Alcohol Attentional Bias Is Associated With Autonomic Indices of Stress-Primed Alcohol Cue-Reactivity in Alcohol-Dependent Patients

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When alcohol-dependent individuals are exposed to drinking-related cues, they exhibit psychophysiological reactivity such as changes in heart rate variability (HRV) and skin temperature. Moreover, such alcohol cue-reactivity may co-occur with attentional bias (AB) toward alcohol cues. In turn, stress may promote appetitive responses by exacerbating these autonomic and attentional factors. Although cue-reactivity paradigms have been used for decades to probe such automatic appetitive processes in persons with alcohol-use disorders, less is known about the attentional correlates of alcohol cue-reactivity. In this study, alcohol-dependent adults (N = 58) recruited from a residential treatment facility completed a spatial cueing task as a measure of alcohol AB and affect-modulated cue-reactivity protocol. Multiple linear regression analyses revealed that alcohol AB was significantly positively associated with para-sympathetically mediated HRV and finger temperature slope and inversely associated with sympathetically mediated HRV during stress-primed alcohol cue-exposure, independent of alcohol dependence severity, time in treatment, alcohol craving, and perceived stress. Study findings suggest that alcohol AB is linked with physiological cue-reactivity and that different attentional strategies are associated with distinct profiles of autonomic responses that may ultimately index or confer additional risk for alcohol dependence.

Keywords: alcohol dependence, attention bias, cue reactivity, heart rate variability, skin temperature

It is known that recurrent alcohol use results in heightened alcohol approach motivations evoked by conditioned stimuli associated with drinking, such as the sight of a bar or a familiar “drinking buddy.” Exposure to such cues can result in a conditioned appetitive response coupled with a “wanting/craving” for alcohol (e.g., O’Brien, Childress, Ehrman, & Robbins, 1998). This response plausibly imparts compulsivity to alcohol-seeking behaviors, motivating the alcohol-dependent person to consume alcohol even after extended periods of abstinence and in spite of counter-vailing reasons to remain abstinent (Robinson & Berridge, 2008), particularly under conditions of stress and negative affect (Garland, Boettiger, & Howard, 2011). Neural sensitization to the rewarding effects of alcohol and alcohol-related cues may promote the compulsion to drink (Robinson & Berridge, 2001). As such, cues associated with drinking can elicit a constellation of somatic sensations (Stewart, De Wit, & Eikelboom, 1984) that co-occur with broad array of physiological reactions (i.e., cue reactivity), including autonomic, corticolimbic, corticostriatal, and neuroendocrine responses (Heinz, Beck, Grusser, Grace, & Wrase, 2009; Sinha et al., 2009).

Physiological cue-reactivity appears to be mediated in part by activation of a network of central (e.g., prefrontal cortex [PFC], anterior cingulate cortex [ACC]) and autonomic nervous system structures, and, as such, may be evidenced by changes in visceral and peripheral parameters. One autonomic index that may reflect attentional and motivational processing of alcohol cues is heart rate variability (HRV). High-frequency HRV, observed in the beat-to-beat modulation of heart rate by the vagus nerve, is thought to be parasympathetically mediated, whereas low-frequency HRV is held to be a product of sympathetic and parasympathetic influences (Berntson et al., 1997). The ratio of low- to high-frequency HRV is considered to reflect predominately sympathetic nervous system activation (Malliani, 2005). HRV is governed by a network of central (e.g., PFC and ACC) and autonomic structures, which exert regulatory influences over perturbations to visceral homeo-
stasis, such as those that might be evoked in abstinent alcohol-dependent individuals exposed to alcohol cues (Thayer & Lane, 2000, 2009). Increased HRV during exposure to emotionally salient cues may indicate regulation of stress (Butler, Wilhelm, & Gross, 2006; Pu, Schmeichel, & Demaree, 2010) or appetitive responses (Segerstrom & Nes, 2007). Yet, HRV can also be elicited as a classically conditioned response to conditioned stimuli (Stockhorst, Huening, Ziegler, & Scherbaum, 2011). Studies reveal cue-elicited increases in HRV associated with craving for addictive substances such as methamphetamines and nicotine (Col bertson et al., 2010; Erblich, Bovbjerg, & Sloan, 2011) and increased HRV during exposure to food cues, which abates upon consumption of a meal (Nederkoorn, Smulders, & Jansen, 2000). Similarly, alcohol-dependent persons participating in alcohol cue-reactivity paradigms evince elevated HRV (Ingjaldsson, Laberg, & Thayer, 2003; Rajan, Murthy, Ramakrishnan, Gangadhar, & Janakiramaiyah, 1998).

