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Alcohol-induced place conditioning in moderate social drinkers

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Abstract

Aims—To test whether non-dependent drinkers show place preference for a location paired with alcohol, and to test if the amount of time spent in the alcohol-paired location is related to self-reported subjective alcohol effects experienced in that environment.

Design—Two groups of subjects completed six conditioning sessions: three with alcohol (0.8g/kg) and three without alcohol. Individuals were randomly assigned to 2 groups, Paired and Unpaired, in a 2:1 ratio. The Paired group (N=78) received alcohol in one testing room and no-alcohol in another testing room (biased assignment). The Unpaired group (N=30) received alcohol and no-alcohol in each testing room.

Setting—Human Behavioral Pharmacology Laboratory, University of Chicago, Chicago, Illinois, USA (single site).

Participants—Healthy male and female social drinkers (N=108) aged 21–37 participated in the study (consisting of 10 separate laboratory visits) between March 2012 and August 2014 (an average of 36 separate subject visits per month).

Measurements—The primary outcome measure was the pre- to post-conditioning change in percent time spent in the least preferred room (obtained during drug-free exploration tests conducted at separate visits before and after the six conditioning sessions were completed). Secondary measures included self-reported subjective mood and drug effects obtained during the conditioning sessions.

Findings—The groups differed in the change in percent time spent in the initially least preferred room, from pre- to post-conditioning; Paired group = 11.0%, Unpaired group = −1.4%, mean difference = 12.4%, 95% CI = 1.9–23.0, $p=0.02$. The change in percent time spent in the least-preferred room was related to the self-reported sedative effects of alcohol during conditioning sessions among Paired group participants only.

Conclusions—Non-dependent consumers of alcohol appear to develop a behavioral preference for locations paired with alcohol consumption, more so for those who experience sedative effects from alcohol in those locations.

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Declaration of Interests

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Introduction

Learned associations between a drug and the cues surrounding drug experiences are considered critically important in the development of addiction (1–3). These associations, formed through the processes of drug conditioning, are robust and long-lasting, inducing cravings and relapse long after the user is drug-free (4, 5). However, few clinical studies have examined the conditioning processes and little is known about how associations are formed and how they influence behavior including drug use. Thus, there are few effective treatment strategies to specifically address these pathological associations, and conditioned responses to cues remain a significant barrier to prolonged abstinence. A better understanding of conditioned associations and how they control behavior will help us to design novel approaches to counteract their powerful influences.

Until now, most clinical research on conditioned drug associations has been conducted in drug dependent individuals. This research has provided valuable data on conditioned responses to drug cues (e.g., images) in established drug users, yet few clinical studies have examined acquisition of the conditioned responses. To fully understand the basic conditioning processes it is essential to conduct laboratory studies in which we can control drug and cue exposure and clearly interpret the acquired responses. The first step to achieving this goal is to develop a human laboratory model of de novo drug conditioning.

Conditioned place preference (CPP) is a widely used pre-clinical model of drug reward (6). It is thought that a preference for the drug-paired place is established via classical Pavlovian conditioning processes whereby rewarding drug effects become associated with the context. Thus, CPP is essentially based upon drug conditioning and can also be used to study and better understand the conditioning process and its influence on behavior. Recently, using similar methodology, we developed a human laboratory model of drug conditioning and showed that healthy men and women come to exhibit an explicit subjective liking and preference for an environment paired with *d*-amphetamine administration (7, 8). Yet, interpreting the results in line with the preclinical model has been limited because of the fundamental difference in outcome measures; behavioral exploration in animals vs. subjective liking in humans. In this study, we sought to extend the model by incorporating an objective measure of preference i.e., “time spent”, as a direct analogue of the conditioned behavior measured in animal CPP.

