A Combined Alcohol and Smoking Cue-Reactivity Paradigm in People Who Drink Heavily and Smoke Cigarettes: Preliminary Findings

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Abstract

Aims: Previous studies have shown that there may be an underlying mechanism that is common for co-use of alcohol and tobacco and it has been shown that treatment for alcohol use disorder can increase rates of smoking cessation. The primary aim of this study was to assess a novel methodological approach to test a simultaneous behavioral alcohol-smoking cue reactivity (CR) paradigm in people who drink alcohol and smoke cigarettes.

Methods: This was a human laboratory study that utilized a novel laboratory procedure with individuals who drink heavily (≥15 drinks/week for men; ≥8 drinks/week for women) and smoke (>5 cigarettes/day). Participants completed a CR in a bar laboratory and an eye-tracking (ET) session using their preferred alcohol beverage, cigarettes brand and water.

Results: In both the CR and ET session, there was a difference in time spent interacting with alcohol and cigarettes as compared to water (Ps < 0.001), but no difference in time spent interacting between alcohol and cigarettes (P > 0.05). In the CR sessions, craving for cigarettes was significantly greater than craving for alcohol (P < 0.001), however, only time spent with alcohol, but not with cigarettes, was correlated with craving for both alcohol and cigarettes (P < 0.05).

Conclusion: This study showed that it is feasible to use simultaneous cues during a CR procedure in a bar laboratory paradigm. The attention bias measured in the integrated alcohol-cigarettes ET procedure predicted participants’ decision making in the CR. This novel methodological approach revealed that in people who drink heavily and smoke, alcohol cues may affect craving for both alcohol and cigarettes.

INTRODUCTION

Individuals with alcohol use disorder (AUD) are three times more likely than the general public to smoke tobacco products and those with tobacco use disorder are four times more likely to develop AUD (Grant et al., 2004). The co-use of both alcohol and tobacco has a multiplicative effect on adverse health outcomes due to the increased risks associated with using both substances (Berg et al., 2016).
A study of 259 people who smoke cigarettes that reported frequently drinking alcohol examined the subjective consequences of naturally occurring simultaneous use of alcohol and tobacco. The study utilized ecological momentary assessment techniques (Moskowitz and Young, 2006). This work showed that co-use of alcohol and tobacco products elicits enhanced craving for both substances (Piasecki et al., 2011). Similarly, the release felt from smoking may make an individual more likely to crave an alcoholic beverage. People who both drink and smoke cigarettes are also at a heightened risk not only due to the multiplicative morbidity of their substance use habits, but also due to the resistance to interventions aimed at traditional substance use populations, because the experienced cravings in these individuals are often stronger (Berg et al., 2016).

Experimental presentation of simultaneous cues has been utilized in animal studies (Larson and Sieprawska, 2002). Conditioned place preference (CPP) is a form of Pavlovian conditioning that is used to measure subject motivation due to objects or experiences (Lucke-Wold, 2011). By measuring the amount of time a subject spends with a stimulus, we can infer the subject’s liking for that specific object. Therefore, the CPP represents a subject’s preference due to continuous association with that stimulus (Bardo and Bevins, 2000) and can be translated into human laboratory studies. Furthermore, bar laboratories provide a naturalistic environment to assess alcohol-related behavior within a controlled setting (Fox et al., 2012; Thomas et al., 2012; Haass-Koffler et al., 2015, 2017; Kenna et al., 2016), where a CPP approach can be applied.

