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Social multi-sensory alcohol cue reactivity and ad libitum social drinking: An fMRI study

Helle Larsen[a,1,*], Lauren Kuhns[a,1], Anne-Wil Kramer[a], Hilde M. Huizenga[a], Reinout W. Wiers[a], Kristen G. Anderson[c], Janna Cousijn[a,b]

[a] Department of Psychology, University of Amsterdam, Amsterdam, the Netherlands
[b] Neuroscience of Addiction (NofA) Lab, Department of Psychology, Education & Child Studies, Erasmus University Rotterdam, Rotterdam, the Netherlands
[c] Adolescent Health Research Program, Department of Psychology, Reed College, Portland, Oregon, USA

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ABSTRACT

Research demonstrates the effects of social context on individual drinking, but the underlying neural processes remain unclear. For this purpose, we developed a social multi-sensory alcohol cue-reactivity (SMAC) fMRI task. Neural activity during visually presented offers to drink beer or water while listening to audio fragments of social drinking contexts were compared in 38 social drinkers and associations with craving, drinking willingness, and ad libitum alcohol consumption in a social context were investigated. Procedures were repeated one week later assessing test-retest reliability. The SMAC increased craving in Sessions 1 and 2, with post-task craving predicting drinking willingness in Session 1. Post-task craving in Session 2 predicted the chance of ad libitum drinking. No other effects were significant. Alcohol-cue specific activity in a priori regions of interests (ROIs) did not correlate with alcohol use measures, however, lower ratings of willingness to accept soft drinks was associated with higher activity in response to alcohol cues in the insula (Session 1). Test-retest reliability of the task was poor. Whole-brain and ROI activity during beer *and* water conditions correlated consistently with multiple measures of alcohol use. One possible interpretation of these findings is that social context itself may act as a phasic alcohol-relevant cue regardless of whether a water or alcohol cue is displayed.

1. Introduction

Heavy alcohol consumption is an enormous problem among college students in many countries (>5 beverages on one occasion; [24,41]). Around 49% college students report one or more problems when having consumed alcohol, including engaging in activities that are later regretted, such as unprotected sex or activities that results in physical injury [1]. In young people, alcohol use typically takes place in social contexts and accumulating evidence implicates social processes as key risk factors in the development of alcohol use problems [13]. Therefore, it is crucial to take the social context into account when investigating risk and protective factors related to heavy alcohol consumption in youth.

Young people usually consume alcohol in social contexts among peers, and an abundant amount of research has demonstrated the effects of social context and peer drinking on individual drinking levels [28,30,36]. In line with this, social drinking motives and peer alcohol use are some of the strongest predictors of heavy use in adolescence [11,26,32]. For example, young adults consume more alcohol when in the presence of a heavy compared to light or non-drinking individual [30]. Furthermore, accumulating evidence suggests that social processes play an important role in the escalation of alcohol use and contribute to the development of alcohol use disorder in young people. Acute alcohol consumption has an observed effect on socio-emotional processes within groups of people, with enhanced positive effect at the individual and group level as well as elevated social bonding [39]. Additionally, drinking for social facilitation is prospectively associated with a higher likelihood of alcohol abuse and dependence in college students [9]. Individual differences in factors ranging from personality traits such as extraversion to genetic polymorphisms appear to increase the social rewarding effects of alcohol and are potential pathways to problematic drinking [14,18]. Despite this, little is known about the underlying neuromechanisms of social drinking behavior.

However, including social context in alcohol research can have high practical demands and is not always achievable. Audio simulations of social contexts are feasible alternatives to other laboratory-based techniques, which can still provide rich contextual information and im-

* Corresponding author at: University of Amsterdam, Developmental Psychology. Nieuwe Achtergracht 129B, 1018 WS Amsterdam. Room REC G 1.11, the Netherlands.
E-mail address: H.Larsen@uva.nl (H. Larsen).
[1] Shared first authorship

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prove the ecological validity. Anderson and colleagues [4] developed the Collegiate-Simulated Intoxication Digital Elicitation (C-SIDE), which consists of audio vignettes of social drinking contexts. Willingness to drink alcohol was assessed after each audio simulation and was concurrently associated with alcohol expectancies and drinking motives, and also predicted alcohol use and hazardous drinking over time [3]. This, and subsequent work [2,4,21,22,29] show the validity of audio simulations as a sound method to investigate risk (e.g., peer pressure, social context, impulsivity) and protective factors (e.g., availability of nonalcoholic beverages and food, monitoring, non-drinking peers, self-control) related to alcohol use (for smoking, see [31]). Thus far, audio simulations of social drinking contexts have been validated in behavioral research, but the underlying neurocognitive mechanisms remain unknown. Therefore, the goal of the current neuroimaging study was to investigate social drinking context-induced brain activity and the relation with ad libitum alcohol consumption.

The functional magnetic resonance imaging (fMRI) compatible audio simulation paradigm we have developed can be considered a social multi-sensory alcohol cue-reactivity (SMAC) paradigm that combines audio fragments with images displaying alcohol and non-alcohol social contexts. Theoretically, cue-reactivity paradigms aim to measure sensitized and conditioned behavioral and neural responses to alcohol-related stimuli that develop over the course of use towards dependence [37]. Previous research in heavy and dependent drinkers has demonstrated that alcohol cues are able to illicit craving [42], cognitive biases [19,47,50,51], and increased brain activity in reward-related mesocorticolimbic brain areas like the striatum, medial prefrontal cortex (mPFC), insula and anterior cingulate cortex (ACC; [27,54]). Importantly, cue-reactivity is considered to play a role in the continuation of heavy alcohol use and dependence [16,49]. For example, brain activity in response to alcohol cues compared to neutral cues in the bilateral caudate, ACC, and left insula were elevated in moderately drinking college students who later escalated to heavy drinking [15]. Furthermore, compared with other baseline risk factors such as impulsivity and family history of substance abuse, brain activity in these areas in response to alcohol versus control cues was the best predictor of increased drinking in the future in moderate drinkers [15]. These findings suggest that the relevance of cue-reactivity paradigms extends to moderate and heavy social drinkers and is not limited to clinical samples.