In this study, we sought to test whether healthy social drinkers would exhibit an alcohol place preference. Participants were assigned to a Paired condition who received alcohol (0.8g/kg, ALC) and no alcohol (0g/kg, NoALC) in separate distinct rooms, or an Unpaired condition who received ALC and NoALC in both rooms. We aimed to 1) compare Paired and Unpaired groups on the pre- to post-conditioning change in time spent in the rooms during drug-free exploration tests, 2) assess the relationship between the change in time spent in the rooms with the self-reported subjective effects of alcohol. We hypothesized that there would be a significant group difference in the pre- to post-conditioning change in time spent in each room; time spent in the ALC-paired room would increase among Paired group individuals but would not change in the Unpaired group. Further, we hypothesized that the

change in time spent in the ALC-paired room would be related to positive pleasurable alcohol effects i.e., stimulation, among Paired group participants.

Methods

Design

Participants completed 10 study visits; in-person screening interview, orientation session, six conditioning sessions, testing session, and debriefing visit. Participants were randomly assigned to two groups in a 2:1 ratio; a Paired group (N=78) always received ALC in one room and NoALC in the other room, and an Unpaired group (N=30) received ALC and No ALC in both rooms. Treatment orders were pseudo-randomized between participants (ALC, NoALC, NoALC, ALC, ALC, NoALC, or NoALC, ALC, ALC, NoALC, NoALC, ALC, to prevent temporal conditioning) and a non-counterbalanced room assignment procedure (6) was used; participants received ALC in the room that they spent the least time in during the initial exploration test.

Design Considerations—This report is part of a larger experiment in which the Paired condition underwent tests post-conditioning in the ALC-paired or NoALC-paired room. Thus, the Paired group sample was approximately twice that of the Unpaired for later comparisons. Sample sizes were based on effect sizes in pre-clinical alcohol CPP experiments e.g., (9).

In previous studies, we (7, 8) used 4 conditioning sessions (2 each with amphetamine and placebo). For the present study, we wanted to increase the number of conditioning sessions without substantially increasing time commitments for subjects to minimize dropouts, thus we decided on six conditioning sessions (3 each with ALC and NoALC).

A non-counterbalanced assignment procedure was used in line with our previous human studies (8) and typical practices for pre-clinical CPP alcohol experiments (10).

Subjects

Healthy men and women (N=144) attended an in-person screening interview at the laboratory; exclusion criteria included a current or prior diagnosis of a major axis I DSM-IV disorder (11), including past year drug dependence or history of alcohol dependence, hypertension, abnormal ECG, regular medications, less than high school education or lack of fluency in English, >4 caffeinated beverages/day, >5 cigarettes/day, nightshift work, and pregnancy or lactation in women. Inclusion criteria were age 21–40, body mass index 19–26kg/m², 10–30 drinks/week and 1 binge/month (to avoid adverse alcohol effects). Twenty-four subjects dropped out after enrollment; 15 did not begin testing and 8 (4 Paired, 4 Unpaired) dropped out after starting the study due to scheduling difficulties, 1 (Paired) dropped out due to side effects (nausea). Data were lost for 12 subjects (8 Paired, 4 Unpaired) due to video malfunction or incorrect dosing. Missing data were deleted list wise from analyses; subjective data were lost for 3 subjects, cardiovascular data for 3 subjects.

Experimental Procedure

The University of Chicago Institutional Review Committee for the use of human subjects approved the protocol. Conditioning was performed in two adjacent testing rooms of equal size that were comfortably furnished as a living room (see Figure S1) and distinct in terms of couch/cushion colors, pictures on the walls, and scents, but were designed to be equally attractive. When participants were not completing study measures they could relax, read, or watch movies (all movies were available in both rooms; books/magazines differed between rooms but the reading content was similar e.g. fiction vs. nonfiction, different editions of the same magazines).

Orientation Session—At the orientation session (conducted in a separate neutral room), subjects read and signed the consent form (which stated that the study aim was to investigate interactions between drug effects and the environment, and would involve consuming beverages that may or may not contain alcohol) and practiced the subjective questionnaires. They also completed a 10min drug-free exploration test in which they were allowed to explore the two conditioning rooms moving freely between them (see Figure S1 for instructions).