Although the CR paradigm has been used in many different domains, a single CR session combining preferred alcohol and smoking cues in a bar laboratory has its challenges when assessing simultaneous cravings. Human laboratory studies that evaluated the effects of alcohol cues on cigarettes craving and cigarettes-related cues on alcohol craving have cast mixed results (for extensive review, see Verplaetse and McKee, 2017). For example, alcohol CR procedures to assess alcohol and cigarettes craving (Gulliver et al., 1995; Rohsenow et al., 1997) have demonstrated that exposure to alcohol cues resulted in significantly greater craving for alcohol and cigarettes in individuals with AUD who also smoke. The effect of alcohol cues also resulted in increased craving for cigarettes, but did not increase alcohol craving (Colby et al., 2004) in individuals experiencing tobacco deprivation who are moderate to heavy users of cigarettes and alcohol. Virtual smoking-related cues (pictures) increase alcohol craving in individuals with AUD who also smoke (Drobes, 2002). Fixed-dose alcohol administration in individuals who smoke has been utilized to assess addictive-related behaviors such as a decreased latency to start smoking (Kahler et al., 2012).

However, these studies presented only one cue (alcohol or cigarettes-related product) and did not provide simultaneous exposure to real cues within the same laboratory procedures. A cross CR that presented alcohol and cigarettes pictures (Oliver and Drobes, 2015) has also shown that exposure to alcohol cues resulted in significantly greater craving for alcohol and cigarette in individuals with AUD who smoke. Clearly, literature has shown that alcohol and cigarette-related products influence alcohol and tobacco cravings, however, no human laboratory studies have administered simultaneous real alcohol- and cigarette-related cues in a bar laboratory to examine the subjective substance-related behavioral response.

Eye tracking (ET) has been validated as an indicator of attention, cognitive processing and memory and is widely used in tobacco control regulation (Meernik et al., 2016). With ET, an objective approach to assess and measure attentional bias can be executed. Rapid eye movements, or saccades, are used to align the high resolution fovea area of the retina with objects of interest and predict attentional shifts (Zhao et al., 2014). Additionally, volitional control of gaze position via saccades has been shown to predict choice behavior in decision making tasks. When observers are presented with multiple items and tasked to choose an item, individuals choose items that are viewed for longer overall and immediately before their response (Shimozono et al., 2003; Krajbich et al., 2010). This is consistent with the notion that attention is biased toward valuable items during visually mediated decision making. Laboratory studies using ET procedures have been utilized to evaluate the effect of alcohol and cigarette cues on selective attention and motivation. For example, ET was used to validate the reduction of attention to a neutral image during the presentation of an alcohol image (Laude and Fillmore, 2015). Also, it was shown that the eye gaze dwell time was longer in response to cigarette-related cues compared to neutral cues, confirming that there is attentional bias towards smoking-related cues (Kang et al., 2012). While selective attention can be routinely measured in the ET laboratory procedure, there are however no ET studies that have evaluated the simultaneous presentation of alcohol and cigarette-related cues.

The goal of this study was to test a novel methodological approach for a simultaneous behavioral alcohol-smoking CR paradigm in people who drink and smoke cigarettes. We paired an alcohol-cigarette CR (real cues) with an ET (virtual cues) procedure to evaluate mechanisms by which substance-associated cues influence alcohol and cigarette related responses (individuals’ substance interaction and selective attention).

We hypothesized that people who drink and smoke cigarettes in the CR will spend more time interacting with, and in the ET will pay more attention to, alcohol and/or cigarettes rather than water. Finally, we also explored if this novel integrated protocol will provide a more comprehensive human laboratory model with improved quantitative and predictive value that may help to determine which substance induces cravings for alcohol and/or cigarettes in the bar laboratory.

**MATERIALS AND METHODS**

**Study setting**

This was a human laboratory study that combined alcohol and smoking CR with an ET procedure in non-treatment seeking individuals who drink and smoke (N = 32). The CR procedure was conducted at the Center for Alcohol and Addiction Studies (CAAS) and the ET procedure was conducted at the Department of Cognitive, Linguistic and Psychological Sciences (CLPS) at Brown University, Providence, RI, USA. The study was approved by the Brown University Institutional Review Board. All participants signed an informed consent document prior to enrollment in the study.