Insofar as the autonomic nervous system governs cardiovascular function to mobilize energy resources in service of motivated goal attainment (Gendolla & Richter, 2006), it directs blood flow to the viscera and throughout the body. As such, alterations in blood flow to the periphery lead to changes in skin temperature that are reflective of autonomic activation and may therefore serve as an index of cue-reactivity. In that regard, several studies indicate that exposure to alcohol cues is associated with changes in skin temperature (Lundahl & Lukas, 2001; Newlin, 1986; Turkkan, McCaul, & Stitzer, 1989).

Moreover, cue-reactivity may be modulated by stress (Fox, Bergquist, Hong, & Sinha, 2007; Sinha et al., 2009). Stress alters sensitization to pharmacological reward and cues signaling such reward (Koob, 2008). Further, drinking in response to stressors leads to formation of behavior-outcome associations that motivate further alcohol consumption (Elsner & Hommel, 2001), as the palliative effects of alcohol negatively reinforce drinking behaviors. Initially, stress-precipitated drinking may be motivated by explicit expectancies that alcohol will provide relief from stress and negative emotion (Cooper, Frone, Russell, & Mudar, 1995). Over time, recurrent drinking under stressful circumstances can lead to stimulus-response habits that may not be affected by aversive consequences (Dickinson, Wood, & Smith, 2002). Inasmuch as stress biases responses toward habitual behaviors that are resistant to changes in outcome contingencies (Dias-Ferreira et al., 2009), stress coupled with alcohol cues may precipitate drinking by evoking automatized, associative networks that encode information for the nonvolitional execution of drinking behaviors (Garland, Boettiger, & Howard, 2011; Schwabe, Dickinson, & Wolf, 2011; Tiffany, 1990).

Although cue-reactivity paradigms have been used for decades to probe such automatic appetitive processes in persons with alcohol-use disorders (Carter & Tiffany, 1999), less is known about the attentional correlates of alcohol cue-reactivity. This lacuna may result from the fact that many cue-reactivity protocols involve passive exposure to alcohol-related stimuli, such as passive viewing of alcohol-related photographs. These paradigms, in themselves, cannot be used to ascertain the extent to which observed changes in physiological response are a function of how alcohol cues are attended and processed. Elucidating linkages between attentional functions and alcohol cue-reactivity is of importance to the study of psychopharmacology in light of the neurobehavioral coupling between attention and appetitive motivation (Lang, Bradley, & Cuthbert, 1997). Attention allows salient subsets of data to gain preeminence in the competitive processing of neural networks at the expense of other subsets of data (Desimone & Duncan, 1995). Thus, attended stimuli receive preferential information processing and are likely to govern behavior. The goal relevance of a stimulus guides attention to select and distinguish it from the environmental matrix in which it is embedded (Corbetta & Shulman, 2002). Attention gates perceptions of the stimulus for further cognitive processing (including evaluation of its motivational relevance) and ultimately, for execution of approach behaviors in response to appetitive objects or avoidance behaviors in response to aversive ones. Thus, depending on its salience to the survival of the organism, the object of attention elicits the motivation to approach or avoid, while the resultant emotional state, as the manifestation of approach or avoidance motivations, tunes and directs attention (Friedman & Förster, 2010; Lang & Bradley, 2011).

The drive to consume alcohol can also be regarded as a motivational state (Baker, Morse, & Sherman, 1987) and several theories postulate a role of attention in alcohol-use disorders and approach motivation (Franken, 2003; Garland, Boettiger, & Howard, 2011). For example, Franken (2003) suggests that alcohol cues are motivationally salient for alcohol-dependent individuals and are consequently able to capture their attention, a phenomenon known as alcohol attentional bias (AB). Alcohol AB, which has been associated with craving and increased alcohol consumption (Field, Munafò, & Franken, 2009), is evidenced on dot probe tasks by shorter reaction times (RTs) to probes replacing alcohol photos relative to probes replacing neutral photos (Field & Cox, 2008). In spite of reports that heavy drinkers have AB toward alcohol cues that likely reflect approach motivations (hereafter referred to as an approach bias, Field, Schoenmakers, & Wiers, 2010), other research has identified AB away from such cues (hereafter referred to as an avoidance bias) among abstinent alcohol-dependent persons in treatment that presumably reflect the motivation to avoid alcohol (Stormark, Field, Hugdahl, & Horowitz, 1997; Townsend & Duka, 2007). Hence, the presence of such alcohol approach or avoidance biases may be indicative of the degree of appetitive drive toward alcohol, the degree to which an individual attempts to inhibit that drive, or an aversive response to alcohol. Stress may also impart motivation to consume alcohol by biasing attention toward alcohol-related cues that have been conferred incentive salience by recurrent drinking (Field & Quigley, 2009; Garland, Boettiger, & Howard, 2011). Further, it has been hypothesized that autonomic indices like HRV and skin temperature may also reflect both attentional and motivational processes in alcohol cue-reactivity (Carter & Tiffany, 1999).