Drug Conditioning Sessions—Participants completed six drug conditioning sessions (3x ALC, 3x NoALC) that were always conducted between 1–6pm at 2–7day intervals (Figure 1). Upon arrival, subjects provided breath and urine samples to test for the presence of drugs and alcohol, and for pregnancy in women. No one tested positive. Participants relaxed in the neutral room for 15min before baseline mood and vital signs were assessed. They were then escorted to the testing room for that session where beverages were consumed. To mimic naturalistic drinking, the dose (0.8g/kg) was divided into two separate drinking periods (0.4g/kg each) separated by 15min. Each 0.4g/kg dose was further divided into 3 equal portions to be consumed over 5min each (15min total) in the presence of the researcher. Participants spent a total of 2h in the testing room then were escorted back to the neutral room where they relaxed until breath alcohol was 0.02–0.04mg% (as per NIAAA guidelines). Subjective measures, vital signs and breath samples were collected at repeated intervals throughout.

Post-Test Session—After all conditioning sessions had been completed, participants returned to the lab for a testing session. The first task completed at this testing session was a 10min drug-free exploration test (see Figure S1 for instructions). Additional tests and questionnaires conducted as part of the larger study will be presented separately.

Debriefing Session—Subjects were fully debriefed about the study aims and received payment.

Dependent Measures

Place conditioning—Surveillance cameras captured participants' movements during the 10min exploration tests. Videos were double-scored by research assistants who calculated the amount of time spent in each room (% of total).

Subjective mood and drug effects—Standardized questionnaires were used to assess mood and drug effects; Profile of Mood States [POMS; (12)], Addiction Research Center Inventory [ARCI; (13)], Drug Effects Questionnaire [DEQ; (14)], Biphasic Alcohol Effects Scale [BAES, (15)].

Vital signs—Heart rate and blood pressure were measured using a monitor (Critikon Dinamap Plus, GE Healthcare Technologies, Waukesha, WI).

Breath alcohol concentration (BrAC)—Breath samples were collected using a Breathalyzer (Alco-sensor IV, Intoximeters, Inc., Saint Louis, MO).

Drugs

ALC drinks (8% solution) were prepared with 95% alcohol (Everclear, Luxco, Inc., Saint Louis, MO) and fruit juice [volumes were adjusted for female participants (16)]. NoALC drinks consisted of fruit juice mixer only. Participants chose their mixer from a selection of fruit juices (e.g. cranberry, orange, apple) that were equicaloric, to enhance palatability and liking.

Data Analysis

Demographic characteristics were compared between the groups using Independent samples *t*-test. The change in %time in the initially least preferred (ALC-paired) room was compared between groups using independent samples *t*-test. Regression analyses were also performed upon the change in %time in the rooms controlling for all demographic characteristics; characteristics were entered in a single step using a backwards stepwise model to remove variables that did not significantly contribute to the model.

Subjective and physiological responses to drinks were analyzed using Drug*Time*Session*Group rmANOVA. Summary measures of subjective and physiological responses were calculated as the area under the curve (AUC, to 210min when subjects left the conditioning room) relative to baseline (17), and compared across successive sessions between groups using Group*Drug*Session rmANOVA. Changes in BrAC across successive sessions were compared using Group*Session*Time rmANOVA, and mean peak BrAC (averaged across sessions) was compared between groups using independent samples *t*-test.

Relationships between ALC subjective responses during conditioning sessions and changes in time spent in the initially least-preferred (ALC-paired) room were explored using regression analyses. To reduce the number of measures to key components (18, 19), factor analysis was conducted on scale scores from the POMS, BAES, ARCI and DEQ using mean AUC averaged across alcohol sessions (alcohol responses did not differ significantly across successive administrations). We conducted an initial principal axis factor analysis with direct oblimin rotation (to allow correlation between factors). Scales that showed little or no correlation with others (e.g. DEQ Dislike, ARCI LSD), or that demonstrated significant loading on more than one factor (ARCI BG) were omitted. Although, the sample size did not meet recommended guidelines (20), the results confirmed those of earlier studies with larger samples (18, 19) and were entered into a hierarchical regression model. In the first step,

factor scores and Group were entered. In the second step, the independent variables and interaction terms between the factors and Group were entered. A backwards stepwise approach was used to remove variables that did not significantly contribute to the model.