**Inclusion and exclusion criteria**

Participants were recruited from the community using flyers, identified after a telephone pre-screening assessment and enrolled after an in-person screening in the laboratory. Males and females, age 18–65 years old, were enrolled according to the Center for Disease Control and Prevention (CDC) guidelines for heavy drinking (≥15 drinks/week for men; ≥8 drinks/week for women) (DeSalvo, 2016). Participants were eligible to participate in this study if they also smoked at least 5 cigarettes/ day (<10 light; 10–19 moderate; ≥ 20 heavy smokers) (Okuyemi et al., 2001). Participants had to have a
breath alcohol concentration of 0.00 mg/L at each session. Individuals with a self-reported diagnosis of a severe Substance Use Disorder (SUD) for a substance other than alcohol, caffeine, marijuana or nicotine were excluded from the study and if they had a history of seizures in adulthood. For the ET session, individuals had to have 20/20 normal vision or corrected to normal vision.

Study procedures

A diagram of the simultaneous (neutral, alcohol and cigarettes cues) CR and ET procedures are depicted in Fig. 1. The study consisted of the following phases: (a) telephone pre-screening, (b) signing of the consent document and in-person screening, (c) CR session in the bar laboratory at CAAS with real cues and (d) an ET session in the virtual laboratory at CLPSS with virtual cues. Both sessions were completed in the same day and were counterbalanced. Participants were asked if they prefer alcohol or cigarettes and their preferred alcoholic beverage and cigarettes brand to prepare the sessions in the laboratories.

Assessments included: a demographic questionnaire and a time life follow-back for alcohol consumption and cigarettes use during the 90 days prior to their first session (Pedersen et al., 2012); the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fifth Edition (DSM-5) (SCID-5) short form questionnaire, Alcohol Dependence Scale (ADS) and Fagerstrom Test for Nicotine Dependence (FTND) (Eter et al., 1999; Doyle and Donovan, 2009; Shankman et al., 2018). Alcohol Craving Questionnaire (ACQ) (Tiffany and Carter, 1998) and Tobacco Craving Questionnaire (TCQ-SF) (Heishman et al., 2003) were utilized to assess craving in the bar laboratory. In order to ensure that the participants understood the task and test for cognitive and neurological impairments that could influence the response to the procedure, we used a three-part explanation protocol that was standardized across all participants. First, we verbally explained the task and reiterated the instructions until we received verbal confirmation from the participant that they understood the task. Second, we showed them how to perform the task by demonstrating the stimulus setup (e.g. how to use the buttons to make their selection). Third, we had participants perform a few example trials where they used the experimental setup themselves (e.g. for the ET procedure they put their head in the chin rest and practiced the task) to ensure they felt comfortable using the setup.

The CR in the bar laboratory

The CR was comprised of four trials: two fixed-order interaction trials (T1–T2) and two free-choice interaction trials (T3–T4). The entire procedure took about 1 hour. Participants were presented with three simultaneous real cues: neutral (water), favorite brand of alcoholic drink and favorite cigarette brand for 2 minutes. They were asked to interact with (smelling and touching) each substance by following the direction of an audio recording. After exposure to T1, the cues were removed and participants completed the ACQ (Tiffany and Carter, 1998) and TCQ-SF (Heishman et al., 2003). After a 2-minute relaxation period to avoid carryover effect, a second cue fixed-interaction trial was repeated for another 2-minute session.
to expose participants to each substance and administer the craving questionnaires in a counterbalanced manner (Fig. 1A).

The three cues were then reintroduced and participants proceeded to the 2-minute free-interaction trial (T3–T4). They were asked to touch and smell any of the substances that they preferred and then they completed the ACQ and TCQ. This free-interaction trial was also repeated twice, with a relaxation period in-between T3 and T4 (Monti et al., 1999). Dependent variables measured in the CR included: time spent interacting with each cue in each free-interaction trial (T3 and T4), proportion of time spent interacting with real substances, and alcohol craving and tobacco craving. All sessions were video recorded to accurately capture and quantify the time spent interacting with each substance.

