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Alcohol conditioned contexts enhance positive subjective alcohol effects and consumption

Joseph A. Lutz [a], Emma Childs [a,b,*]

[a] University of Illinois at Chicago, Department of Psychiatry, 1601 W Taylor St MC912, Chicago, IL, 60612, USA
[b] University of Chicago, Department of Psychiatry and Behavioral Neuroscience, 5841 S. Maryland Avenue, Chicago, IL, 60637, USA

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ABSTRACT

Associations between alcohol and the places it is consumed are important at all stages of alcohol abuse and addiction. However, it is not clear how the associations are formed in humans or how they influence drinking, and there are few effective strategies to prevent their pathological effects on alcohol use. We used a human laboratory model to study the effects of alcohol environments on alcohol consumption. Healthy regular binge drinkers completed conditioned place preference (CPP) with 0 vs. 80 mg/100 mL alcohol (Paired Group). Control participants (Unpaired Group) completed sessions without explicit alcohol-room pairings. After conditioning, participants completed alcohol self-administration in either the alcohol- or no alcohol-paired room. Paired group participants reported greater subjective stimulation and euphoria, and consumed more alcohol in the alcohol-paired room in comparison to the no alcohol-paired room, and controls tested in either room. Moreover, the strength of conditioning significantly predicted drinking; participants who exhibited the strongest CPP consumed the most alcohol in the alcohol-paired room. This is the first empirical evidence that laboratory-conditioned alcohol environments directly influence drinking. The results also confirm the viability of the model to examine the mechanisms by which alcohol environments stimulate drinking and to test strategies to counteract their influence on behavior.

1. Introduction

Learned associations between alcohol and the people, places and paraphernalia (cues) surrounding drinking experiences are considered important in the initiation, maintenance, and escalation of drug and alcohol abuse (Anton, 1999; Drummond, 2000; Everitt and Robbins, 2005; Glautier and Drummond, 1994; Monti et al., 2000; Robinson and Berridge, 1993; Tiffany and Conklin, 2000; Volkow et al., 2010). These associations are incredibly durable and cause relapse to drinking even after long periods of abstinence (Ludwig, 1986; Sinha and Li, 2007; Tiffany, 1990). Thus, learned alcohol associations are a major barrier to the effective long-term treatment of alcohol use disorder (AUD). However, despite their importance in addiction, there is limited clinical empirical evidence of how the associations are formed or how they are able to influence behavior including drug taking. A better understanding of these processes may lead to more effective strategies to prevent their detrimental effects on the progression of AUD and on relapse to drinking. In this study, we tested the feasibility of using a human laboratory model of alcohol conditioning to examine the influence of alcohol-paired environments on alcohol self-administration.

Numerous preclinical studies have investigated how discrete cues e.g., lights, tones, paired with drug and alcohol influence drug seeking or taking (reviewed by See, 2002; Valyear et al., 2017; Weiss, 2010; Weiss et al., 2001). In recent years, researchers have become increasingly interested in the effects of drug-paired environments on behavior, including drug taking (for reviews see LeCocq et al., 2020; Martin-Fardon and Weiss, 2013; Valyear et al., 2017). These studies have shown that environments paired with alcohol function as excitatory stimuli eliciting approach behavior (Bechtholt and Cunningham, 2005; Nentwig et al., 2017; Pina and Cunningham, 2016; Risinger et al., 1994), can renew extinguished drug seeking (Bouton and King, 1983; Crombag and Shaham, 2002), elicit cue-induced (Chaudhri et al., 2008a, 2008b, 2009) and drug-primed (Tsiang and Janak, 2006) reinstatement, and enhance responding to a discrete alcohol cue (Remedios et al., 2014;

Abbreviations: CPP, conditioned place preference; ALC, 80mg alcohol/100 mL blood; No ALC, 0mg alcohol/100 mL blood; BrAC, breath alcohol concentration; HR, heart rate; BP, blood pressure.

* Corresponding author at:University of Illinois at Chicago, Department of Psychiatry, 1601 W Taylor St MC912, Chicago, IL, 60612, USA.
E-mail address: echilds@uic.edu (E. Childs).

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Sciascia et al., 2015). It is important to translate these findings to humans to improve our understanding of the psychobiological bases of alcohol conditioned environmental associations (Valyear et al., 2017) and also to improve the predictive validity of preclinical models to develop clinically effective treatments that dampen the effects of environmental alcohol cues on drinking.

Most clinical studies of cue or context associations have focused on the influences of already established alcohol cue associations formed outside the laboratory. Together these studies have shown that generic alcohol-associated stimuli i.e., pictorial, actual, or environmental cues or a combination of these, increase responding for alcohol or actual consumption (Engels et al., 2009; Field and Jones, 2017; Jones et al., 2013; Koordeman et al., 2011; Ludwig et al., 1974; Van Dyke and Fillmore, 2015). However, the mechanisms by which the cues increase consumption are not clear. For example, studies that demonstrate cue-induced alcohol seeking or taking have reported mixed findings upon craving which is widely believed to mediate cue-induced drinking (Field and Jones, 2017; Jones et al., 2013; Mackillop and Lisman, 2007; Van Dyke and Fillmore, 2015; Willner et al., 1998). A potential reason for the discrepancy in findings is that the cues used in these studies are generic and the conditioning history of individual subjects is unclear. For example, images of personalized smoking environments evoke stronger reactivity than generic images (Conklin et al., 2010). Human laboratory conditioning paradigms offer the opportunity to better understand how conditioned associations are formed and how they are able to influence behavior because exposure to drug and cues are carefully controlled allowing a full interpretation of findings.

Clinical de novo conditioning studies with alcohol have employed distinctive flavors, colors, abstract shapes, and pictorial stimuli paired with administration of alcohol or placebo (Field and Duka, 2002; Glautier et al., 2001; Kareken et al., 2012; Mayo and de Wit, 2016; Oberlin et al., 2018). These studies have demonstrated the ability of controlled laboratory paradigms to produce conditioned alcohol associations with previously neutral stimuli and that the cues acquire the ability to elicit conditioned responses including subjective craving (Field and Duka, 2002), attention biases (Mayo and de Wit, 2016), increased skin conductance (Field and Duka, 2002) and neural activity (Kareken et al., 2012; Oberlin et al., 2018). To the best of our knowledge, no studies have examined how the laboratory-paired alcohol cues or environments influence drug seeking or taking.

In recent years, we have translated the preclinical conditioned place preference (CPP) procedure to humans to study the processes of drug conditioning and its influences on behavior. In the model, two distinct environments are paired with drug and placebo administration. After several conditioning sessions, subjects are given the opportunity to explore the two environments freely. Drugs that are known to produce pleasurable effects in humans produce a conditioned place preference (CPP) in rodents; that is they induce approach toward and increase the time spent in the room paired with the rewarding drug. Similarly, in our clinical studies we have shown that people will approach and spend more time in a room paired with alcohol (Childs and de Wit, 2016), and that they exhibit a subjective preference and increased liking of a room paired with D-amphetamine (Childs and de Wit, 2009, 2013). Our studies have also shown that drug subjective effects experienced during conditioning sessions predicted the strength of conditioning (Childs and de Wit, 2009, 2013, 2016). Finally, we found that contextual conditioning altered the subjective effects of D-amphetamine; it increased stimulant-like effects and drug craving (Childs and de Wit, 2013). Together, the findings mirror those of preclinical and clinical conditioning studies (Blaser et al., 2010; Cunningham and Noble, 1992; Hinson and Poulos, 1981; Le et al., 1979; McCusker and Brown, 1990; Ostlund and Balleine, 2008; Post et al., 1981; Schiltz et al., 2005; Tiffany et al., 1987; Tzschentke, 2007; Vezina and Stewart, 1984; White et al., 2002). Thus, the human CPP model may be an ideal procedure to investigate the mechanisms by which alcohol conditioned associations influence alcohol consumption.