Given the added information that cue reactivity paradigms can potentially add to our understanding of the underlying processes in drinking patterns of social drinkers, it is critically important to have a clear methodological understanding of cue reactivity paradigms. A recent systematic review of neuroimaging studies of cue reactivity suggest that multi-sensory substance-stimuli elicit more robust brain activation in reward related areas compared to mono-sensory cues [53]. Moreover, because of the demonstrated role of social context in drinking [8,12], animal and human research suggesting that social contexts amplify the rewarding effects of alcohol [46,48], and the importance of social-based behavioral treatments of addiction [34], incorporating social contexts in cue reactivity paradigms may also lead to more robust reward-area activation, especially in non-clinical social drinkers. However, an often-overlooked gap is the reliability of cue reactivity over time. To our knowledge, few studies have employed multiple fMRI scans over time to assess the test-retest reliability of cue-reactivity. Schacht and colleagues [40] looked at the stability of cue-elicited activation in the ventral and dorsal striatum of ten alcohol dependent participants (not seeking treatment) across two fMRI scans. Cue activation in the right striatum was largely stable across two weeks. More recently, Bach and colleagues examined reliability in a larger sample of 144 alcohol dependent patients over two weeks and observed poor reliability (ICC < 0.40) in the alcohol versus neutral cue subtraction contrast of interest (2022). This is in line with findings from a meta-analysis of task-based fMRI which demonstrated poor reliability in a priori regions of interest across eleven common tasks [17]. Overall, further research establishing the reliability of alcohol cue reactivity, especially in non-alcohol dependent samples, is needed for a more complete understanding of the value of the measure for research into mechanisms of harmful alcohol use and the role of individual differences therein.

In sum, given the importance of cue-reactivity and social processes related to alcohol use, the suggested robustness of multi-sensory cue-reactivity paradigms, and the need to validate cue-reactivity paradigms on a neural and behavioral level, we developed and used a novel audio-visua cue reactivity task within social contexts to elicit cue reactivity in the scanner. To avoid problems with systematic biases related to retrospective self-reports, next to self-report assessments, alcohol consumption was also assessed in an ad libitum social drinking session, during which participants could choose to consume alcohol or not. As such, the aim of the present study was twofold: (1) validate the novel multi-sensory social cue reactivity task on a behavioral and neural level in 38 social drinkers, and (2) examine test-retest reliability of brain activity over the course of one week. To validate the task, we investigated the relationships between social drinking context-induced neural activity on the one hand and alcohol consumption in an ad libitum social drinking session and willingness to drink on the other hand. We hypothesized that the alcohol-specific activity (i.e. alcohol cue > neutral cue contrast) in the social cue reactivity task would activate mesocorticolimbic areas consistently implicated in alcohol cue-reactivity [54], namely the dorsal ACC (dACC), mPFC, insula, NAcc, putamen, and caudate. Moreover, we also expected activity in these Regions of Interest (ROIs) to positively correlate with willingness to drink, self-reported alcohol use and ad libitum alcohol consumption. All whole-brain analyses were examined on an exploratory basis. Regarding our second aim, we expected substantial test-retest reliability—based on Landis and Koch's benchmarks of intraclass correlation coefficients[31]—in each ROI.

2. Materials and methods

2.1. Participants

Forty participants were recruited from a previous alcohol study as well as through advertisements on social media. Participants were all of Dutch nationality. They were required to report liking beer to ensure the alcohol cues were relevant for all participants. Participants were required to report no other drug use in the past month to be eligible for enrollment. Other exclusion criteria included any current major psychopathology or learning disorders, left-handedness, and MRI contraindications. Participants were asked to refrain from consuming alcohol 24 h before each scan.

2.2. Materials

Alcohol use. Alcohol use history and severity was assessed with the 14-Day Timeline Followback (TLFB; [44]), and the Alcohol Use Disorders Identification Test (AUDIT) assessing alcohol use and problems in the past year [38].

Alcohol Craving was assessed with the Desires for Alcohol Questionnaire (DAQ; [33]) and state craving with a visual analogue scale ranging from 1–10.

Willingness to accept alcohol (AW)or non-alcohol beverage offers. After both MRI sessions, participants rated their willingness to accept an alcoholic or non-alcoholic drink for each scene (e.g. "Would you accept a beer in the festival context) from 1 (not at all willing) to 10 (very willing), assessing willingness to accept alcohol (AW alcohol; $\alpha = 0.81$ Session 1 and Session 2) or non-alcohol offers (AW control; $\alpha = 0.87$ Session 1 and $\alpha = 0.82$ Session 2). Mean AW was computed for alcohol and non-alcohol offers separately.

Ad libitum alcohol use. In a social drinking session, alcohol consumption was indicated if participants drank one or two alcoholic beverages versus non-alcoholic beverages. The full session procedure is described in the Procedure section below.

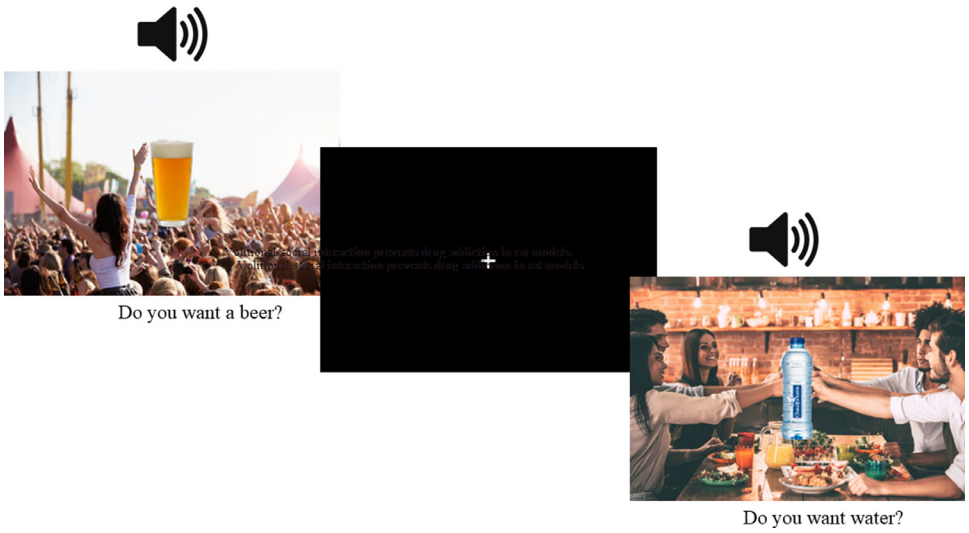

Fig. 1. Depiction of the SMAC task. During the cue reactivity task, participants saw beer or water stimuli overlaid on three social drinking situations while listening to corresponding audio fragments of each situation.