Analyses were conducted using SPSS® Version 23 for Windows. Differences were considered significant at $p < 0.05$.

Results

Demographics

Table 1 shows demographic and drug use characteristics for each group. Overall, most participants were male (68%), aged in their mid-twenties (24.7, $SD=3.6$) who reported drinking on 15.8 days/month ($SD=5.4$) and consuming 15.2 ($SD=6.9$) alcohol drinks/week. They reported drinking in a binge pattern on 5.2 ($SD=3.4$) occasions/month and a maximum of 8.8 ($SD=3.7$) drinks on a single occasion. RAPI and AUDIT scale scores were elevated [respectively 9.6 ($SD=7.5$) and 10.6 ($SD=4.2$) indicating an enhanced propensity to develop alcohol problems.

Room biases

Overall, 87 participants (80.6%, $SD=39.8$) exhibited a room preference at the initial room exploration test ($>10\%$ difference in time spent in each room) and this did not differ significantly between groups (Table 1). Of the 87 individuals who exhibited a room bias, 41 exhibited a bias for Room A that was not significantly different to chance (Binomial test, $p=0.7$), and room biases did not differ significantly between groups. Thus, the number of Paired group subjects assigned to receive ALC in Room A or B did not differ significantly. Among the Unpaired group, 15 subjects were (randomly) assigned to receive ALC twice in their least preferred room and 15 were assigned to receive ALC twice in their preferred room.

Change in time spent

There was a significant group difference in the change in %time in the initially least-preferred (ALC-paired) room; subjects in the Paired group spent significantly more time in the ALC-paired room after conditioning (Table 2). At debriefing, 9 subjects in the Paired group (11.5%) indicated that they had noticed the room pairings, thus analyses were repeated omitting these subjects; the findings were unchanged [mean difference=12.9%, 95% $CI=2.1-23.8$, $t(97)=2.4$ $p=0.02$]. Unpaired subjects did not notice any pairings.

The final regression model (shown in Table S1) controlled for habitual smoking, maximum drinks on a single occasion, RAPI, and AUDIT scores and enhanced the significance of conditioning (Table 2).

Alcohol responses

Mean peak BrAC (0.069mg%, $SD=0.013$) did not differ significantly across successive administrations or between groups (Table 2). ALC produced typical subjective and cardiovascular effects (Table 2, Figure 2); it increased stimulation (ARCI A, BAES

Stimulation) and euphoria (ARCI MBG) early after drinking while BrAC rose, and sedative effects (ARCI PCAG, BAES Sedation) as BrAC plateaued and began to fall. ALC also increased ratings of “feel drug effects”, “like drug effects”, “feel high”, and “urge to drink”. In comparison to NoALC, ALC increased heart rate and decreased blood pressure. Subjective and cardiovascular effects of ALC did not differ significantly between groups (Table 2) or across successive administrations.

Relationship between alcohol subjective responses and conditioning

Factor analysis of alcohol responses (AUC) revealed a four-factor solution (Table S2). Initial analyses showed four factors with eigenvalues >1 (Kaiser’s criterion) that explained 64.5% of the variance; each factor contributed 26.3, 17.9, 11.3 and 9.0% respectively. The Keyer-Meyer-Olkin measure (0.73) verified the sampling adequacy for the analysis (21). The scree plot suggested a four-factor solution as did previous studies (18, 19), thus four factors were retained in the final analysis. Factor 1 comprised POMS Vigor, Elation, Friendliness, ARCI A and MBG, and BAES Stimulation representing stimulatory and positive emotional alcohol responses. Factor 2 consisted of BAES Sedation, ARCI PCAG, POMS Fatigue and POMS Confusion representing sedative alcohol effects. Factor 3 was composed of POMS Anxiety, Anger and Depression suggesting a component providing relief from negative affect. Factor 4 comprised the four DEQ scales, “I feel some drug effects”, “I feel high”, “I like the effects I am feeling”, and “I would like more of what I consumed” representing overall drug effects with a motivational aspect (e.g. liking and desire to consume).