As such, the aim of the present study is to use two autonomic measures, HRV and skin temperature, to characterize individual differences in stress-primed alcohol cue-reactivity between persons with alcohol approach and avoidance biases as assessed by a spatial cueing task. Because stress is known to precipitate relapse, we were interested in investigating the association between stress-primed alcohol cue responses and the alcohol attentional bias. We examined these responses in a sample of alcohol-dependent adults in residential treatment. Because participants had been treated for alcohol dependence, we expected substantial heterogeneity of AB responses: some individuals might have learned to avoid tempta-
tion by directing their attention away from alcohol (manifested as an avoidance bias), whereas others might have continued to harbor unchecked urges to drink indexed by alcohol approach bias in spite of extensive treatment. Given the characteristic psychophysiological signatures of appetitive versus defensive emotional responding (Lang & Bradley, 2011; Lang, Bradley, & Cuthbert, 1998), we hypothesized that alcohol-dependent patients with approach biases would exhibit predominately parasympathetic physiological cue-responses, whereas those with avoidance biases would exhibit cue-responses characterized by sympathetic dominance.

Methods

Sample Characteristics and Study Design

Study participants had resided for ≥18 months in a treatment facility serving persons with alcohol and substance-use disorders. Treatment consisted of participation in a therapeutic milieu, psychoeducation on topics related to addiction, process therapy groups, and coping skills training. For clinical and logistical reasons, facility administrators required that residents had completed 18 months of treatment to participate in the study. Notably, 18 months marked the time of transition to employment and residence outside of the facility and thus represents a time of heightened stress and vulnerability to relapse. Potential participants met study inclusion criteria if they were ≥18 years old and satisfied lifetime Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM–IV) alcohol dependence criteria as assessed with a semistructured psychiatric interview adapted from section I of the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Interviews were conducted by a licensed psychiatrist and licensed clinical social worker trained in making DSM–IV substance use and other psychiatric disorder diagnoses. Potential participants were recruited through flyers, direct referrals from facility staff, and through an informational presentation about the study made at the treatment facility. A total of 71 residents were eligible for study participation. Of these residents, 10 declined to participate, and three did not meet DSM–IV criteria for lifetime alcohol dependence. Participants were paid $25 in remuneration for their participation. This study was approved by the University of North Carolina at Chapel Hill Institutional Review Board and was performed in accordance with the ethical standards embodied in the Declaration of Helsinki. All participants gave informed consent prior to their inclusion in the study.

Study participants were 58 alcohol-dependent adults who had resided for an average of 22.2 (SD = 3.6) months in the facility. The mean participant age was 39.8 years old (SD = 9.3). More than half of the sample was African American (55.2%), with the rest of the sample identifying themselves as Caucasian (39.7%), Latino/a (3.5%), or Native American/Alaskan Native (1.6%). Most participants were men (81%). With regard to personal income in the year before entering treatment, 56.9% had earned $20,000, 29.3% had earned $20,000 to $40,000, and 13.8% had earned $40,000. The mean total Alcohol Use Disorders Identification Test (AUDIT) score for the sample was 32.4 (SD = 5.6), and the mean number of standard alcoholic drinks consumed per day in the year before entering treatment was 18.9 (SD = 10.8), indicating that participants evidenced significant levels of alcohol dependence. All participants reported continuous abstinence from psychoactive substances during their residence in the treatment facility. Reports of abstinence were corroborated by random urinalyses conducted at the treatment center on an as-needed basis, as well as through daily observation by program staff.

During a single, hour-long assessment period conducted at the residential treatment facility, study participants first completed a computer-based spatial cueing task as a measure of alcohol AB and next participated in an affect-modulated cue-reactivity protocol intended to induce stress prior to alcohol cue-exposure (Cheetham, Allen, Yucel, & Lubman, 2010). All measures were administered in the same order across participants in a single session.