2.3. Procedure

The present study used a test-retest reliability protocol in which participants were scanned twice and completed various behavioral tasks and questionnaires. The Ethical Review Board of the University of Amsterdam, Faculty of Social and Behavioral Sciences approved the study (2017-DP-7697) according to the Declaration of Helsinki. All participants gave informed consent prior to participation.

The scanning sessions took place one week apart at the same time of day, always between 5:00 pm and 10:00 pm, coinciding with typical drinking hours. Both sessions lasted 2,5 h, including one hour of scanning and one hour of questionnaires. Participants were also exposed to a learning task in the scanner and completed questionnaires related to this task. These measures are not included in the current study. Informed consent and a fMRI screening questionnaire were presented prior to participation. Scanning immediately followed, and the participants were presented with the social multi-sensory alcohol cue-reactivity task (SMAC). Using a blocked design, participants listened to an audio fragment corresponding to each of three different situations; festival, dinner party, and birthday party. These fragments were adapted versions of the Dutch version of the Collegiate-Simulated Intoxication Digital Elicitation (C-SIDE), which are professionally scripted and recorded audio scenes of typical social drinking situations [3]. The scenes consisted of conversations and background sounds relevant to each social context (e.g., music, clinking glasses, etc.). We ensured that the volume of the headphones was consistent for every participant. During each scene, participants viewed an image of either an alcohol or non-alcohol drink, beer and water respectively, overlaid over an image of the social situation. Below the image, participants saw written offers of beer or water (Fig. 1). Participants were asked to imagine themselves in the simulation and consider the written offer on the screen. Each scene lasted two minutes and was repeated two times, once with alcohol and once with water (six total blocks). The condition of the first trial was randomized between participants and counterbalanced across sessions within participants. Between each block, there was a 16 second fixated inter-trial-interval. There were six possible orders for the blocks given the alternation of condition and a requirement that no two scenes were shown back to back (e.g., alcohol-birthday party followed by water-birthday party). Immediately before and after the end of the cue reactivity task, participants rated their current level of craving for alcohol on a visual analogue scale from 1 to 10. The task and craving questions were presented using E-Prime 2.0 software [5] (Psychology Software Tools, Pittsburgh, PA.) After the task, participants reported their willingness to accept alcohol and non-alcohol offers within the three contexts. Participants completed an online demographics questionnaire after the scan session. In Session 2, the scanning procedure was the same. After scanning, participants completed an online questionnaire containing the AUDIT and TLFB. Impulsivity-related measures were also assessed but not included in this study. *Ad libitum* drinking levels were then assessed in a social drinking setting.

2.3.1. Ad libitum drinking

Upon completion of scanning, questionnaires, and behavioral tasks in Session 2, participants engaged in an adapted social drinking session [30]. The goal of the social drinking session was to create a semi-naturalistic drinking environment and allow for ad libitum drinking behavior where participants could choose either soft drinks or alcoholic beverages. The experimenter informed participants that there was a brief unexpected break in the study due to logistical concerns (i.e. the testing room for the final task was being used for another experiment). During this break, the experimenter led the participant to a kitchen area with refreshments where they were to wait until the study could resume. In this area, a confederate—who was pretending to be another participant who was also waiting to finish the study—was already seated with a glass of (non-alcoholic) wine in order to set a norm that drinking during this period was acceptable. The experimenter offered the participant refreshments—wine, beer, soda, juice, or water—while waiting. The experimenter then poured the refreshments for the participant, informed the participant and confederate that they were welcome to help themselves to more beverages and food, and then left the area for thirty minutes. After approximately 15 min, the confederate finished their first alcoholic beverage, announced they would have one more wine, and asked whether the participant wanted something to drink. This ensured that it was clear to the participant that alcohol could be consumed without applying direct peer pressure. The confederate was instructed to act neutral, not too social but also not completely quiet. At the end of the second session, the participants were asked to comment on the perceived aims of the study in a questionnaire. Most participants indicated topics like 'learning and alcohol or substance use.' Importantly there were no comments about the confederate and therefore no indications that they were suspicious about the confederate in the social drinking session. This was crucial as we wanted to make sure that participants' actual drinking behavior was not influenced by their suspicion. After all sessions, participants were debriefed. We used a binary outcome measure indicating whether participants consumed one or two alcohol beverages (1) versus non-alcohol beverages (0).

2.4. Data analysis

2.4.1. Imaging parameters and pre-processing

Imaging was conducted using a Phillips 3T Achieva Scanner. During the SMAC task, the blood oxygen dependent (BOLD) signal was measured with a T2*gradient echo-planar imaging (EPI) sequence (TR 2 s, TE 27.63 ms, 37 slices, slice thickness 3 mm, interslice gap 0.3 mm, FOV 240 × 240, in-plane resolution 80 × 80, flip angle 76.1°). A high-resolution T1-weighted structural scan was acquired after the functional scan in Session 1 for anatomic referencing (T1 turbo field echo, TR 8.28 s, TE 3.8 ms, 220 slices, slice thickness 1 mm, FOV 240 × 220, in-plane resolution 240 × 240, flip angle 8°).

Data pre-processing and statistical analysis of fMRI data was conducted with FMRI Expert Analysis Tool (FEAT) version 5, part of FSL [43]. Non-brain and skull tissue were removed with the Brain Extraction Tool (BET). Imaging preprocessing consisted of slice-time alignment, non-linear motion correction, temporal high pass filter (sigma=148 s), spatial smoothing with a 5 mm full-with-half-maximum Gaussian kernel, and pre-whitening [52]. The functional data was registered to participants' structural T1 image and then transformed into MNI space (Montreal Neurological Institute) using FNIRT (FMRIB's Non-Linear Image Registration Tool). Data available on request from the authors.