The ET procedure

Participants sat at a desk with a computer monitor located 57 cm away and a keyboard placed in front of them. Eye position was measured with an Eyelink 1000 (SR Research, Ottawa, Ontario, Canada) infrared eye tracker at 1000 Hz. To ensure that head movements did not interfere with our measurement of eye position, participants sat with their forehead and chin braced against a chin rest attached to the desk. Each trial consisted of a fixation display and a stimulus display. The fixation display consisted of a gray background and a white fixation cross located at the center of the screen. After a variable period of 250–500 ms, the stimulus display appeared and remained on the screen until an item was chosen. Each picture was located 6° above, lower left or lower right and equidistant from screen center and spanned a maximum of 6° in height and 6° in width. The ordering of picture locations was randomized in each trial (Fig. 1B).

The ET procedure took about 1 hour and consisted of four blocks of 40 trials for a total of 160 trials. For 80 trials (50%), we included pictures of the cues the participant interacted with during the CR procedure along with a picture of water. Prior to each block, participants completed a six-point eye tracker calibration routine to ensure accurate measurement of eye position. On each trial, participants performed a three-alternative forced-choice decision. Participants were instructed to view the three pictures and select one of them as if they were choosing from the actual items. Participants chose an item by pressing a button corresponding to its location on the screen. Eye position was measured during the time the stimulus display was presented. Dependent variables measured in the ET session included: time spent viewing each item and the proportion of time spent fixating on the virtual substances.

Data analytic strategy

For the CR procedure, data were analyzed to assure normal distribution. Means were calculated and compared across the three substances in the two different sessions. One-way analysis of variance (ANOVA) with repeated measures was used to evaluate the time spent interacting with each cue in each free-interaction trial (T3 and T4) in the CR session. Post hoc analyses were utilized to further assess the direction of the effect.

To integrate the time spent interacting with each substance in the CR procedure (real cues) with the time fixating on each substance in the ET procedure (virtual cues), we used the proportion of time (ranging from 0 to 1) spent with each substance. This approach was used because during the free-interaction CR procedure, participants were not always engaged with the substances using their hands, while in the ET procedure, participants performed a three-alternative forced-choice decision.

Craving was assessed by repeated measures across the entire CR session (T1–T4). Since all the cues were administered simultaneously during each trial, two fix-order trials (T1–T2) and two free-interaction trials (T3 and T4), it was not possible to capture a difference in craving due to a neutral trial (water) compared to substances (alcohol and cigarettes) trials. Alcohol craving (ACQ) was compared to cigarettes craving (TCQ) within the same trial. Two questions from the ACQ were excluded to account for two questions that were not included in the TCQ when the questionnaires were administered to participants in order to effectively correspond to data collected between the two measures. Two-way ANOVA was used to evaluate the effect of substance (alcohol or cigarettes) on craving according to trial (T1, T2, T3 and T4) and substance by trial interaction. Post hoc analyses were utilized to further assess the direction of the effect. Then, linear regressions were conducted to determine the relationship between craving of each substance and total time spent with a substance (behavioral subjective response) in the CR session. Statistical Package for the Social Sciences (v.24) (Armonk, NY, U.S.) was used to conduct the analysis.

For the ET procedure, participants were instructed to view three presented pictures and select one of them as if they were choosing from the actual cues in the bar laboratory. The images of the cues were obtained from the actual substances utilized in the CR. Eye position data were analyzed offline using custom Python scripts. Saccades were detected by using a velocity thresholding procedure. Eye position data were first smoothed by subjecting 2D velocity scalars to a second-order low-pass Butterworth filter with a cutoff frequency of 100 Hz. The resulting velocity profile was then compared against a threshold value to determine when saccades occurred throughout each trial. Fixations were defined as time points where velocity did not exceed the threshold. Saccade onset was defined as the first time point after a fixation at which velocity exceeded the threshold. Saccade offsets were defined as the final time point that velocity exceeded the threshold before a fixation. Thresholds were chosen on a trial by trial basis via visual inspection of the data to ensure accuracy of saccade detection.