In this study, we aimed to test the feasibility of using the human CPP procedure to study how alcohol conditioned environments influence alcohol drinking. We trained human participants in an alcohol CPP paradigm with double blind administration of 0 mg alcohol/100 mL blood (0 mg/dL, No ALC) vs. 80 mg alcohol/100 mL blood (80 mg/dL, ALC). After training, participants completed an alcohol self-administration session in either the ALC- or No ALC-paired rooms. We hypothesized, based on previous preclinical (Remedios et al., 2014; Sciascia et al., 2015) and clinical studies (Engels et al., 2009; Field and Jones, 2017; Jones et al., 2013; Koordeman et al., 2011; Ludwig et al., 1974; Mackillop and Lisman, 2007; Van Dyke and Fillmore, 2015; Willner et al., 1998), that participants with CPP training tested in the ALC-paired room would consume significantly more drinks than those tested in the No ALC-paired room and also control participants (without CPP training) tested in either room. We also hypothesized that the strength of conditioning would be positively related to the number of drinks consumed by participants in the ALC-paired room i.e. participants who exhibited the strongest conditioning (CPP) would also consume the most drinks in the ALC-paired room. Finally, based on our prior findings (Childs and de Wit, 2013), we hypothesized that participants with CPP training tested in the ALC-paired room would report significantly greater positive alcohol effects (i.e., stimulant-like effects) and less negative effects (i.e., sedative effects) than those tested in the No ALC room and control participants.

2. Methods

2.1. Study design

The overall design is shown in Fig. 1. Participants were assigned randomly (stratified by sex) to three groups; Paired Group 1 $N = 37$, Paired Group 2 $N = 34$, Unpaired Group $N = 27$. The study comprised 3 phases; pre-conditioning, conditioning, post-conditioning. During pre-conditioning, participants completed a Room Exploration Test (see below) to assess initial room preferences. During conditioning, participants completed 6 experimental sessions with consumption of 80 mg/dL alcohol (ALC x3) or 0 mg/dL alcohol (No ALC x3) under double-blind conditions. Experimental sessions lasted 4 h and were conducted after

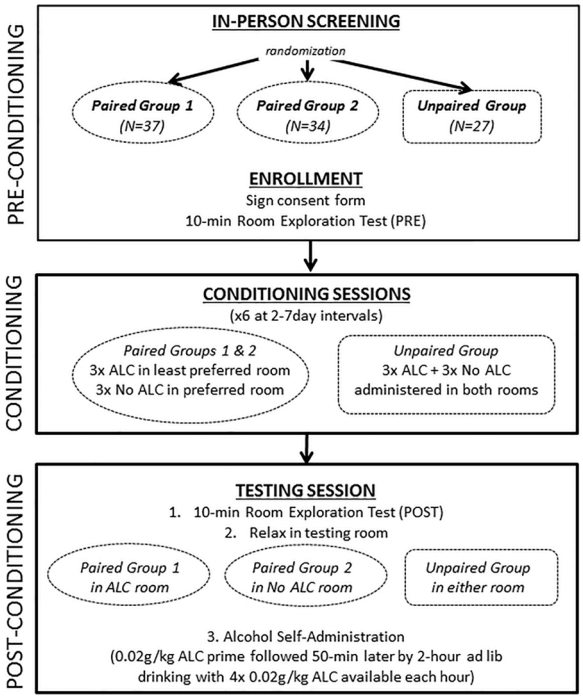

Fig. 1. Schematic of study design.

1 pm, at least 2 but no more than 7 days apart (31.0 ± 11.3 days, range 12–63). Participants in the Paired Groups ($N = 71$) always received ALC in one testing room and No ALC in the other room (assigned to each participant using a biased procedure; ALC was administered in the room that the participant spent least time in during the pre-conditioning Room Exploration Test). The order of drug administration was pseudo-randomized to avoid temporal conditioning (i.e. ALC, No ALC, No ALC, ALC, ALC, No ALC or No ALC, ALC, ALC, No ALC, No ALC, ALC). Unpaired Group participants ($N = 27$) received ALC and No ALC in both rooms i.e., 2x ALC + 1x PL in one room and 2x PL + 1x ALC in the other room, counterbalanced among participants and stratified by sex. During post-conditioning, participants completed a testing session with ad lib drinking in the ALC room (Paired Group 1) or No ALC room (Paired Group 2). Participants in the Unpaired Group were assigned to post-conditioning testing rooms in a counterbalanced manner stratified by sex (ALC room $N = 14$, No ALC room $N = 13$). *Note*: For the Unpaired group, ALC room indicates the initially least preferred room.

2.2. Participants

Healthy men and women were recruited without regard to ethnicity or race via adverts and flyers posted in the local community. Potential participants completed an online questionnaire and eligible participants attended an in-person screening interview with a medical and psychiatric interview (research SCID; First et al., 2015) and electrocardiogram (ECG) that were approved by a physician. Inclusion criteria were; 21–40 years old, body mass index (BMI) 19−26 kg/m^2, weekly alcohol consumption with ≥1 binge (defined as ≥4/5 drinks for women/men on a single occasion) in the month prior to participation (to avoid adverse reactions to the dose of alcohol administered during experimental sessions). Exclusion criteria were; current or past year diagnosis of Major Depression, Panic Disorder, Social Anxiety/Phobia Disorder, Generalized Anxiety Disorder, Obsessive-Compulsive Disorder, Eating Disorder, Post-traumatic Stress Disorder, or Hypomanic Episodes, and any history of Psychosis, current severe substance use disorder (SUD score>5), current or past history of severe AUD (score>5), hypertension, abnormal ECG, regular use of medications, less than high school education, lack of fluency in English, >4 caffeinated beverages per day or >5 cigarettes per day (to avoid effects of withdrawal on mood measures), nightshift work (to avoid influences on baseline fatigue), and pregnancy, planned pregnancy or lactation in women.

2.3. Experimental protocol

The University of Chicago Institutional Review Committee for the use of human subjects approved the protocol. Informed consent was obtained from all volunteers prior to participation. Participants were required to abstain from drugs and alcohol for 24 h before experimental sessions (verified by a negative urine drug screen and breathalyzer sample on arrival, and negative THC saliva sample for cannabis users). Women were also tested for pregnancy before each experimental session; no one tested positive. During sessions, when participants were not completing study measures, they could relax and read or watch television. Researchers who conducted study sessions (and scored the data) were blind to group assignment (using blinded breathalyzers).