2.4.2. Statistical analyses

2.4.2.1. Behavioral analyses. To validate the SMAC task on a behavioral level, we tested whether the SMAC task induced craving with a paired samples *t*-test on self-reported pre- and post-task craving ratings, separately for each session. Also, a paired samples *t*-test was conducted on the craving pre- and post-task difference scores for each session to test whether there was a significant difference in the effect of the task on craving scores across sessions. To investigate the relationship between task-induced craving and ad libitum drinking (only assessed in Session 2), we conducted a hierarchical logistic regression analysis of post-task craving in Session 2 (Step 2) on the chance of consuming alcohol in the ad libitum social drinking session, above and beyond the predictive value of pre-task craving and alcohol use patterns as measured by the AUDIT and TLFB (Step 1). Similarly, a hierarchical linear regression analysis was conducted with willingness to drink as dependent variable, pre-task craving, alcohol use patterns and willingness to accept soft drink in Step 1, and post-task craving added to Step 2. Regression analyses were conducted with bootstrapping of coefficients. Behavioral analysis were all conducted with IBM SPSS Statistics, version 25 [6] (IBM Corp., Armonk, N.Y., USA).

2.4.2.2. fMRI analyses. For subject-level analysis, preprocessed images were entered into a standard general linear model (GLM, ordinary least squares), which included separate regressors for condition (alcohol and water) and the fixated ITI. Each regressor was convolved with a double gamma hemodynamic response function. Temporal derivatives and filtering were added as regressors of no interest to improve model fit. The Alcohol>Water contrast was computed to investigate alcohol-specific activity.

2.4.2.3. ROI analyses. The cortical ROIs were created based on the results of Zeng et al.'s [54] meta-analysis of neural alcohol cue reactivity in alcohol use disorders. While many other areas were activated by alcohol cues in AUD (such as the DLPFC, visual areas, angular gyrus, superior frontal gyrus), we specifically included the ROIs in which cue-reactivity significantly differed between individuals with AUD and controls (dACC, mPFC) and areas know to play an important role in reward/salience processing (striatum) and interception/craving (insula). Using the MNI coordinates for the voxels with the highest activation for AUD patients compared to healthy controls across 17 studies, 10 mm diameter spherical masks were computed for the mPFC (MNI coordinates: 12, 62, 0) and dACC (0, 2, 34). Based on the meta-analytic results showing the greatest decrease in activity after treatment for AUD in the insula across studies, 10 mm spherical masks were created for the left (32, 22, 2) and right (-36, 16, 8) insula. To create binarized lateral masks for the NAcc, caudate, and putamen, a high-resolution probabilistic subcortical atlas was used with a threshold of 0.3 for voxel inclusion [35].

Mean activation in the ROIs was extracted for the alcohol > water contrast. We then conducted univariate correlational analyses to assess whether activity in these regions during the task was related to alcohol use and problems. We computed correlations between ROI activity and TLFB, AUDIT, DAQ, and craving. In addition, univariate binary logistic regressions were run to assess whether ROI activity predicted alcohol consumption during the social drinking session. Holm-Bonferroni corrections controlled the family-wise error rates for omnibus tests within sets of analyses; this is a stepwise rejection procedure used to retain power in detecting effects [25].

2.4.2.4. Exploratory whole-brain analyses. Exploratory whole-brain voxel-wise group analyses were conducted with FEAT FLAME stage 1+2 mixed effects analyses to test for a main effect of the Beer and Water conditions, as well as alcohol-specific activation with the alcohol > water contrast in both sessions separately. Additionally, whole-brain voxel-wise exploratory correlation analyses were run to test whether

Table 1
Correlations, means and standard deviations of measures of alcohol consumption, craving and willingness to consume beer and soft drinks at Session 1 and Session 2.

	M (SD)	1	2	3	4	5	6	7	8	9	10	11
1. AUDIT	8.61 (*4.18*)	-										
2. TLFB	20.21(*15.03*)	0.41**	-									
3. Ad lib S2	0.29 (*0.57*)	0.14	0.23	-								
4. DAQ	32.21 (*13.00*)	0.15	0.07	0.40*	-							
5. AW beer S1	7.74 (*1.87*)	0.31+	0.21	0.10	0.16	-						
6. AW beer S2	7.81 (*1.64*)	0.30	0.16	0.03	0.33*	0.83**	-					
7. AW soft S1	6.92 (*2.01*)	-0.31	-0.28	-0.04	0.13	0.03	0.08	-				
8. AW soft S2	6.71 (*1.82*)	-0.09	0.01	0.11	0.28	0.36*	0.43**	0.73**	-			
9. Pre-craving S1	4.95 (*2.04*)	0.30+	0.12	0.27	0.54**	0.51**	0.50**	-0.12	0.11	-		
10. Post-craving S1	5.37 (*2.07*)	0.22	0.25	0.35*	0.40*	0.64**	0.52**	-0.12	0.16	0.88**	-	
11. Pre-craving S2	4.68 (*2.27*)	0.19	0.14	0.45**	0.62**	0.31+	0.44**	-0.21	-0.00	0.62**	0.61**	-
12. Post-craving S2	5.24 (*2.20*)	0.32*	0.26	0.55**	0.61**	0.42**	0.49**	-0.16	0.06	0.69**	0.72**	0.85**

Note. $N = 38$. AUDIT = Alcohol Use Disorders Identification Test; TLFB = Timeline Follow Back Total sum score; Ad lib S2 = ad libitum amount of alcohol consumption Session 2; DAQ = Desires for Alcohol Questionnaire sum score; AW beer S1 = Willingness to consume beer Session 1; AW beer S2 = Willingness to consume beer Session 2; AW soft S1 = Willingness to consume soft drinks Session 1; AW soft S2 = Willingness to consume soft drinks Session 2. $^{***}p < .001$. $^{++}p = .068$.

* $p < .05$.

** $p < .01$.

$^{+}$ p=.058.

and where task-related activity was related to alcohol use and problems (separate analysis for TLFB, AUDIT, AW, ad libitum drinking in social drinking session). A cluster-wise multiple comparison correction was used for each whole-brain analysis, with a Z-threshold of 2.3 and a cluster-p significance threshold of 0.05.

