude of the activation may have been more limited due to the combination of the shortened trial duration and use of a nonappetitive control thus hindering efforts to detect intervention effects on neural processing of alcohol cues.

Considered together, both factors likely posed significant challenges to the primary aims of the study, which fundamentally represented an interaction effect between treatment type and cue type. Given this, large magnitude main effects for both experimental factors would be optimal to bring the interaction into sharpest relief. Thus, the relatively modest effect size of the intervention and the sufficient but potentially smaller effects in the neuroimaging paradigm constrained the experimental tests. Future studies using neuroimaging to understand brief interventions will require at least substantially larger sample sizes for a detectable clinical effect and potentially different neuroimaging paradigms.

Regarding the prediction of drinking outcomes, the most compelling finding in the present study is that activation to alcohol tastes in the precuneus and medial frontal gyrus was negatively associated with PHDD. The effect was such that individuals who had greater neural reactivity to alcohol taste in the precuneus and PFC had fewer PHDD in 4 weeks following the fMRI scan. Likewise, across groups, activation to alcohol tastes in the precuneus was negatively associated with average drinks per week. This pattern of results suggests that greater activation of the precuneus and frontal cortex during neural processing of alcohol taste cues, compared to control cues, predicts less drinking in the subsequent month.

This effect was found across conditions, control and experimental, and is generally consistent with previous work suggesting that the precuneus is sensitive to changes in cue reactivity and possibly to changes in addiction severity (Courtney et al., 2014). The precuneus has also been implicated in a meta-analytic review of functional neuroimaging studies of alcohol cue reactivity (Schacht et al., 2013a). Thus, the implication of precuneus activation as a predictor of subsequent drinking in the real world extends this line of