2.3.1. Contextual conditioning procedure

Participants completed alcohol CPP procedures as previously described (Childs and de Wit, 2016). The rooms used for conditioning comprised two rooms of equal size that lay adjacent to each other along a corridor. The rooms were furnished as a comfortable living room with a sofa, easy chair, side table, television, and a desk with a computer to complete questionnaires and tasks. The rooms were distinct in terms of the color of the couch and soft furnishings, pictures on the walls, and room scents (for more information on room layouts, see supplementary data from Childs and de Wit, 2016). In brief, participants first completed a 10-min Room Exploration Test at the enrollment session during which they could move freely within and between the two CPP testing rooms (curtains were pulled across the corridor outside the rooms to form an enclosed CPP chamber). Closed circuit cameras recorded their movements. They then completed 6 conditioning sessions on separate days, 3 with alcohol (ALC, 80 mg/dL) and 3 with no alcohol (No ALC, 0 mg/dL). During the conditioning sessions, participants completed standardized subjective mood and drug effects questionnaires before and at 20-, 60-, 90-, 120-, 150-, 180-, and 210-min after beverage administration. At these time points, they also performed a breathalyzer test, and heart rate (HR) and blood pressure (BP) were monitored. At the end of each session, participants completed a questionnaire to rate their overall experiences and indicated if they thought they had received ALC or No ALC. They could leave if breath alcohol concentration (BrAC) was ≤40 mg/dL otherwise they remained in the lab until BrAC was ≤40 mg/dL.

2.3.2. Testing and ad lib drinking

Once all conditioning sessions were complete, participants completed a separate testing session. At this session, they first completed a 10-min Room Exploration Test. They then relaxed in the designated CPP room for 15-min (i.e., Paired Group 1 in ALC room, Paired Group 2 in No ALC room, Unpaired Group participants were assigned to each room in a counterbalanced manner stratified by Sex). After the relaxation period, they completed mood and drug effects questionnaires, and HR and BP were measured. They then consumed a priming dose of alcohol (20 mg/dL). At 15-, and 45-min after consuming the priming dose, they completed mood and drug effects questionnaires. At 15-, 30-, and 45-min post-drink, BrAC, HR and BP were measured. Participants then began a 2-h free drinking paradigm (modified from O'Malley et al., 2002). At the start of the first hour, a tray with 4 drinks (20 mg/dL each) was brought to the room. Participants were told that they could consume as much or as little as they pleased over the next hour. One hour later, the tray and any remaining beverages were removed and replaced with a second tray of 4 drinks (20 mg/dL each) that participants could again consume freely over the next hour. During ad lib drinking, participants completed mood and drug effects questionnaires, and BrAC, HR and BP were measured every 30-min. At the end of the session, participants could leave unaccompanied provided BrAC≤40 mg/dL (0.04 mg%). If BrAC was >40 mg/dL, participants were allowed to leave with a sober companion and provided with transport to their home (to avoid the influence of having to remain at the lab until BrAC≤40 mg/dL on choice to consume alcohol).

2.4. Beverage preparation and consumption

ALC drinks (8% solution) consisted of 95% alcohol (Everclear, Luxco, Inc., Saint Louis, MO) and a non-carbonated mixer of the participant's choosing (e.g. cranberry, orange, apple, etc.) to enhance palatability. Mixers were equicaloric. Volumes were calculated based on body weight and sex. The dose administered for men was 0.8 g/kg and 0.7 g/kg for women to achieve equivalent BrACs of 80 mg/dL (80 mg alcohol per 100 mL blood) across sex due to differences in total body water (Mulvihill et al., 1997; Sutker et al., 1983). No ALC beverages consisted of mixer only.

During conditioning sessions, participants consumed the total dose (80 mg/dL) over two drinking periods (40 mg/dL each). During each drinking period, the 40 mg/dL dose was split into 3 equal servings that were administered every 5-min (to standardize pace of drinking). The two drinking periods were separated by a 15-min interval, thus total beverage consumption took place over 45-min. During testing sessions, the 20 mg/dL priming dose was consumed within 5-min.

2.5. Measures

2.5.1. Demographic and drug use characteristics

Participants completed an in-person interview to obtain

demographic characteristics, and current and past history of drug use. They also completed the Timeline Followback questionnaire (TLFB, Sobell and Sobell, 1992) to record past month alcohol use.

2.5.2. Alcohol conditioning

The amount of time spent in the ALC-paired room (i.e., initially least preferred room) as a percentage of the total test time was calculated for each Room Exploration Test (i.e., pre-conditioning, post-conditioning) from the videos. Videos were double-scored by researchers who were blind to participant group assignment. Correspondence between scores was checked by a third person. Any differences in room scores of >10 s were double-checked and videos rescored if necessary (for large discrepancies). Overall, the concordance between coders was highly significant ($ps<0.001$) and only one video required rescoring.

2.5.3. Alcohol consumption

The number of drinks consumed during each 1-h free drinking period was recorded.

2.5.4. Alcohol effects

2.5.4.1. Subjective. Standardized self-report questionnaires were used to assess mood and alcohol effects (Addiction Research Center Inventory, ARCI, Martin et al., 1971; Drug Effects Questionnaire, DEQ, Morean et al., 2013, Biphasic Alcohol Effects Scale, BAES, Martin et al., 1993). Summary measures of subjective responses to ALC and No ALC during conditioning sessions were calculated as area under the curve (AUC, Altman, 1990) relative to baseline. Mean AUCs were calculated for ALC sessions and No ALC sessions for use in analyses.

2.5.4.2. Breath alcohol concentration (BrAC). Breath samples were collected using a Breathalyzer (Alco-sensor IV, Intoximeters, Inc., Saint Louis, MO). Participants rinsed their mouth with water prior to tests to avoid contamination by any alcohol present in saliva. Mean peak values (i.e., highest value recorded) were calculated for ALC and No ALC conditioning sessions for use in analyses.

2.5.4.3. Cardiovascular. Heart rate (HR) and blood pressure (BP) were measured using a monitor (Critikon Dinamap Plus; GE Healthcare Technologies, Waukesha, WI, USA). Mean AUCs were calculated for ALC sessions and No ALC sessions for use in analyses.

2.6. Data analysis

$N = 153$ participants enrolled in the study and $N = 118$ completed all testing requirements; $N = 24$ dropped out before starting the study and $N = 11$ dropped out after completing at least one conditioning session (only one participant dropped out due to adverse effects of ALC, all other participants dropped out due to scheduling difficulties, dropouts were replaced for each group). Data for $N = 20$ participants were not included in the analyses ($N = 10$ due to corruption of pre- or post-video file; $N = 6$ were assigned incorrectly i.e., received ALC in the preferred room; $N = 4$ received incorrect drug order i.e., 4x ALC or 4x No ALC) thus the final sample size for analyses was $N = 98$ (Note: subjective data during conditioning was lost for 1 subject due to database malfunction, thus the sample size for those analyses is 97).

All analyses were conducted in SPSS® version 24 for Windows. Differences were considered significant at $p < 0.05$ for the primary dependent measures (i.e., alcohol consumption, self-reported stimulation and sedation during free drinking, relationship between conditioning strength and drinking). For other measures, differences at $p < 0.05$ are reported but considered exploratory. Sex was included as a factor in all analyses but was dropped if there was no significant influence on results. Effects sizes are reported using $\eta\rho^2$.

2.6.1. Group comparisons

First, to ensure successful randomization, we compared the groups on demographic and drug use characteristics using one factor analysis of variance (ANOVA) for continuous variables and Pearson's $\chi 2$ tests (with Bonferroni corrected pairwise comparisons) for categorical variables. We also compared mean subjective, HR, and BP responses to ALC and No ALC during conditioning sessions between the groups using three-factor (Time*Group*Drug) ANOVA for repeated measures (rmANOVA). For BrAC responses, we compared mean peak values between groups using one factor (Group) ANOVA, and we also compared the mean time course of changes in BrAC across ALC conditioning sessions using two factor (Group*Time) rmANOVA.