2.4.4.5. Test-retest reliability in ROIs. To test the stability of the mean activation across the two test sessions, intraclass correlation coefficients were calculated for each ROI. The two-way mixed single measures coefficient—ICC (3,1)—has previously been established as an adequate test of reliability in functional neuroimaging [10,20]. The ICC (3,1) models Sessions 1 and 2 as fixed factors and the measurements as random factors to compute the test-retest reliability of the measurements across the time points. The reported *p*-values refer to significance against zero.

3. Results

Two participants were excluded from further analyses due to excessive movement, failure to follow instructions during the cue reactivity task and due to excessive alcohol use the day prior to the scan, resulting in 38 participants (22 women; *M*age=24.21; *SD* =2.64). Despite reporting no drug use during screening, two participants indicated having used laughing gas and ketamine, respectively, one time within the past 30 days. These participants were retained in the sample because they did not indicate repeated use. The average AUDIT score was 8.86 (*SD* = 4.18) indicating harmful alcohol use [38]. On average, participants reported consuming alcohol on 5.13 (*SD* = 3.49, range 0–14) days in the previous two weeks. While three participants reported no alcohol consumption in the past two-weeks, they were retained in the sample since they did report liking beer. All means and correlations are presented in Table 1.

3.1. Behavioral analyses

3.1.1. Cue-reactivity effects on self-reported craving

Paired sample t-tests demonstrated small but significant increases between pre- and post-craving at both Session 1 (pre: $M = 4.95$, $SD = 2.04$; post: $M = 5.37$, $SD = 2.07$), $t(37) = -2.59$, $p = .014$) and Session 2 (pre: $M = 4.68$, $SD = 2.27$, post: $M = 5.24$, $SD = 2.20$), $t(37) = -2.78$ $p = .008$). This effect did not differ between sessions $t(37) = -0.57$, $p = .576$.

3.1.2. Ad libitum drinking and willingness to accept beer

Paired sample *t*-test showed that participants were significantly more willing to accept beer than soft drink in Session 2 (beer: $M = 7.81$, $SD = 1.64$; soft drink: $M = 6.71$, $SD = 1.81$), $t(37) = 3.65$, $p < .001$. In Session 1, the direction of the mean difference was similar but not significant (beer: $M = 7.75$, $SD = 1.87$; soft drink: $M = 6.92$, $SD = 2.01$), $t(37) = 1.90$, $p = .066$). To examine whether self-reported craving after the SMAC task in Session 2 predicted ad libitum drinking, we conducted a logistic regression analyses. Four participants were excluded in this analysis because they did not complete the session ($N = 34$). Post-task craving at Session 2 significantly predicted the chance of drinking alcohol in the social drinking session above and beyond pre-task craving and alcohol use patterns (Table 2).

There was no difference between willingness to accept alcohol or to accept soft drink between Sessions 1 and 2. Hierarchical regression analyses demonstrated a significant association between post-task craving and willingness to drink beer above and beyond alcohol use patterns, pre-task craving and willingness to drink soft drink at Session 1; this was not true for Session 2 (see Table 2).

3.2. fMRI analyses

3.2.1. ROI analyses

In the first session, alcohol-specific activity (alcohol > water) in the left insula was negatively correlated with reported willingness to accept

Table 2
Hierarchical regression analyses predicting *ad lib* alcohol consumption and willingness to accept beer.

	Ad libitum alcohol consumption					Willingness to accept beer Session 1				Willingness to accept beer Session 2			
	B	*SE*	Wald	Exp(B)	95% CI (B)	B	*SE*	*β*	95% CI (B)	B	*SE*	*β*	95% CI (B)
Step 1													
AUDIT	0.02	2.27	0.04	1.02	-0.70–0.58	0.09	0.07	0.21	-0.03–0.24	0.12	0.08	0.30	-0.01–0.30
TLFB	0.03	1.21	0.68	1.03	-0.03–0.42	0.01	0.01	0.10	-0.02–0.04	0.01	0.02	0.08	-0.03–0.04
Pre-task craving	0.58	17.41	5.28	1.79*	0.11–6.94	0.38	0.14	0.46*	0.12–0.66	0.27	0.11	0.36*	0.07–0.48
Willingness soft drink	-	-	-	-	-	0.29	0.14	0.31*	-0.04–0.50	0.34	0.13	0.36*	0.03–0.54
Step 2													
Post-task craving	1.07	50.53	4.00	2.92*	-0.39–136.6	0.57	0.23	0.70*	0.10–1.01	0.23	0.18	0.31	-0.11–0.58
Nagelkerke $R^2 = 0.48$													
df = 1, $R^2 = 5.23$, $p = .02$													
Session 1: R^2*change* = 0.09, $p = .02$.													
R^2*total* = 0.50.													
Session 2: R^2*change* = 0.02, $p = .30$.													

Note. AUDIT = Alcohol Use Disorders Identification Test; TLFB = Timeline Follow Back Total sum score. For ad libitum alcohol outcomes pre-task and post-task craving of Session 2 was used (N = 34). For Willingness to accept beer outcome, the average across the two sessions was used (N = 38). 95% CI based on bootstrapping 400 replications for the logistic regression predicting ad libitum, and 1000 replication for hierarchical regressions predicting willingness to drink.

* $p < .05$.

Table 3
Session 1 - Correlations between alcohol measures and alc > water neural activity in ROIs.

ROI	AUDIT	TLFB S1	DAQ	AW beer S1	AW soft S1	Pre-craving S1	Post-craving S1
Left Caudate	-0.075	0.089	-0.054	0.069	-0.083	-0.165	-0.107
Right Caudate	-0.282	-0.086	0.027	0.079	0.134	-0.16	-0.086
dACC	-0.101	-0.181	0.066	0.114	-0.202	-0.209	-0.191
Left Insula	-0.011	0.056	-0.085	-0.117	-0.49*	-0.048	0.02
Right Insula	-0.061	0.07	-0.067	0.021	-0.192	-0.203	-0.161
mPFC	-0.175	0.032	0.073	0.081	-0.301	0.174	0.33
Left NAcc	0.047	0.07	-0.107	0.036	-0.368	0.104	0.094
Right NAcc	-0.245	-0.14	-0.153	-0.059	-0.208	-0.118	-0.085
Left Putamen	-0.089	-0.044	0.077	0.108	-0.194	-0.191	-0.144
Right Putamen	-0.108	-0.043	0.05	0.157	-0.2	-0.03	0.029

Note. *N*=38. AUDIT = Alcohol Use Disorders Identification Test; TLFB = Timeline Follow Back Total sum score; Ad lib = ad libitum amount of drinks; DAQ = Desires for Alcohol Questionnaire sum score; AW beer S1 = Willingness to consume beer session 1; AW beer S2 = Willingness to consume beer session 2; AW soft S1=Willingness to consume soft drinks Session 1; AW soft S2 = Willingness to consume soft drinks Session 2. Pearson's r and spearman's rho reported based on results of Shapiro-Wilk's test for normality.
* Significant after Holm-Bonferroni correction for multiple comparison.