To measure the time spent viewing each item, we offline defined a circular region of the screen 4° from the center of each picture location and calculated the total time in the trial the participant fixated within each region. We then averaged the total time spent viewing each picture category across all trials. We report time measures for ET analyses in milliseconds (ms) or proportion of time (0–1) as described in the analysis for the CR data. We conducted repeated measures ANOVAs. Analysis for the ET procedure was conducted using the R statistical programming language (Venables and Smith, 2013) and the ggplot2 graphing package (Wickham, 2016).

For both CR and ET analyses, Cohen’s d (d) was used to report effect size. Results were expressed as means (M) and standard error of the means. All statistical tests were two-sided, and statistical significance was accepted if P < 0.05 was obtained. Follow-up Bonferroni tests were used to correct for multiple comparisons and GraphPad Prism (v.7) (San Diego, CA) was used to generate the figures.

RESULTS

Participant characteristics

Of 51 individuals pre-screened by phone, 32 signed the informed consent, were screened in person and found to be eligible to participate.
These 32 individuals were assigned in a counterbalanced manner to the CR and the ET session (n = 17 to CR first, n = 15 to ET first) and all participants completed both sessions on the same day. There were no significant differences in demographic information between the group that started with the CR session first and the group that started with the ET session first (P > 0.05). Participants all drank alcohol heavily according to CDC criteria and most smoked moderately (44%) to heavily (38%). The majority of participants disclosed cigarettes as their self-reported preferred substance (78%) compared to alcohol. Baseline characteristics of eligible participants who completed both sessions are described in Table 1 and a flow chart during the CR and ET sessions is depicted in Fig. 1.

Primary aim: integration of alcohol and cigarettes cues

Real cues: time interacting with alcohol and cigarettes in the bar laboratory Time spent interacting with each substance in the free-interaction trials (T3–T4) in the CR session is described in Fig. 2A. There was a main effect of interacting with each substance (F(2, 60) = 4.28; ***P < 0.001), but not a main effect of trials (T3 vs T4) and there was not a significant substance by trial interaction (P = 0.73). Post hoc analyses revealed that at T3, there was a significant difference between the time spent interacting with alcohol (t(31) = 4.14; ***P < 0.001; d = 0.73) and cigarettes (t(31) = 4.00; ***P < 0.001; d = 0.70) when compared to time spent interacting with water. At T4, post hoc analyses showed a significant difference between the time spent interacting with alcohol (t(31) = 3.45; **P < 0.01; d = 0.61) and cigarettes (t(31) = 3.84; ***P < 0.001; d = 0.68) compared to time spent interacting with water. For both T3 and T4, there was no significant difference between alcohol and cigarettes (P > 0.5). This was also confirmed across subjective response as stratifying by preferred substance shows no significant difference (P > 0.05).

Virtual cues: selective attention to alcohol and cigarettes cues in the eye tracking laboratory Time fixing on each substance in the ET session is described in Fig. 2B. We excluded trials where the participant blinked or looked away from the computer screen (12.2% ± 2.4%) or trials at which no item was viewed (6.2% ± 2.1%). There was a difference in average time spent viewing each substance (F(4, 124) = 4.59; ***P < 0.001, d = 0.25). A post hoc analysis showed that time spent looking at alcohol (t(28) = 4.36, ***P < 0.001) and at cigarettes (t(28) = 4.41, ***P < 0.001) was significantly greater than time spent looking at water. There was no significant difference between alcohol and cigarettes (P > 0.05). This was true across subjective response as stratifying by preferred substance showed no significant difference (P > 0.05).

Integration of real cues and virtual cues: time in the cue reactivity and eye tracking laboratory The proportion of time spent interacting with real substances in the bar laboratory and the proportion of time spent fixating on the virtual substances in the ET laboratory is depicted in Fig. 2C.