2.6.2. Acquisition of conditioning

We compared the time spent in the ALC-paired room (as a percentage of the total test time) at the pre- and post-conditioning exploration tests between groups using two factor (Time*Group) rmANOVA; first we compared the Paired and Unpaired groups, then we compared the two Paired groups assigned to ad lib drinking in the ALC (Group 1) and No ALC (Group 2) rooms.

2.6.3. Ad lib alcohol consumption

We compared the number of drinks consumed across the 2-h drinking period between groups using two-factor (Time*Group) rmANOVA. We also compared responses to alcohol (subjective, BrAC, HR, BP) across the free drinking session using two factor (Time*Group) rmANOVA.

2.6.4. Influence of conditioning on drinking

We probed relationships between the strength of conditioning and alcohol consumption during each 1-h free drinking period using hierarchical linear regression models. To predict drinking during the first hour, test group (Paired Group 1 vs. 2) and strength of conditioning (change in % time spent in ALC room) were entered in the first step, and an interaction term (Group*ΔTime Spent) was entered in the second step. For drinking during the second hour, # drinks consumed during hour 1 was entered in the first step, test group and ΔTime Spent were entered in the second step, and an interaction term (Group*ΔTime Spent) was entered in the third step. Multicollinearity was assessed using variance inflation factor (VIF); for each model, all VIF values for predictor variables were < 3.2 indicating a very low level of multicollinearity.

3. Results

3.1. Group comparisons

3.1.1. Demographics

Most participants were male (67%) and aged in their mid-twenties (24.9 ± 3.6 years, mean ± SD). In the month prior to study enrollment, they reported drinking 15.2 ± 7.0 drinks per week, consuming alcohol on 15.8 ± 5.3 days, and engaging in 5.1 ± 3.4 binge episodes (defined as ≥4/5 drinks on a single occasion for women/men). The three groups did not differ on demographic characteristics (including Sex), or drug and alcohol use (Table 1). Demographic and drug use characteristics also did not differ between men and women in the overall sample, or between men and women in each group.

3.1.2. Alcohol responses during conditioning

The groups did not differ on subjective and cardiovascular measures at baseline before drinking began ($ps>0.1$). Men and women differed significantly on baseline systolic BP; men exhibited higher values before drinking began [Sex $F(1,92) = 19.3$ $p < 0.001$ $\eta\rho^2 = 0.174$; mean difference = 8.7 ± 1.9 mmHg]. Men and women did not differ significantly on other measures at baseline ($ps>0.05$).

During conditioning sessions, ALC significantly increased euphoria [ARCI MBG, Drug $F(1,94) = 34.6$ $p < 0.001$ $\eta\rho^2 = 0.269$], drug liking

Table 1
Demographic characteristics of study participants in each group.

	PAIRED		UNPAIRED
	Alc room	No Alc room	
N (female/male)	37 (12/25)	34 (9/25)	27 (9/18)
Age (years)	24.5 ± 3.5	25.3 ± 3.9	25.0 ± 3.5
Body mass index (kg/m^2)	23.0 ± 2.0	23.0 ± 2.1	23.3 ± 1.9
Ethnicity and Race[a] (N)			
Hispanic/Not Hispanic	5/32	5/29	1/26
White/AA/Asian/>1/Other	27/2/1/2/5	24/2/2/2/4	21/4/1/0/1
Education level (N)			
High School/College/ Advanced	16/19/2	16/15/3	12/14/1
Past month drug and alcohol use			
Cigarettes/week (N)	6.4 ± 9.7 (15)	9.4 ± 11.6 (18)	8.4 ± 10.0 (14)
Caffeine drinks/week (N)	11.5 ± 7.2 (36)	12.4 ± 7.0 (29)	10.6 ± 8.2 (27)
Cannabis uses/month (N)	7.3 ± 7.6 (20)	12.6 ± 14.9 (14)	17.7 ± 24.5 (16)
Alcohol drinks/week	14.9 ± 6.0	15.8 ± 5.5	14.9 ± 9.8
Binges	4.6 ± 2.6	5.8 ± 3.6	4.9 ± 4.1
AUDIT Score	10.2 ± 3.8	10.2 ± 4.1	10.9 ± 4.2
DSM5 AUD (N)			
None/Mild/Moderate	26/11/0	27/6/1	22/5/0
Drug Use History (% ever used)			
Cannabis	97	100	96
Stimulants	54	59	59
Opiates	32	27	30
Tranquilizers	11	27	26
Psychedelics	49	56	52
Club Drugs	35	41	52
Inhalants	19	21	21

[a] Participants self-identified their Race by selecting ≥1 of the following categories; American Indian or Alaska Native, Asian, Black or African American (AA), Native Hawaiian or Other Pacific Islander, White, More than one race (>1). Individuals in categories other than White, AA, Asian or >1 were grouped as 'Other' due to small Ns in these groups. AUDIT = Alcohol Use Disorder Identification Test, AUD = Alcohol Use Disorder.

[DEQ Like drug effects, Drug F(1,94) = 266.4 $p < 0.001$ $\eta\rho^2 = 0.739$] and craving [DEQ Want More, Drug F(1,94) = 132.0 $p < 0.001$ $\eta\rho^2 = 0.584$] in comparison to No ALC. ALC also demonstrated typical biphasic effects; it increased feelings of stimulation [BAES, Drug F(1,94) = 20.6 $p < 0.001$ $\eta\rho^2 = 0.180$; ARCI A, Drug F(1,94) = 31.0 $p < 0.001$ $\eta\rho^2 = 0.248$] immediately after drinking began that were sustained for 90 min (i.e., for 45 min after drinking ended, Fig. 2A), and produced significant increases in feelings of sedation [BAES, Drug F(1,94) = 42.9 $p < 0.001$ $\eta\rho^2 = 0.314$; ARCI PCAG, Drug F(1,94) = 21.8 $p < 0.001$ $\eta\rho^2 = 0.188$] at 60 min after drinking began (i.e., 15 min after drinking ended, Fig. 2B) that lasted through the end of the session. ALC significantly increased HR [Drug F(1,95) = 56.9 $p < 0.001$ $\eta\rho^2 = 0.38$] and decreased diastolic BP [Drug F(1,95) = 23.0 $p < 0.001$ $\eta\rho^2 = 0.20$]. Participants exhibited a mean peak BrAC of 0.069 ± 0.013 mg/dL that occurred 60 min after drinking began (i.e., 15 min after drinking ended).

Subjective, cardiovascular, and BrAC responses during conditioning sessions did not differ significantly between the groups (*ps*>0.3, see Fig. 2A and B). Overall, men and women differed on ratings of stimulation [ARCI A, Sex F(1,91) = 5.2 $p < 0.05$ $\eta\rho^2 = 0.054$] and dysphoria [ARCI LSD, Sex F(1,91) = 8.1 $p < 0.01$ $\eta\rho^2 = 0.082$]; women reported greater stimulation and less dysphoria than men after both ALC (Group mean ± SEM: ARCI A Women = 1.9 ± 0.3, Men = 0.7 ± 0.2; ARCI LSD Women = 0.5 ± 0.3, Men = 1.2 ± 0.2) and No ALC (Group mean ± SEM: ARCI A Women = 0.06 ± 0.13, Men=-0.23 ± 0.10; ARCI LSD Women = 0.01 ± 0.10, Men = 0.36 ± 0.10). Mean peak BrAC did not differ between men and women [mean difference = 0.005 ± 0.0032 mg/dL, t(96) = 1.8 $p > 0.08$], however the time course of changes in BrAC did differ between sexes [Time*Sex F(6,552)=7.2 $p < 0.001$ $\eta\rho^2 = 0.072$]; women exhibited a steeper increase in BrAC and peaked earlier (at 60-min) in comparison to men (peak at 90-min, Fig. 2C). There were no other significant main effects of Sex or interactions between Sex and Drug on subjective and cardiovascular responses during conditioning sessions (*ps*>0.1).