Table 4
Session 2 - Correlations between alcohol measures and alc > water neural activity in ROIs.

	AUDIT	TLFB S2	DAQ	AW beer S2	AW soft S2	Pre-craving S2	Post-craving S2
Left Caudate	-0.24	0.087	-0.007	-0.092	-0.107	0.073	0.084
Right Caudate	0.013	0.228	0.137	-0.027	-0.118	0.209	0.288
dACC	-0.232	0.038	0.183	-0.109	-0.156	0.034	-0.001
Left Insula	-0.25	0.124	0.05	-0.154	-0.314	-0.083	-0.116
Right Insula	-0.025	0.132	0.212	0.154	-0.182	0.242	0.144
mPFC	0.118	0.396	0.065	-0.042	0.048	-0.015	0.128
Left NAcc	0.008	0.17	-0.055	0.006	-0.149	0.005	0.005
Right NAcc	-0.049	0.211	0.046	-0.172	-0.114	0.004	0.103
Left Putamen	0.017	0.045	0.254	0.147	-0.112	0.17	0.208
Right Putamen	-0.143	-0.022	0.05	-0.03	-0.229	0.044	-0.082

Note. *N*=38. AUDIT = Alcohol Use Disorders Identification Test; TLFB = Timeline Follow Back Total sum score; Ad lib = ad libitum amount of drinks; DAQ = Desires for Alcohol Questionnaire sum score; AW beer S1 = Willingness to consume beer session 1; AW beer S2 = Willingness to consume beer session 2; AW soft S1 = Willingness to consume soft drinks Session 1; AW soft S2 = Willingness to consume soft drinks Session 2. Pearson's r and spearman's rho reported based on results of Shapiro-Wilk's test for normality.

soft drinks during the task. In other words, lower ratings of willingness to accept soft drinks was associated with higher activity in response to alcohol cues in the insula. No alcohol-specific ROI activity was significantly correlated with alcohol measures in session 2.

Univariate binary logistic regressions ($N = 34$) were conducted to assess whether alcohol specific cue reactivity in the ROIs in either session predicted drinking behavior during the social drinking session. Neural alcohol specific cue reactivity in the dACC, mPFC, insula, NAcc, caudate, and putamen did not significantly predict ad libitum drinking (Tables 3 and 4).

3.2.2. *Exploratory whole-brain analyses*

No significant clusters of activation were observed for the alcohol > water contrast in either session. Furthermore, follow-up whole brain correlation analyses were conducted to investigate the association between neural activity, alcohol use, and associated problems. No clusters of activity correlated with alcohol use measures for the alcohol > water contrast in Session 1. However, in Session 2, clusters of activation in the frontal, occipital, and temporal cortex for the alcohol > water contrast correlated with total drinks in the previous week (TLFB total drinks) and drinking in the social drinking session (Fig. 2a).

Whole-brain exploratory analyses of the alcohol and water condition main effects were also conducted to further understand the effect of the task. The alcohol and water conditions activated regions overlapping the visual and auditory cortex in both sessions, as well as the amygdala, thalamus, and cortical regions in the frontal, temporal, and occipital lobes including portions of the prefrontal cortex. For an overview of all cluster activations, see Tables 5 and 6. These findings suggest that the alcohol and water condition activate similar regions across the brain, including regions previously associated with craving such as the insula and putamen (a substrate of the dorsal striatum).

Follow-up whole-brain correlation analyses revealed that in both the alcohol and water conditions, neural activity in overlapping clusters encompassing diffuse cortical and subcortical regions correlated with multiple alcohol measures including AUDIT score, willingness to accept beer, total drinks in the previous week, task-induced alcohol craving, and drinking in the social drinking session in Session 1 (Fig. 2b). In Session 2, no voxel clusters in the alcohol or water conditions significantly correlated with alcohol measures.

3.2.3. *Test-retest reliability in ROIs*

All three ROIs exhibited poor test-retest reliability across sessions for alcohol specific activity (alcohol > water contrast). The intraclass correlation coefficient was 0.262 CI [-0.005, 0.495] for the mPFC, 0.058 CI [-0.213, 0.320] for the dACC, 0.189. CI [.064, 0.345] for the insula, 0.232 CI [.102, 0.389] for the putamen, 0.340 CI [.203, 0.495] for the caudate, and 0.154 CI [.154, 0.308] for the NAcc. Mean alcohol-specific activity did not differ across sessions in any ROI (Table 7), indicating that activity was not significantly higher or lower in session 2 across participants.

4. Discussion

Using the SMAC task, a social multi-sensory alcohol cue-reactivity paradigm, this study assessed task validity and test-retest reliability. We examined relationships between self-reported post-task craving, will-

Table 5
Brain regions activated in the alcohol condition in Session 1 and Session 2: main effect of alcohol.

Cluster size (voxels)	*Brain region*	*Hemisphere*	*MNI Coordinates* *x*	*y*	*z*	*Zmax*
Session 1						
45,578	Superior Temporal Gyrus (auditory Cortex), Lateral Occipital Cortex (visual Cortex), Middle Temporal Gyrus, Lingual Gyrus, Amygdala, Thalamus	L/R	56	-8	-8	7.91
1287	Frontal Pole	L/R	-10	62	34	5.03
594	Middle Frontal Gyrus	L/R	-40	6	58	5.15
579	Precuneus	L/R	8	-48	46	4.74
122	Frontal Pole	L/R	2	64	-8	5.3
Session 2						
30,081	Planum Temporale, Superior Temporal Gyrus (auditory cortex), Middle Temporal Gyrus, Middle Frontal Gyrus, Temporal Pole, Occipital Fusiform Gyrus, Amygdala (L), Thalamus (L),	L/R	64	-22	10	7.74
946	Inferior Frontal Gyrus	L/R	-48	14	26	5.31
119	Middle Frontal Gyrus	R	46	10	50	4.22
115	Temporal Fusiform Cortex	L/R	40	-12	-26	4.17

Note. N=38. L= left, R= right.