On average at T3, participants interacted with alcohol (28% ± 5.0%) more than with cigarettes (25% ± 4.6%) or water (6.7% ± 1.7%). When we analyzed the portion of time spent interacting with either alcohol or cigarettes, there was a significant effect on substance (F(2, 60) = 8.17; ***P < 0.001). Post hoc analysis revealed that there was a significant difference between the time spent interacting with alcohol (t(31) = 3.75; ***P < 0.001) and cigarettes (t(31) = 3.20; P < 0.01) when compared to the proportion of time spent interacting with water. There was no significant difference between the proportion of time spent with alcohol (P > 0.05) when compared to the proportion of time spent with cigarettes.

On average during T4, participants interacted with cigarettes (29% ± 4.1%) more than with alcohol (22.8% ± 3.1%) or water (9.7% ± 2.6%). When we analyzed the portion of time spent interacting with either alcohol or cigarettes, there was a significant effect on substance (F(2, 60) = 8.74; ***P < 0.001). Post hoc analysis revealed that there was a significant difference between the proportion of time spent interacting with alcohol (t(31) = 2.78; P < 0.05) and cigarettes (t(31) = 4.09; ***P < 0.001) when compared to the proportion of time spent interacting with water. There was no significant difference between the proportion of time spent with alcohol (P > 0.05) when compared to the proportion of time spent with cigarettes.

In the ET procedure, participants on average chose the cigarette cue (38.9% ± 2.5%) more than the alcohol (37.2% ± 2.5%) or neutral cues (21.5% ± 2.4%). When we analyzed the proportion of time spent fixating either alcohol or cigarettes, there was a significant effect on substance (F(2, 60) = 15.14; ***P < 0.001). Post hoc analysis revealed that there was a significant difference between the time spent interacting with alcohol (t(31) = 4.48; *P < 0.05) and cigarettes (t(31) = 4.96; ***P < 0.001) when compared to time spent interacting with water. There was no significant difference between the time spent with alcohol when compared to cigarettes (P > 0.05).

Exploratory aims: craving outcomes

Results of the craving outcomes are depicted in Fig. 3. A substance (alcohol and cigarettes) × trial (T1–T4) ANOVA showed that there was a main effect of substance (F(1, 16.75) = 16.75; ***P < 0.001,
Fig. 2. Time spent interacting with each substance in the CR and ET. (A) In the CR session, there was a main effect of interacting with each substance ($F_{93} = 14.878$, $\ast \ast \ast p < 0.001$, $d = 0.498$), but not a main effect of trial (T3 vs T4) and no substance by trial interaction ($p's > 0.5$). Post hoc analyses revealed that at both T3 and T4 there was a significant difference between the time spent interacting with alcohol and cigarettes ($\ast \ast \ast p's < 0.001$) when compared to time spent interacting with water. However, there was no significant difference between the time spent interacting with each addictive substance at T3 and T4 ($p's > 0.5$). (B) In the ET session, there was a difference in time fixating each substance ($F_{84} = 14.596$, $\ast \ast \ast p < 0.001$, $d = 0.258$). Post hoc analysis showed that while there was a statistical difference between alcohol and cigarettes compared to water ($\ast \ast \ast p's < 0.001$), there was no significant difference between the time spent fixating each addictive substance ($p > 0.05$). (C) In the ET procedure, there was a significant effect of substance both during T3 ($F_{93} = 8.172$, $\ast \ast \ast p < 0.001$) and T4 ($F_{93} = 8.737$, $\ast \ast \ast p < 0.001$). Similarly, in the ET procedure there was a significant effect of substance both during T3 ($F_{93} = 15.14$, $\ast \ast \ast p < 0.001$). In both the CR and ET procedures, post hoc analysis showed that while there was a statistical difference between alcohol and cigarettes compared to water ($\ast p < 0.05$, $\ast \ast p < 0.001$), there was no significant difference between the time spent fixating with each addictive substance ($p > 0.05$). Results are expressed as the $M \pm SEM$ of the proportion of time, ($\ast p < 0.05$, $\ast \ast p < 0.01$, $\ast \ast \ast p < 0.001$).