3.2. Acquisition of conditioning

In comparison to the Unpaired group, Paired group participants exhibited a significant pre- to post-conditioning increase in time spent in the ALC-paired room [Time*Group F(1,96) = 4.6 $p < 0.05$ $\eta\rho^2 = 0.05$, Fig. 2D]; Paired group mean change = 10.3 ± 21.3%, Unpaired group mean change=-1.5 ± 31.9. %. The magnitude of conditioning did not differ between the Paired groups [mean between group difference in ΔTime Spent = 3.7 ± 5.0%, t(69) = 0.7 $p = 0.5$]. Sex did not significantly influence conditioning [Sex, F(1,94)=0.4 $p > 0.5$].

3.3. Ad lib alcohol consumption

There was a significant Time*Group interaction on the number of drinks consumed during ad lib drinking; Paired group 1 participants (tested in the ALC room) drank at a consistently high rate throughout the 2 -h free drinking session, whereas drinking rates declined during the second hour of free drinking among Paired group 2 participants (tested in the No ALC room) and Unpaired group participants [Time*Group F(2,95) = 3.3, $p < 0.05$, $\eta\rho^2 = 0.065$, Fig. 3A]. Group differences in drinking did not differ by Sex [Sex, F(1,92) = 2.3 p>0.1; Group*Sex, F(2,92) = 0.4 $p > 0.6$].

Subjective responses also differed between the groups during ad lib drinking (Fig. 3C, D); Paired group 1 participants (tested in the ALC room) exhibited significantly greater stimulation [ARCI A, Group*Time F(12,564) = 2.6 $p < 0.005$ $\eta\rho^2 = 0.053$; BAES Stimulation, Group*Time F(12,564) = 1.9 $p < 0.05$ $\eta\rho^2 = 0.039$] and euphoria [ARCI MBG, Group*Time F(12,564) = 1.8 $p = 0.05$ $\eta\rho^2 = 0.036$] during free drinking than the other groups. Moreover, Paired group 2 participants (tested in the No ALC room) reported greater drug disliking [DEQ, Group*Time F(12,564) = 2.5 $p < 0.005$ $\eta\rho^2 = 0.05$] during drinking than the other groups. Sex influenced subjective stimulant-like [BAES Sex F(1,91) = 6.6 $p < 0.05$ $\eta\rho^2 = 0.07$] and sedative responses during free drinking [ARCI PCAG Sex F(1,91) = 7.5 $p < 0.01$ $\eta\rho^2 = 0.08$]; overall women exhibited significantly less stimulation (Group mean ± SEM = 16.7 ± 2.4) and more sedation (4.7 ± 0.3) than men (BAES = 24.1 ± 1.7, ARCI PCAG = 3.8 ± 0.2).

Ad lib drinking significantly increased HR [Time F(4,644) = 34.9 $p <$ 0.001 $\eta\rho^2 = 0.27$], systolic BP [Time F(7,644) = 2.9 $p < 0.01$ $\eta\rho^2 = 0.03$] and diastolic BP [Time F(7,651) = 3.0 $p < 0.01$ $\eta\rho^2 = 0.03$] similarly across the groups. In addition, the time course of BrAC responses did not differ across ad lib drinking (Fig. 3B). HR and blood pressure responses did not differ between men and women across ad lib drinking. Yet, despite the absence of sex effects on ad lib drinking, BrAC responses did differ between men and women; men exhibited higher BrAC responses than women [Time*Sex F(6,546) = 2.2 $p < 0.05$ $\eta\rho^2 = 0.02$, Mean AUC ± SEM, standard units; Women = 0.13 ± 0.01, Men = 0.17 ± 0.01].

3.4. Influence of conditioning on drinking

The strength of alcohol conditioning predicted drinking during the first hour in a context-dependent manner (Group*ΔTime Spent B = 0.041 SE = 0.015 β = 0.54 $p = 0.007$, Table 2); CPP strength positively predicted drinking among Paired group 1 participants (tested in the ALC room) and negatively predicted drinking among Paired group 2 participants (tested in the No ALC room, Fig. 4). Thus, for participants who exhibited a 10% increase in time spent in the ALC room, the difference in drinking between the ALC and No ALC rooms was 0.41 drinks.

During the second hour of ad lib drinking, the number of drinks consumed during the first hour (B = 0.90 SE = 0.09 β = 0.78 p < 0.001) and environment (Group B = 0.56 SE = 0.23 β = 0.19 $p = 0.019$) significantly positively predicted drinking (Table 3); Paired group 1