The final regression model (Table 3) retained Group and Group*Factor 2 (Sedation) as significant predictors of changes in %time in the ALC-paired room i.e., Sedation factor scores only predicted change in time spent among Paired group subjects.

Discussion

In this study, we sought to translate animal CPP to humans using a behavioral measure analogous to that obtained in animal experiments. In line with our hypothesis and with the pre-clinical literature, we found that individuals spent significantly more time in a context paired with alcohol in comparison to a control group. Further, we found that subjective responses to alcohol predicted preference for the alcohol-paired room which supports the hypothesis that a CPP in animals is based upon interoceptive drug effects analogous to subjective drug effects in humans. However, in contrast to our hypothesis, we found that participants who reported the greatest sedative effects from alcohol exhibited the strongest place preference. These findings add to our understanding of drug place conditioning in several ways.

Primarily, this is the first time that the objective measure of CPP obtained in animals has been directly translated to humans. Limitations of the CPP model have often been debated in the literature and this study serves to validate the paradigm and its relevance to humans. Many intriguing questions remain, for example what does the behavioral index of conditioning represent and how is it related to drug-taking? However, now that we have an analogous human model we can begin to answer these questions.

Second, the results suggest that, in our model, conditioning is related to a sedative-like component of alcohol experiences. Originally, we hypothesized that alcohol conditioning would be related to stimulant-like effects, which are generally regarded as pleasurable and have been linked to greater alcohol liking and preference (22, 23). It is often assumed that a place preference is based upon rewarding drug effects that become associated with the context through Pavlovian processes. Thus, we reasoned that stimulant-like alcohol effects may be related to the index of conditioning. By contrast, sedative alcohol effects are usually considered negative in nature, however this assumption is likely a result of the instrument used to measure the effects and may not necessarily represent the breadth of alcohol-induced sedation (24, 25). For example, most items on the BAES Sedation scale reflect negative mood states e.g. heavy-head, slow thoughts, sluggish. In fact, certain aspects of alcohol-induced sedation could be considered rewarding in terms of inducing relaxation or relieving stress. As noted by others (24, 25), in the future it will be important to differentiate between facets of sedation with positive vs. negative valence using instruments that measure multidimensional aspects of these responses (25).

It is interesting that our factor analysis of alcohol responses replicated the latent structure of alcohol subjective experiences reported by others (18, 19). In their studies with oral and intravenous alcohol among heavy drinkers, Ray and colleagues reported a similar four-factor latent structure of subjective alcohol responses with components representing Stimulation/Hedonia, Craving/Motivation, Sedation/Motor Intoxication and Negative Affect. Thus, despite the use of slightly different instruments to measure alcohol responses between studies, we were able to closely replicate the multidimensional nature of alcohol responses. Thus, our findings support this approach to conceptualizing alcohol subjective response.

An interesting aspect of our findings was that drug conditioning was evident without explicit knowledge of the drug:context contingency; ~10% of Paired group subjects noticed the drug-room pairing and the conditioning effect remained without these individuals. Previous studies suggested that explicit knowledge of the contingency between a Pavlovian stimulus and outcome is necessary to acquire a conditioned response (26, 27). Yet, here we show conditioning in absence of this knowledge. Despite differences between the studies in the conditioning stimulus (aversive noise vs. rewarding drug) and outcomes (elective attention/instrumental avoidance behavior/subjective anxiety vs. time spent), our findings challenge the idea that knowledge of drug reinforcer contingencies controls learned addictive behaviors in humans. This has important implications for the very early stages of drug use suggesting that behavior may be influenced by drug cues before individuals are aware of drug:cue contingencies.

In contrast to our hypothesis, we found that alcohol effects were consistent across repeated administrations in the same versus different contexts. In a previous study with *d*-amphetamine (8), we observed context-dependent changes in subjective drug responses. Possible explanations for the discrepancy in findings could be differences in the subject populations (inexperienced vs. experienced drug users) or simply that different drug classes were used between experiments. Future studies with *d*-amphetamine, alcohol and other drug classes will aid in interpreting these findings.