Table 6
Brain regions activated in the water condition in Session 1 and Session 2: Main effect of water.

Cluster size (voxels)	*Brain region*	*Hemisphere*	*MNI Coordinates* *x*	*y*	*z*	*Zmax*
Session 1						
45,607	Superior Temporal Gyrus (auditory cortex), Lateral Occipital Cortex (visual cortex), Middle Temporal Gyrus, Lingual Gyrus, Amygdala, Thalamus	L/R	56	-8	-8	7.89
1005	Superor Frontal Gyrus, Frontal Pole	L/R	2	54	38	4.84
635	Precuneus	L/R	6	-50	46	5
220	Supplementary Motor Cortex, Superior Frontal Gyrus	L/R	8	4	68	4.65
128	Frontal Pole	L/R	-2	-64	8	5.02
Session 2						
10,158	Planum Temporale, Superior Temporal Gyrus (auditory cortex), Frontal Pole	L/R	64	-22	8	7.76
8764	Occipital Pole, Intracalcerine Cortex, Lingual Gyrus	L/R	14	-92	6	7.07
8596	Superior Temporal Gyrus, Middle Temporal Gyrus,	L/R	-60	-32	6	7.67
953	Thalamus	L/R	14	-30	-4	5.98
899	Inferior Frontal Gyrus, pars opercularis	L/R	-48	14	26	5.4

Note. N=38. L= left, R= right.

Table 7
Mean ROI activity per session.

ROI	S1 Mean	S2 Mean	t	p
Left Caudate	0.70 (SD = 8.121)	1.05 (SD = 10.584)	-0.166	0.869
Right Caudate	0.001 (SD = 7.7)	-1.05 (SD = 10.982)	0.506	0.616
dACC	-1.27 (SD = 13.668)	3.54 (SD = 15.964)	-1.452	0.155
Left Insula	0.31 (SD = 11.037)	2.83 (SD = 12.738)	-0.978	0.335
Right Insula	-0.38 (SD = 10.74)	1.43 (SD = 11.967)	-0.677	0.502
mPFC	0.01 (SD = 10.194)	-0.35 (SD = 11.895)	0.16	0.874
Left NAcc	1.25 (SD = 12.63)	2.20 (SD = 12.952)	-0.321	0.75
Right NAcc	-1.55 (SD = 13.157)	-0.35 (SD = 11.53)	-0.403	0.69
Left Putamen	-0.65 (SD = 8.278)	-0.003 (SD = 7.403)	-0.366	0.717
Right Putamen	-0.40 (SD = 7.8)	0.98 (SD = 7.012)	-0.775	0.443

ingness to drink, alcohol consumption in an ad libitum social drinking session and brain activity. Behavioral results showed that higher self-reported post-task craving in Session 2 was related to the increased odds of drinking alcohol in the social drinking session. This indicated that the multisensory cue-reactivity task worked (generally) as expected at the behavioral level. Listening to the audio simulations of social contexts whilst watching both alcohol and non-alcohol images seemed to elicit cue-reactivity effects on a behavioral level, as alcohol craving increased after the task. In line with this, we found an association between post-task craving and willingness to drink in Session 1, but note that this was not found in Session 2. On a neural level, results showed that willingness to accept non-alcoholic drinks was negatively correlated with left insula activity to alcohol cues specifically (alcohol > water) in the task in Session 1. However, self-reported alcohol use, craving, willingness to accept beer or water, and pre- and post-task craving did not significantly correlate with alcohol specific activity (alcohol > water contrast) in any other ROIs. Finally, all ROIs exhibited poor test-retest reliability across sessions for alcohol specific activity (alcohol > water contrast).

Exploratory findings showed that both the alcohol and water conditions induced activity across diffuse areas of the brain, including sensory processing-, frontal cortical-, and subcortical- regions. Clusters of activity during both conditions were consistently correlated with alcohol-related measures in areas such as the putamen, insula, and auditory and visual sensory processing regions. Task-induced craving and self-reported willingness to drink during the task were both positively correlated with activity in sensory processing regions, frontal cortical regions, and regions involved in reward processing (Fig. 2b). Furthermore, alcohol-specific activity (alcohol > water) correlations with drinking (both in previous, and in the current, sessions) emerged in Session 2 (Fig. 2a). These results provided initial evidence that the task induced alcohol-related activations. However, the similarity of the main effects and alcohol-related correlations across conditions suggested that the au-