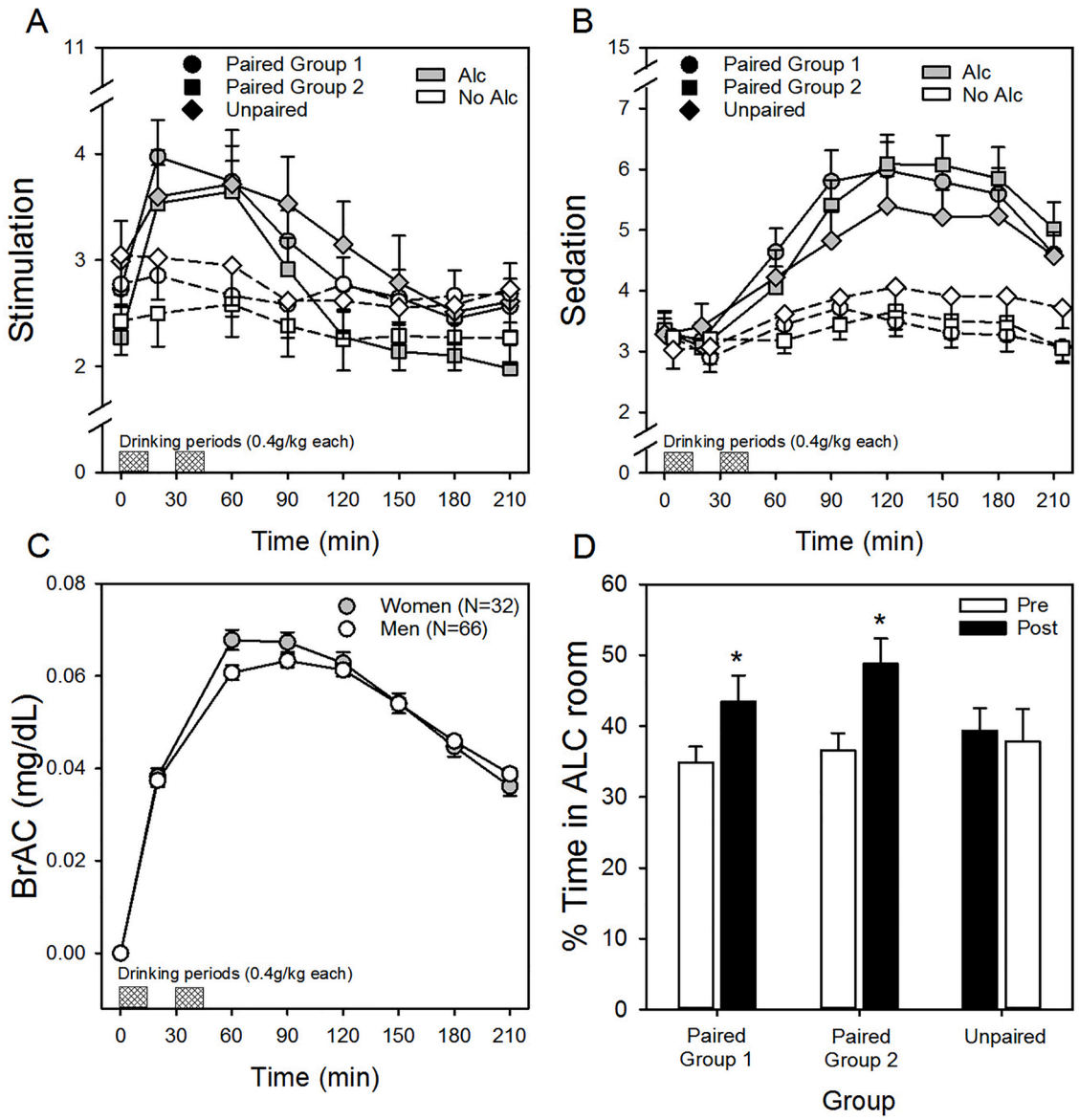

Fig. 2. **A** and **B** respectively show subjective stimulation (ARCI Amphetamine scale) and sedation (BAES) after 0.8 g/kg alcohol (Alc) and 0 g/kg alcohol (No Alc) for each group during conditioning sessions. **C** shows changes in breath alcohol concentration (BrAC) for men and women. **D** shows time spent (as a percentage of total test time) in the alcohol-paired room (i.e., initially least preferred room) during the pre- and post-conditioning Room Exploration Tests. Data points represent mean ± SEM. Asterisks indicate a significant Pre-Post difference (Paired t-test, $p<0.05$).

participants (tested in the ALC room) consumed more drinks than Paired group 2 participants (tested in the No ALC room). There was no significant effect of conditioning strength or interaction between Group and conditioning strength on drinking in the second hour. Thus, after controlling for first hour drinking, participants tested in the ALC room consumed 0.6 more drinks than participants tested in the No ALC room.

4. Discussion

In this study, we examined how an alcohol-paired environment influenced alcohol drinking using a human laboratory model of conditioning. We found that the alcohol–paired environment significantly enhanced positive subjective responses to alcohol (stimulation, euphoria) and promoted high drinking rates throughout a free drinking period. By contrast, an environment paired with the absence of alcohol (No ALC) increased negative subjective responses to alcohol (disliking) and reduced drinking rates during the latter half of the drinking session. Further, we found that the strength of conditioning predicted drinking early in the session (first hour drinking) in a context-dependent manner; conditioning strength positively predicted drinking in the alcohol-paired environment yet it negatively predicted drinking in the environment paired with absence of alcohol. Environmental context (ALC vs. No ALC) significantly predicted drinking during the latter half of the session regardless of conditioning strength. Our results provide the first empirical evidence that environments passively-paired with alcohol administration in the human laboratory directly influence alcohol consumption. The findings also confirm the viability of the human CPP procedure to study the psychobiological basis of alcohol environmental conditioning and the potential mechanisms by which the associations influence alcohol drinking.

The principal finding, that alcohol-paired environments promoted alcohol drinking in comparison to environments paired with absence of alcohol and control groups, is in line with the results of both preclinical and clinical studies. First, rodent studies have shown that alcohol environments invigorate responding to an alcohol predictive cue (Remedios et al., 2014; Sciascia et al., 2015). Second, clinical studies have

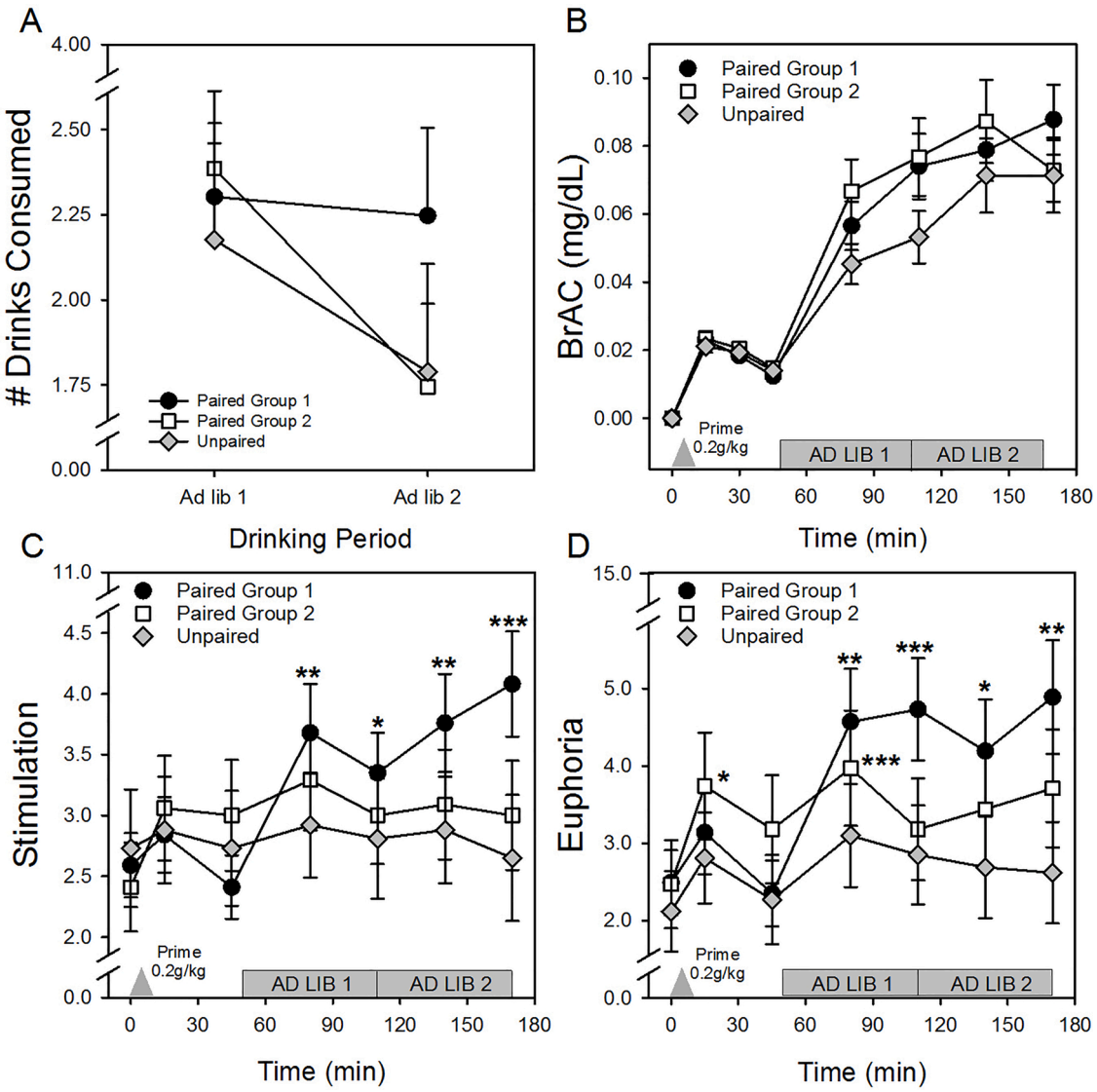

Fig. 3. **A** shows the number of drinks consumed during the first (Ad lib 1) and second (Ad lib 2) hours of ad lib drinking for each group. **B** shows breath alcohol concentration (BrAC) across the testing session for each group. **C** and **D** respectively show subjective stimulation and euphoria across the testing session for each group. Data points represent mean ± SEM. Asterisks indicate a signficant difference to baseline (time 0).