Limitations of the study include that we studied a single dose in a homogeneous sample (moderate drinkers with regular binge episodes). We chose this population because they are accustomed to consuming the alcohol doses administered during conditioning (0.8g/kg) thus minimizing aversive effects. Moreover, these individuals enjoy the effects of alcohol proven by their self-reported habitual alcohol use, maximizing our ability to produce conditioning. It is possible that different results would be obtained with light, non-hazardous drinkers, or at different doses. Another limitation is that the non-drug condition in this experiment was not an alcohol placebo. We chose to use a control beverage to maximize the difference between conditions in each context, yet this design does not allow us to assess the role of drug expectancies in conditioning. This will be important to consider in future studies, particularly because others have shown that cues become associated with drug expectancies (28, 29). Finally, we used a non-counterbalanced procedure to assign the ALC room. This approach is typical in pre-clinical studies, particularly with alcohol (10) but has been criticized for its limitations (30). Analyses of initial room preferences showed that while some individuals exhibited a bias, overall the apparatus was unbiased; equal numbers of subjects exhibited a preference for room A as room B, and the mean amount of time spent in each room at the pre-test did not significantly differ. Previously, (10) reported that alcohol CPP is obtained regardless of whether a counterbalanced or non-counterbalanced assignment procedure is used with an unbiased apparatus. Thus, in line with the pre-clinical literature, we do not believe that the non-counterbalanced assignment procedure used here significantly altered the findings. Nevertheless, this should be confirmed in future conditioning studies using a counterbalanced assignment procedure.

Overall, the present findings provide the first direct translation of animal CPP to humans using analogous procedures and outcomes, thereby validating this popular and widely used model. A reliable human conditioning model, in which drug context exposures can be carefully controlled, will be an essential tool to understand the role of conditioning processes and conditioned drug effects in drug-seeking, drug-taking and the development of dependence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Timeline of procedures during conditioning sessions.

Figure 2. Change in self-reported subjective effects of alcohol (ALC) and no alcohol (NoALC) across conditioning sessions. Data represent mean $\pm$ SEM subjective response across 3 separate ALC and NoALC sessions (left-hand axis). The shaded area represents mean change in breath alcohol concentration (BrAC, right-hand axis) across the 3 ALC sessions. The lined area represents the time spent in the conditioning room, and filled bars represent drinking periods.

Table 1

Demographic characteristics of participants. Data indicate mean (SD) unless otherwise indicated.

	Paired Group (n=78)	Unpaired Group (n=30)	Difference (p value)
Sex (% male, n)	69.2, 54	63.3, 19	
Age (years)	24.7 (3.6)	24.7 (3.5)	0.1 (0.9)
BMI (kgm ²)	22.9 (2.0)	23.2 (1.6)	-0.3 (0.5)
Race * (% , n)			
White	74.4, (43.9)	76.7, (43.0)	2.3 (0.8)
Black	5.1, (22.2)	16.7, (37.9)	11.5 (0.1)
Asian	3.9, (19.4)	3.3, (18.3)	0.5 (0.9)
Other	16.7, (3.8)	3.3, (18.3)	13.3 (0.02)
Education			
Full time Student (% , n)	21.0, (46.6)	30.0, (53.5)	9.5 (0.4)
College degree or higher (% , n)	57.7, (49.7)	50.0, (50.9)	7.7 (0.5)
Current Drug Use:			
Cigarettes/week	5.2 (10.4)	4.6 (8.4)	0.7 (0.8)
Caffeine (cups/week)	11.1 (6.2)	12.7 (21.8)	-1.6 (0.6)
Marijuana (past month)	9.4 (20.0)	10.3 (22.7)	-1.0 (0.8)
Alcohol Use (past month TLFB):			
Drinks/week	15.3 (5.7)	14.9 (9.3)	0.4 (0.8)
Binges	5.2 (3.2)	5.0 (4.0)	0.2 (0.8)
Drinking days	16.2 (5.1)	15.4 (5.9)	0.8 (0.5)
Max drinks on single occasion	8.6 (3.3)	9.1 (4.4)	-0.5 (0.5)
Alcohol Problems			
RAPI	8.9 (6.3)	11.6 (9.9)	-2.7 (0.1)
AUDIT	10.3 (4.0)	11.4 (4.6)	-1.1 (0.2)
Pre-conditioning Exploration Test			
% exhibiting room bias	80.8 (39.7)	80.0 (40.7)	0.8 (0.9)
% exhibiting bias for room A	49.2 (50.4)	41.7 (50.4)	7.5 (0.5)