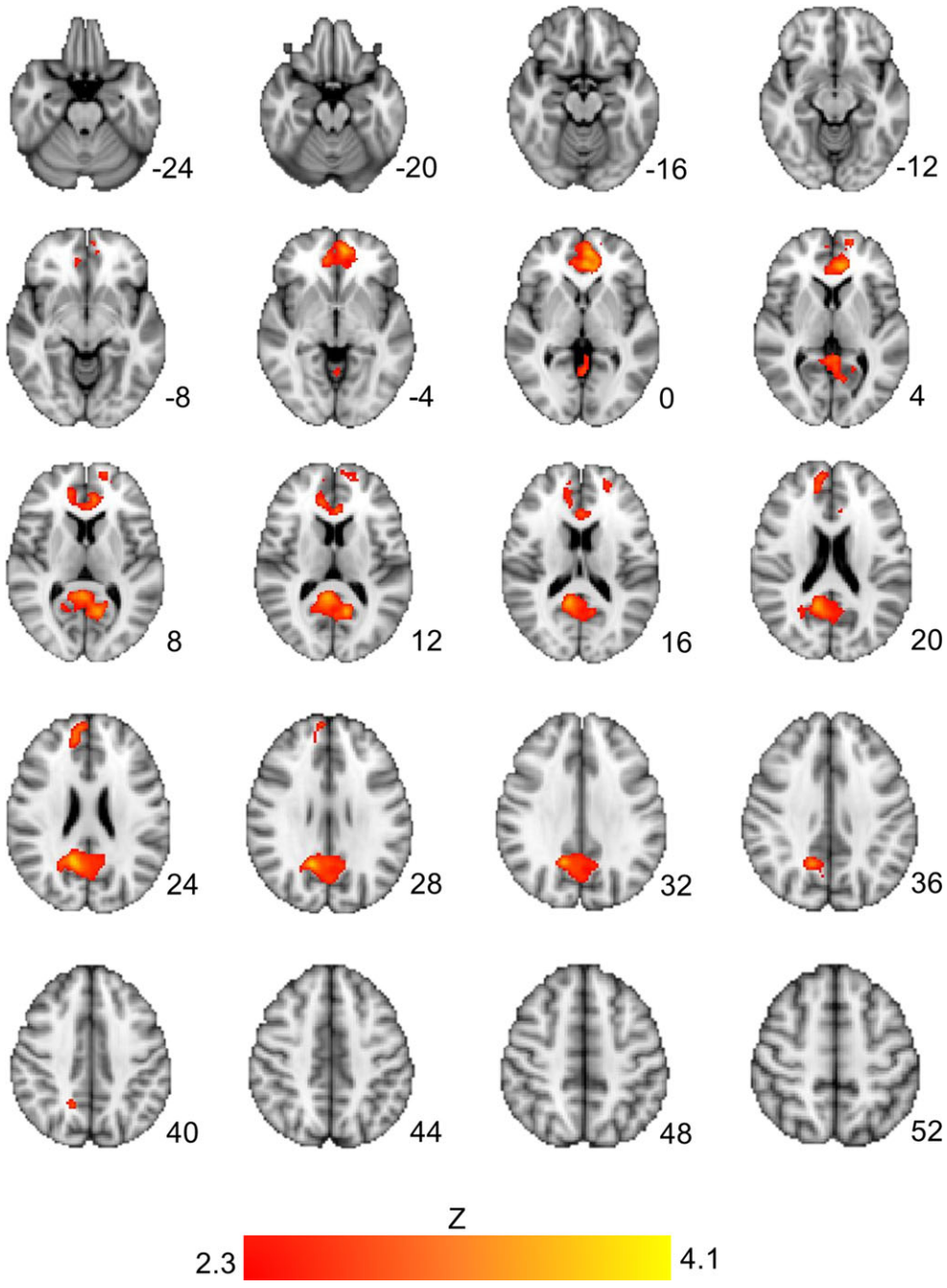

Fig. 3. Brain activation to alcohol taste cues in the precuneus and prefrontal cortex was significantly associated with decreased PHDD in the 4 weeks following the fMRI. *Z*-statistic maps are whole-brain cluster corrected, $Z > 2.3$, $p = 0.05$. Coordinates are in MNI space. Brain is displayed in radiological convention (L = R).

research and suggests that this region may serve as an intervention target, particularly with regard to the salience of alcohol cues. Although the vast majority of neuromodulation studies to address motivation in addiction have focused on the frontal lobes (Naish et al., 2018), and dorsolateral PFC in particular, recent investigations have shifted attention to the precuneus (Koch et al., 2018; Muller et al., 2018), with some success.

This prospect is particularly exciting in the context of psychological interventions. The precuneus has been functionally implicated in self-related cognition (Cabanis et al., 2013; Freton et al., 2014; Shad et al., 2012; Ye et al., 2018), which in many cases is essential for behavioral interventions to have an impact. For example, in the context of a brief intervention, a person must encode the factual information provided and square it with their own self-perceptions. Furthermore, in the current study's intervention, participants were specifically asked what they wanted to do next and this necessarily demands meaningful self-related cognitive processing to generate behavior

change. To illustrate this by contrast, we would have no expectation that a brief intervention would have a meaningful impact for a hypothetical individual who had no capacity to think abstractly about him or herself (in contrast to a pharmacological intervention). Thus, self-related cognition is a necessary (albeit not sufficient) elementary information processing capacity for this type of intervention to be useful and the current study suggests that the extent to which this was engaged (putatively reflected by precuneus activity) was associated with a more favorable outcome. Of course, this interpretation requires considerable caution because it is inherently conjecture and the precuneus has been implicated in a number of other cognitive functions. A recent review of psychosocial interventions for addiction medicine identified increased recruitment of self-referential processing regions, including the precuneus and mPFC, in response to targeted motivational interventions (Zilverstand et al., 2016). Additionally, in cannabis users, greater precuneus activation during an MI intervention was associated with a reduction in cannabis problems at follow-up (Feldstein Ewing et al., 2013); further indicating that activation of self-referential processing circuitry may be important for treatment response. Other psychological interventions, including cue-exposure extinction and episodic future thinking training, may be successful at increasing self-related cognition through precuneus activation. Precuneus activation has been demonstrated in cigarette smokers who were told to engage in self-focused coping during a cue-exposure task (Wilson et al., 2013), indicating the interventions targeting self-focused coping during exposure to drug cues may effectively activate this brain region. Exposure to episodic future thinking activates the precuneus and mPFC (Hu et al., 2016) and results in alcohol-dependent individuals increasing their valuation of future monetary rewards while lowering demand intensity for alcohol rewards (Snider et al., 2016). Frontoparietal circuitry, including the precuneus, is activated when participants make voluntary choices to cognitively reappraise craving responses or freely view craving cues (Cosme et al., 2018). Of note, the precuneus is not neuroanatomically uniform, with distinct functional subregions according to both the anterior–posterior and dorsal–ventral axes, and distinct patterns of functional connectivity by subregion (Zhang and Li, 2012). The current study reveals associations for the precuneus in general, but cannot speak to subregional activation.

In sum, the current study sought to examine whether a brief intervention would reduce both drinking and alcohol motivation as measured by neural reactivity to alcohol cues and neither hypothesis was supported. This conclusion, however, must be tempered by effect size considerations for both the intervention and the paradigm, as well as the apparently substantial reactivity effects present in the control condition. Each of these has important methodological implications for future studies of the neural mechanisms of alcohol-related behavior change. In addition, independent of intervention, exploratory analyses revealed differential neural reactivity that predicted more favorable outcomes, particularly in the precuneus, suggesting that it is a promising neural substrate warranting further study in this line of inquiry.

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CONFLICT OF INTEREST

None of the authors have any conflicts of interest or financial disclosures.

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SUPPORTING INFORMATION

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

Fig. S1. Brief intervention session checklist.

Fig. S2. Association between average drinks per week and neural alcohol taste reactivity.

Table S1. Whole-brain activation to alcohol taste cues negatively correlated with average drinks per week.