Table 2
Summary of hierarchical regression analysis for variables predicting number of drinks consumed during the first hour among Paired groups ($N = 71$).

	Model 1			Model 2		
Variable	B	SE B	β	B	SE B	β
Step 1						
Test Group	−0.090	0.317	−0.035	−0.116	0.303	−0.044
ΔTime spent	−0.002	0.007	−0.032	−0.029	0.012	−0.466*
Step 2						
Group*ΔTime spent				0.041	0.015	0.539**
Model Statistics						
R^2 change F	0.07			7.64**		
ANOVA	F(2,70) = 0.07			F(3,70) = 2.60 $p = 0.06$		

Note: Test Group was coded as a dummy variable (1=Paired Group 1, 0=Paired Group 2). ΔTime spent was centered at the mean. *$p<0.05$, **$p<0.01$.

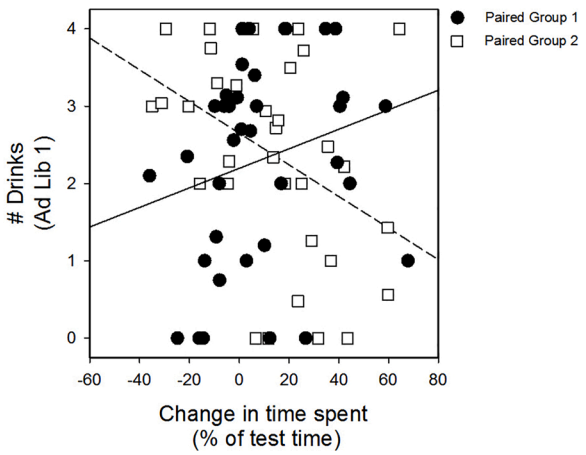

Fig. 4. Relationship between the strength of CPP (change in % time spent in alcohol-paired room) and the number of drinks consumed during the first hour of ad lib drinking (Ad lib 1) for Paired group participants tested in the alcohol-paired room (● solid line) and no alcohol-paired room (□ dashed line).

shown that a combination of alcohol environments and proximal cues (i.e., "bar lab" with alcohol beverage taste and/or smell) increased alcohol consumption in comparison to neutral environments and cues i.e., neutral laboratory with water (Field and Jones, 2017; Jones et al.,

Table 3
Summary of hierarchical regression analysis for variables predicting number of drinks consumed during the second hour among Paired groups ($N = 71$).

	Model 1			Model 2			Model 3		
Variable	B	SE B	β	B	SE B	β	B	SE B	β
Step 1									
1 st h # drinks	0.86	0.09	0.74***	0.86	0.09	0.75***	0.90	0.09	0.78***
Step 2									
Test Group				0.55	0.23	0.18*	0.57	0.23	0.19*
ΔTime spent				−0.01	0.01	−0.08	0.003	0.01	0.04
Step 3									
Group*ΔTime spent							−0.01	0.01	−0.15
Model Statistics									
R^2 change F	85.58***			3.56*			1.19		
ANOVA	F(1,70) = 85.58 ***			F(3,70) = 33.01***			F(4,70) = 25.13***		

Note: 1st h # drinks and ΔTime spent were centered at their means. Test Group was coded as a dummy variable (1=Paired Group 1, 0=Paired Group 2). *$p<0.05$, ***$p<0.001$.

2013). These studies concluded that a combination of proximal and environmental cues produce stronger stimulatory effects on alcohol consumption. Our results support this theory, given that participants consumed a priming dose (i.e., CS+) at the beginning of the free drinking session. Thus, together the pharmacological and interoceptive cueing effects of alcohol and the alcohol-paired environmental cues enhanced drinking. Also in agreement with the existing literature, is the finding that the environment paired with alcohol absence exerted an inhibitory influence on alcohol consumption. Similar effects have been observed in studies with smokers; environments and social cues associated with smoking abstinence evoke less craving and smoking (Conklin et al., 2013; Stevenson et al., 2017). Together the findings recommend further research into the role that environments associated with alcohol abstinence play in drug taking and how this may be harnessed in treatment approaches. For example, given that visualization of personalized drinking situations stimulates alcohol intake (Blaine et al., 2019), it is feasible that visualization of environments paired with alcohol absence may attenuate alcohol consumption and cue-induced behaviors.

Another main finding of the study was that conditioning strength predicted drinking in the first hour of ad lib drinking. Both preclinical and clinical studies have shown that the strength of conditioning (Cofresi et al., 2019) or intensity of cue-induced responses (Grusser et al., 2004; Rohsenow et al., 1994) predicts alcohol consumption. Similarly, cue-reactivity has been shown to predict relapse and abstinence among smokers (Janes et al., 2017, 2010; Powell et al., 2010; Waters et al., 2004) and stimulant users (MacNiven et al., 2018). Together, the findings suggest that our methodology may be used to examine individual predictors of susceptibility to strong environmental conditioning and whether these also predict susceptibility to develop AUD i.e., whether the strength of laboratory conditioning also predicts longitudinal changes in real-world drinking.

It is important to note a critical difference between our study and previous preclinical and clinical studies that reported effects of alcohol-associated environments on alcohol seeking or taking. In our study, alcohol was freely available for consumption during the testing sessions (albeit with hourly constraints on intake), whereas preclinical studies (Bouton and King, 1983; Chaudhri et al., 2008a, 2008b, 2009; Crombag and Shaham, 2002; Tsiang and Janak, 2006) and some clinical studies (Ludwig et al., 1974; Van Dyke and Fillmore, 2015; Willner et al., 1998) used instrumental procedures to explicitly measure drug seeking. Thus, it is possible that our results would be different if we had used an instrumental alcohol self-administration paradigm or one with availability of alternative reinforcers (e.g. O'Malley et al., 2002). In addition, the lack of a drug seeking measure in the current study precludes the conclusion that alcohol-paired environments increased the reinforcing efficacy of alcohol. However, to the extent that CPP strength represents drug seeking associated with the incentive-motivational properties of alcohol-paired environments (Martin-Fardon and Weiss, 2013), and given that CPP strength predicted drinking in our study, we speculate that the alcohol-paired environment enhanced drinking due to association with the incentive motivational properties of alcohol experienced during conditioning. Nevertheless, to definitively conclude that the alcohol-paired environment increased the reinforcing efficacy of alcohol, future experiments that assess alcohol seeking instrumental responses in the CPP rooms are essential.

It is interesting that all groups consumed similar amounts of alcohol during the first hour of free drinking and that differences emerged during the second hour; participants tested in the alcohol-paired environment continued to drink at a high rate throughout the free drinking period whereas participants tested in the no alcohol-paired room and control participants reduced consumption during the second hour. This finding is counterintuitive given that conditioning strength predicted drinking during the first hour but did not predict drinking during the second hour. The biggest predictors of drinking during the latter half of the session were the amount of alcohol consumed during the first hour and also the environment. Thus, the findings suggest that conditioning strength contributes to early drinking, and in turn early drinking (i.e., amount consumed) largely contributes to later drinking together with the influence of environmental cues regardless of conditioning strength. In other words, while the environmental cues predicted drinking overall, the strength of conditioned associations stimulated early drinking which then contributed to drinking over a longer period. In our study, only a limited amount of alcohol was available for a limited period. It is feasible that in real-world alcohol environments where availability and time is unrestricted, individuals will consume greater amounts over longer periods reaching hazardous levels. Thus, the findings contribute to our understanding of how alcohol-paired environments may promote binge drinking among individuals with strong conditioned associations.