$d = 0.213$ and a main effect of trial ($F_3 = 6.676$, $\ast \ast \ast P < 0.001$, $d = 0.097$). Substance by time interaction was not significant ($F_3 = 0.885$, $P = 0.450$, $d = 0.258$) (Fig. 3A).

The relationship between time spent interacting with alcohol and craving during the CR procedure is depicted in Fig. 3B–E. Time spent interacting with alcohol during T3 and T4 was significantly and positively correlated with alcohol craving (T3: $r_{29} = 0.367$, $\ast P < 0.05$; T4: $r_{29} = 0.468$, $\ast \ast P < 0.01$; Fig. 3B–C), as well as with cigarettes craving (T3: $r_{29} = 0.418$, $\ast P < 0.05$; T4: $r_{29} = 0.459$, $\ast P < 0.05$, Fig. 3D–E). Time spent interacting with cigarettes during T3 and T4 was not significantly correlated with alcohol or cigarettes craving ($P's > 0.05$).
DISCUSSION

The findings of this study align with previous research confirming that in individuals with SUD, there is a preference for substance-related cues over neutral cues (Carter and Tiffany, 1999). This was observed in the CR sessions of our study where more time was spent interacting with alcohol and cigarettes compared to time spent interacting with water during both T3 and T4. In this study, in an attempt to improve ecological validity, we have incorporated a virtual environment to study the hierarchical value of multiple cues (alcohol and cigarettes) to predict the behavioral response, measured by time spent interacting with each substance. Consistent with our hypothesis, the results obtained in the CR sessions were also validated in the ET sessions, as participants fixated on alcohol and cigarettes for a greater amount of time compared to their fixation on water. Data collected through the integrated CR and ET paradigm showed that measures of behavioral interaction in the CR session predicted the measure of selective attention in the
ET session and vice versa, as the sessions were counterbalanced for this study. The measure of attention towards alcohol and cigarettes compared to water in the ET session was consistent with the behavioral response across the two free-interaction trials in the CR session.

Linking a CR procedure with an ET procedure is helpful in combining the decision-making process (time interaction with substance) to selective attention (bias to substance). The ET procedure allowed us to test and validate the effect of more than one cue by using an objective approach that measures attentional bias. The ET procedure has provided us with an objective indicator of attention and cognitive processing during choice (Shimojo et al., 2003; Krajbich et al., 2010) and acted as support when deciphering preference between substance-related and neutral stimuli in the CR session. The temporal pattern of gaze behavior in a virtual environment allowed us to determine attention directed to substances compared to neutral stimuli. Furthermore, using a virtual environment (ET), incorporated with a natural environment (CR in the bar laboratory), allowed us to examine the relationship between measures of visual orienting and the motivational valence of each cue presented simultaneously.

The ET dual cues paradigm supports the primary findings of the CR study, which provides promising evidence suggesting that selective attention toward alcohol and/or cigarettes leads to an increased interaction with these substances in the bar laboratory in individuals who drink and smoke cigarettes.

The results of this study begin to show that time spent with alcohol is a greater factor for craving of both alcohol and cigarettes than time spent with cigarettes. This is further compounded by the fact that time spent with cigarettes did not correlate with craving for alcohol or cigarettes consistently in either of the two free-interaction trials. These data are in line with a human laboratory study, which showed that acute alcohol administration was able to limit the ability to resist smoking in individuals who drink heavily and smoke moderately to heavily (Kahler et al., 2014), the same population analyzed here.

Future studies utilizing a larger sample are necessary to replicate these findings and create a better representation of individuals who use alcohol and cigarettes. More specifically, the sample should be refined to include more participants who report alcohol as their preferred substance (as most participants listed cigarettes as their self-reported preferred substance). This could have been an important factor concerning how participants engaged with one substance as compared to the other during both the CR and ET sessions. Individual differences on variables such as “preference” may have skewed the results of a subjective measure associated with craving (Sayette et al., 2000).