* Participants self-identified their Race by selecting one or more of the following categories; American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, More than one race. Individuals in categories other than Black, White and Asian were grouped as 'Other' due to small numbers in these groups.

BMI: Body mass index; RAPI: Rutgers Alcohol Problem Index; AUDIT: Alcohol Use Disorder Identification Test; Caffeine cup; 6 oz. cup of coffee, 8 oz. of tea or 12 oz. of soda.

Table 2

Comparison of outcomes between study groups. Data indicate mean (SD).

Outcome Variable	Paired Group (n=78)				Unpaired Group (n=30)				Change Difference (95% CI), t-value, p-value	Adjusted Change Difference (95% CI), t-value, p-value
	Pre-	Post-	Change		Pre-	Post-	Change			
% Time in least preferred room	35.5 (13.5)	46.5 (21.5)	11.0 (22.3)		39.2 (16.8)	37.8 (23.4)	-1.4 (30.4)		12.4 (1.9–23.0), 2.3, 0.02	13.0 (3.0–23.0) 2.6, 0.01
Alcohol Responses (mean Peak Change _{ALC} – mean Peak Change _{NoALC})										
BrAC		0.070 (0.013)				0.068 (0.013)			Drug*Time 251.3, <0.001	Group 1.5, 0.2
ARCI MBG		2.7 (3.7)				2.8 (4)			30.3, <0.001	1.9, 0.2
ARCI A		1.4 (2.2)				1.2 (2.2)			16.2, <0.001	0.6, 0.5
BAES Stimulation		4.6 (10.3)				5.9 (10.4)			22.4, <0.001	0.4, 0.6
BAES Sedation		7.9 (9.5)				6.1 (10.4)			21.0, <0.001	1.2, 0.3
ARCI PCAG		2.3 (3.3)				1.5 (3.3)			22.2, <0.001	0.1, 0.7
DEQ “feel drug effects”		49.1 (17.8)				47.7 (25.8)			159.9, <0.001	0.03, 0.9
DEQ “like drug effects”		53.1 (25.1)				48.6 (38.1)			83.6, <0.001	0.3, 0.6
DEQ “feel high”		32.2 (21.9)				28.8 (28)			59.0, <0.001	1.5, 0.2
VAS “Urge to drink”		1.6 (2.4)				2.0 (2.7)			16.0, <0.001	0.3, 0.6
Heart rate (bpm)		8.6 (11.6)				9.6 (8.3)			20.1, <0.001	1.7, 0.2
Systolic blood pressure (mmHg)		-1.5 (16.5)				-4.2 (16)			2.2, <0.05	0.9, 0.3
Diastolic blood pressure (mmHg)		-6.5 (11.3)				-4.3 (14.1)			4.0, <0.001	3.2, 0.1

[/] Statistics for main effects and interactions of rmANOVAs described in Statistical Analyses section.

BrAC = Breath alcohol concentration.

Table 3

Final regression model of subjective response factors, Group and interaction terms upon pre- to post-conditioning change in time spent in least preferred (ALC-paired) room.

Predictor	r	β	t	R ²	R ² Change	F Change
Group	0.21	0.21	2.2*	0.08	0.10	5.3**
Group*Factor 2:Sedation	0.23	0.22	2.4*			

Key: r=partial correlation of predictor with dependent variable; β=standardized coefficient, t=statistic of each predictor variable.

Asterisks indicate levels of significance $p<0.05$, **0.01.