An alternative interpretation for the finding that differences in consumption emerged later in the drinking session is that self-control may have been slowly eroded in the presence of alcohol-paired environmental and interoceptive cues (Muraven and Baumeister, 2000). For example, prior studies have reported that alcohol environmental cues reduce self-efficacy to refuse alcohol (Loeber et al., 2006; Monk and Heim, 2013) and impair inhibitory control (Field and Jones, 2017). Another potential mechanism by which the alcohol environment influenced alcohol intake is via altered alcohol outcome expectancies, that is, the belief that alcohol drinking will produce positive or negative effects (Brown et al., 1980). Indeed, drinkers report greater positive and less negative expectancies in alcohol-related environments (Monk and Heim, 2013; Wall et al., 2000, 2001; Wiers et al., 2003). Our findings do not indicate the mechanisms by which the alcohol-paired environments enhanced drinking, thus future studies using this methodology will focus on identifying *how* alcohol-paired environments are able to alter consumption.

In line with our hypothesis, alcohol-paired environments enhanced positive subjective responses to alcohol (stimulation, euphoria). Again,

it is interesting that this effect was evident during the first hour of drinking despite comparable drinking between the groups. This result suggests that alcohol conditioning enhanced the psychostimulant effects of alcohol in the alcohol-paired environment. Alternatively, given that we did not observe a similar change in alcohol effects across successive conditioning sessions (see Childs and de Wit, 2016), it is possible that the change in contingencies between conditioning and testing sessions contributed to the effect. During conditioning sessions, alcohol consumption was compulsory and carefully monitored by the research staff, yet during the testing session participants controlled their intake which may have enhanced the rewarding subjective properties of alcohol. This idea is supported by preclinical data showing differences in the positive reinforcing effects of contingent alcohol in comparison to yoked alcohol (Moolten and Kornetsky, 1990) and in the physiological effects of cocaine and nicotine (Donny et al., 2006, 2000).

Unexpectedly, we saw that drinking in an environment paired with the absence of alcohol produced greater disliking of alcohol effects. This finding suggests that drinking alcohol in a place where alcohol has not previously been consumed produces a more negative experience, which may in turn limit consumption (Leigh, 1987; O'Malley and Maisto, 1984). As mentioned earlier, previous studies with nicotine have shown that cues predictive of drug unavailability (e.g. non-smoking environments, social cues) attenuated craving and smoking (Conklin et al., 2013; Stevenson et al., 2017). Our result adds to this literature and suggests that alcohol environments predictive of drug unavailability also influence drug subjective responses in a manner that may negatively impact consumption. However, since this finding was not expected, it should be regarded with caution until replicated.

Finally, we found interesting sex differences in the results that are worthy of discussion. First, women exhibited an earlier peak in BrAC during conditioning sessions in comparison to men. However, this did not selectively influence subjective responses to alcohol during conditioning; overall, women exhibited greater stimulant-like and less sedative responses to both ALC and No ALC in comparison to men. It is not clear why we observed sex differences in BrAC in this study, as they are not usually evident in other studies with challenge doses of alcohol. Potential explanations are the influence of sex hormones on alcohol pharmacokinetics (Jones, 2010; Lynch et al., 2002). Due to the long time commitment for the study, we did not control for menstrual cycle phase among women at each session. Thus, it is possible that menstrual cycle phase or the use of hormonal birth control influenced BrAC responses to alcohol. In future studies, we could try to control menstrual cycle phase during conditioning sessions. However, the feasibility of this approach is uncertain given the number of conditioning sessions, the pseudo randomized order of sessions, and scheduling constraints (i.e., 2–7 day intervals between training sessions). At the testing session, women exhibited significantly lower BrAC responses, and also less positive and more negative subjective effects than men during free drinking. Nevertheless, despite the sex differences in subjective and BrAC responses to alcohol during free drinking, men and women did not differ in the amount of alcohol consumed across the self-administration session. This finding is counterintuitive and may be spurious, however it should be noted that the number of women in each group was relatively low which likely enhanced variation in the measures and reduced power to observe sex differences in drinking. Thus, in future studies we will aim to increase the number of female participants to clarify this unusual finding.

Our study was not without limitations. First, we did not include a placebo condition during the free drinking session, thus it not possible to dissociate influences of pharmacological effects and expectations on consumption. This will be an important condition to include in future experiments. Second, de novo conditioning studies have been criticized for their lack of generalizability to real-life situations where conditioned associations have been formed over hundreds and thousands of drug experiences (Walsh et al., 2018). Nevertheless, controlled de novo conditioning studies will be useful to examine the psychobiological mechanisms underlying the formation of conditioned associations and the mechanisms by which they are able to influence behavior. They may also provide important information to optimize clinical trials of drug therapies to impair drug and alcohol conditioned associations via extinction or reconsolidation techniques (e.g., timing and route of administration, Walsh et al., 2018). Third, we used a biased procedure for room assignment. This approach is typical for alcohol CPP experiments in rodents, and studies show that using a biased assignment procedure with a non-biased apparatus does not significantly influence outcomes (Cunningham et al., 2003). Data from the initial exploration test show that our 'apparatus' was unbiased (see Childs and de Wit, 2016). Nevertheless, use of a biased assignment procedure raises the issue that alcohol-induced preferences may be formed due to anxiolytic alcohol effects that attenuate aversion to the drug-paired room i.e., negative rewarding effects, as opposed to positive rewarding alcohol effects such as stimulation and euphoria. Indeed, we previously found that the self-reported sedative effects of alcohol predicted alcohol CPP (Childs and de Wit, 2016). However, the questionnaires used in the study measured the negative sedative effects of alcohol e.g., difficulty concentrating, dizziness, heavy headed, sluggish, fatigued, etc., and alcohol did not significantly influence scales that specifically measure tension/relaxation. In our current alcohol CPP studies, we have included questionnaires to measure alcohol-induced calming effects and future analyses of the data will help to elucidate the role of positive and negative sedative alcohol effects in forming alcohol conditioned associations.

Despite these limitations, the methodology used here represents a significant advance in studying the influence of environmental contexts on alcohol drinking in humans. Future research using this experimental approach will seek to identify the mechanisms through which alcohol-paired environments are able to promote drinking. We can also use this procedure to probe the neural circuitry involved in environmental conditioning using imaging techniques. Finally, the results confirm the feasibility of using this approach to examine novel approaches to counteract the effects of alcohol-paired environments on drug taking.

5. Conclusions

The results of this study provide the first evidence that laboratory-conditioned alcohol environments directly influence alcohol effects and alcohol drinking. The findings provide a basis for future studies to examine the psychobiological mechanisms by which conditioned environmental associations are formed, individual differences in the susceptibility to conditioning, and how the associations are able to influence alcohol consumption. Finally, the methodology can also be used to develop novel strategies to dampen the conditioned associations and their influences on behavior and drinking.

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CRediT authorship contribution statement

Joseph A. Lutz: Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Emma Childs:** Visualization, Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.beproc.2021.104340.

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