Previous studies have stated that alcohol cues during CR can elicit craving for alcohol in individuals with AUD (Wittmann et al., 2015). This is seen in our study as time spent with alcohol in both free-interaction trials were significantly correlated with craving for alcohol. Additionally, we found that there was a correlation between time spent with alcohol and craving for cigarettes. This observation is consistent with previous work that showed that alcohol cues elicit smoking craving in individuals with AUD who also smoke (Gulliver et al., 1993; Rohsenow et al., 1997; McGrath et al., 2015). This suggests that exposure to alcohol may be a driving force for craving of both alcohol and cigarettes. This study could be further improved by administering alcohol and smelling cigarettes smoke or lighting a cigarette during the CR sessions, as olfactory cues can elicit strong craving responses. Also, an ET combined with functional magnetic resonance imaging may highlight brain regions that are affected by decision making in this population. For example, the prefrontal cortex and the primary motor cortex have been linked to the attentional bias related to smoking-related cues (Kang et al., 2012). Interestingly, the orbitofrontal cortex, the insula and the temporal gyrus have been linked to craving elicited by smoking-related cues (Kang et al., 2012).

This study should be evaluated based on its strengths and limitations. The strengths include: all individuals drank alcohol heavily and smoked cigarettes moderately to heavily, the CR was performed under a well-controlled paradigm in a bar laboratory to ensure a more naturalistic environment, and the two sessions (CR and ET) were performed the same day. Limitations include the small sample size, the different smoking groups (light, moderate and heavy) and the lack of administration of the craving questionnaire in the ET procedure.

At a behavioral pharmacology level, simultaneous CR paradigms can elucidate mechanisms by which alcohol and cigarette potentiate addictive-related behaviors since it is well-known that there is a shared reward pathway involving the nicotinic acetylcholine and the mesolimbic dopamine systems. A simultaneous CR procedure in a human laboratory also may inform clinical treatment outcomes in individuals who drink heavily and also smoke. In fact, treatment for smoking cessation can be less successful if individuals who drink and smoke are exposed to alcohol cues (Oliver and Drobes, 2015). A larger study should be developed to gain further understanding of drivers of craving in people who drink and smoke to help tailor more specific interventions since tendency to selectively attend to substances can make recovery that much more difficult.

Finally, currently there are several tools available to measure craving, but no single approach represents a ‘state-of-the-art’ instrument to measure and capture craving from both the psychological and biological perspectives (Kavanagh et al., 2013). Craving assessments include both subjective measures (questionnaires) and objective parameters (autonomic responses) with limited validity (Haass-Koffler et al., 2014). With this work, we could develop and test more objective tools that can assess attention to multiple cues in order to develop and validate specific CR paradigms for comorbid populations that may have stronger experimental and clinical value.

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CONFLICT OF INTEREST
The authors listed above have no conflict of interest related to this work. There are no relationships between financial supporters or other organizations.
and these authors that could have influenced the study and results. The data that support the findings of this study are available on request from the corresponding author (CLH-K).

AUTHORS CONTRIBUTION

C.L.H.-K. and R.D.S. designed the alcohol laboratory study; J.W. and J.-H.S. designed the ET study; C.L.H.-K. provided funding used to conduct both studies. R.D.S. and J.W. conducted the study, including collection of the research data. C.L.H.-K., R.D.S. and J.W. conducted all the analyses. C.L.H.-K., J.-H.S., J.P.W. and R.D.S. participated in the interpretation of data for important intellectual contents. E.R.A. contributed through questionnaire design and data interpretation. R.D.S. and J.W. wrote the first draft of the manuscript. C.L.H.-K., J.-H.S. and R.D.S. contributed to the writing of the manuscript. All authors approved the final version of the manuscript.

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