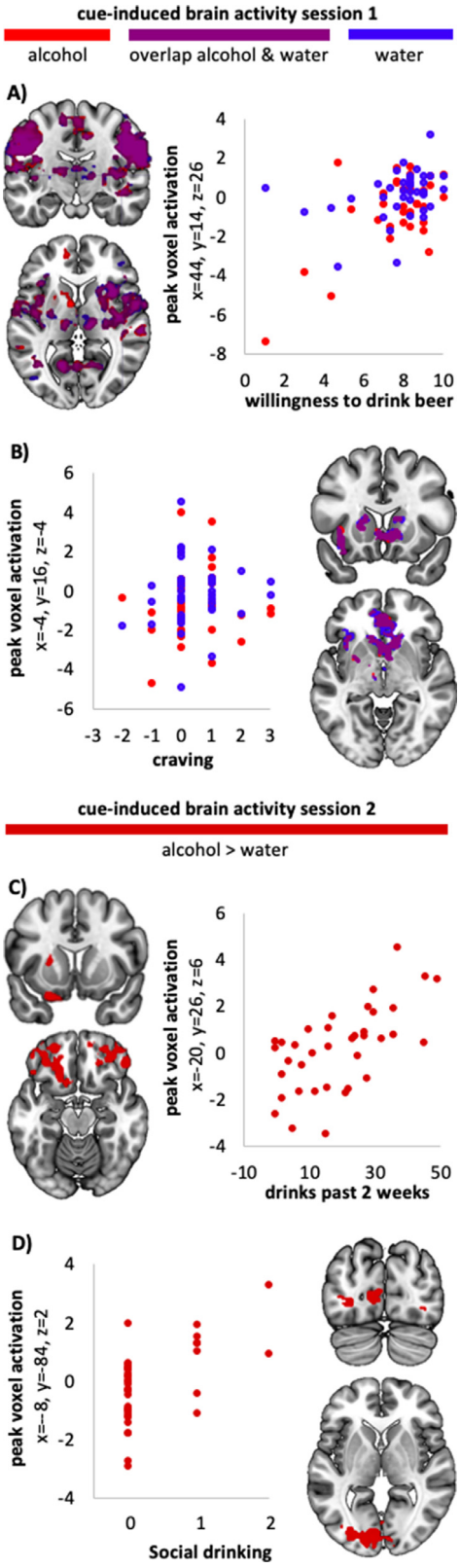

Fig. 2. **a**: The activation of brain regions in the water and alcohol condition, measured in Session 1, in relation to the willingness to drink beer (AW). B: Activation of brain regions in the water and alcohol condition, measured in Session 1, in relation to craving for alcohol.
2b C: The alcohol specific activation of brain regions, measured in Session 2, in relation to the total drinks in the previous week (TLFB). D: Alcohol specific activation of brain regions, measured in Session 2, in relation to drinking in the social drinking session.

ditory stimuli—identical across conditions—may be driving these activations, as opposed to the visual cues and written offers. Mean session activations in the ROIs did not significantly differ between sessions. This indicates that cue habituation did not have an effect on brain activation in these regions during the task. The audiovisua cue-reactivity paradigm did appear valid (given that it induces craving and brain activity in expected regions), however, the test-retest reliability was poor. Given the poor reliability and the use of a liberal cluster threshold (Z = 2.3), these findings should be interpreted cautiously and replication is required to draw firm conclusions.

Based on the results, a new hypothesis is that the mere presence of the social context may contribute to the sensitized reaction to alcohol, regardless of whether an alcohol or neutral cue is visually displayed and offered. This hypothesis is of theoretical interest and can be examined more extensively in further research by exploring the neural activity to alcohol cues with and without social audio simulations to specifically clarify the role of the audio social context. Additionally, comparisons of social alcohol cue reactivity with the SMAC task in social versus solitary drinkers could further elucidate the importance of social contexts in the neuromechanisms of drinking behavior. Prospective designs that follow young people over time are also essential for examining the predictive value of social alcohol cue reactivity in trajectories of alcohol use. Furthermore, comparisons of social alcohol cue reactivity in adolescents versus adults are also necessary as the role of social context may differ in older drinkers as compared to youth. Moreover, an alternative explanation for the similar cross-condition results is that the visual stimuli of drinking water or alcohol were not a sufficiently valid operationalization of actual drinking. Further research can be improved by using a more valid method for alcohol and non-alcohol beverage conditions, for example, by combining visual images with odors of beer/alcohol. The combination of different senses would make the cueing more realistic. The use of odors alone or in combination with visual stimuli has been proven to be a valid operationalization [23,45].

The current study is one of the few studies that investigated test-retest reliability of alcohol cue reactivity. The findings demonstrated low test-retest reliability. This is in contrast to Schacht and colleagues previous study in which alcohol cue-induced striatal activity was stable across multiple scans in heavy and dependent drinkers [40]. The use of a less severe and more heterogeneous sample of drinkers may have contributed to the lower reliability of alcohol-elicited activity. However, it is in line with the results of a more recent, larger study of alcohol cue reactivity in alcohol-dependent patients [7] and a meta-analysis of task-based fMRI generally [17]. An important note to make is that we examined this with a novel cue reactivity paradigm in which social context was included. It is possible that the inclusion of the social context inhibited the ability to show the stability of cue reactivity tasks in general. We conducted assessments at the same day and time of the week to avoid confounding effects, but it may be that reactivity differs dependent on mood and schedule of the day. Importantly, the poor reliability of the alcohol cue reactivity signal in the regions of interest does require

4.1. Strength and limitations of the study

The strengths of the current study include first steps to develop a multisensory cue-exposure paradigm, inclusion of an ecologically valid social ad libitum drinking paradigm, and the assessment of test-retest reliability. We included social contexts both in the cue-exposure paradigm and in the drinking paradigm. However, the limitations need to be considered. Firstly, we tested a sample of social drinkers possibly limiting the generalizability. Moreover, the relation between alcohol use-related problems (AUDIT) and brain activity suggested that effects will be stronger, and probably more alcohol-specific, in heavier users. However, this remains to be tested in heavy users *compared* to light users. Besides this, at a behavioral level, we cannot distinguish between effects of alcohol versus non-alcohol images. Therefore, the results between the conditions needs to be interpreted with caution. Furthermore, the SMAC

task currently uses relatively long blocks (two minutes) which can result in habituation effects which reduce signal to noise ratio. For the current study, block length was determined by the length of the previously validated social drinking audio scenes. Future research should aim to validate shorter audio scenes to optimize the block length for fMRI research.

4.2. Conclusion and implication

The current study adds to the validity of using audio simulations of social drinking contexts to elicit motivations to use alcohol. In contrast to our expectations, the presentation of an offer of alcohol versus water while listening to audio fragments of social contexts did not differentially activate brain areas implicated in alcohol use and addiction in social drinkers. However, exploratory analysis showed that the social context elicited brain activity in areas implicated in alcohol use and addiction, regardless of the offer to drink alcohol or water, and this consistently correlated with a range of alcohol measures. This adds to the strength of the audio simulations in inducing willingness to drink. The test-retest reliability was poor, which should be taken into consideration in future use. Nevertheless, the task holds promise for investigating the role of social context in the neural underpinnings of alcohol use behavior. Given the association between alcohol use measures and brain activity during exposure to social contexts regardless of drink type, it appears that drinking-relevant social contexts may act as phasic alcohol-relevant cues.

Author contributions

HL, LK, JC, AK, HH contributed to the design of the study. LK and AK collected the data. LK, HL, and JC performed data analyses. HL and LK wrote the first draft of the manuscript. JC, KA, RW, AK and HH edited the manuscript. All authors contributed to and approved of the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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