Measures

Alcohol attentional bias. A spatial cueing task was used to measure alcohol AB. This task was generated in E-Prime 2.0 (PST Inc., Pittsburgh, PA) and was presented on an IBM T60 laptop with a 15-in. screen. Each trial began with a fixation cross presented for 500 ms. Next, two grayscale images appeared side by side: one image was alcohol-related, and the other was neutral in content. The pair of images was presented for 2000 ms. Left/right position of the alcohol images was randomized and counterbalanced across 20 practice trials and 160 trials. A target probe (two dots) replaced one of the images, and a distracter probe (one dot) replaced the other image after a 50-ms interstimulus interval. Probes appeared for 100 ms. Participants were instructed to indicate the location of the target by responding with a left or right button press on a keypad. Target probes randomly replaced alcohol and neutral cues with equal frequency.

In this task, emotionally salient (i.e., alcohol-related) and neutral images serve as potential cues for the spatial location of the subsequent target, which must be discriminated from the distractor. Some parameters of the task used in the present study vary slightly from the visual probe tasks often used to assess alcohol AB, yet accord with well-validated cognitive neuroscience methods used to probe attentional processes. In light of research that demonstrates attentional effects are more robust when targets co-occur with distracters relative to when targets are presented alone (Carrasco, 2006), in our spatial cueing task, stimuli (i.e., one or two dots) appear in both cue locations. The design of this task requires participants to discriminate between target and distracter probes, thereby enhancing power to resolve attentional effects elicited by alcohol cues and eliminating confounding contributions of automatic, reflexive attention driven by bottom-up visual processing that are not related to the emotional salience (e.g., alcohol-relatedness) of the images (Hopfinger & Maxwell, 2005; Theeuwes, 1991). Among persons with alcohol approach biases, the use of two probes may lead to longer RTs when attention is incorrectly cued to a nontarget location by an emotionally salient alcohol stimulus and greater facilitation of responding when attention is correctly cued to the target location by such a stimulus. Although the use of two probes may add an additional mental task compared to single-probe tasks, other forms of discrimination tasks, such as those requiring participants to report the direction of a target arrow, have been widely and successfully used to assess alcohol AB (e.g., Field & Powell, 2007). Indeed, the construct validity of this task was supported in a recent investigation of alcohol-dependent individuals, which found that AB for alcohol cues
presented for 2000 ms was significantly associated with the number of alcoholic drinks consumed per day in the year prior to entering treatment, \( r = .33, p = .02 \), and marginally correlated with the AUDIT total score, \( r = .26, p = .06 \) (Garland, Boettiger, Gaylord, West Channon, & Howard, 2011).

Alcohol stimuli included 13 photographs of alcoholic drinks (i.e., liquor, beer, wine, etc.), as well as seven photos of persons drinking alcohol. Neutral stimuli included 13 photos of kitchen items and seven photos of persons in kitchen scenes. Stimulus sets were matched in terms of human content and figure-ground relationships. In addition, stimuli were analyzed with respect to spatial frequency to ensure they did not differ significantly in terms of their basic visual properties (e.g., contrast and brightness), which could otherwise influence bottom-up visual processing and elicit reflexive attention. Stimulus sets did not significantly differ on measures of spectral peak (Neutral: 0.0180, Alcohol: 0.0176, \( t_{(38)} = 0.383, p = .704 \)) or spectral width (Neutral: 59.20, Alcohol: 59.29, \( t_{(38)} = -0.027, p = .979 \)).

Psychophysiological cue-reactivity. Psychophysiological responses to stress-primed alcohol cues were measured by an affect-modulated, cue-reactivity protocol. First, electrocardiogram (ECG) electrodes were attached to participants’ right and left pectoral muscles, and a skin temperature thermistor was attached to the palmar surface of the distal phalange of the forefinger on the participant’s nondominant hand. A Biopac MP150 data acquisition system (Biopac Systems, Goleta, CA) acquired raw ECG and skin temperature data sampled at a frequency of 500 Hz. Participants were instructed to remain motionless, silent, and “not think about anything in particular” for a 5-min baseline. Next, stress cues consisting of 30 aversive photographs from the International Affective Picture System were serially presented on a 15-in. monitor for 10 s each (total duration: 5 min). Participants were asked to fixate on the image stream while holding as still as possible. Next, 30 photographs of alcoholic beverages (12 that included individuals drinking or preparing to drink alcohol) were serially presented for 10 s each (total duration: 5 min), and participants were again instructed to remain motionless and fixate on the image stream.

Subjective cue-reactivity. During the cue-reactivity protocol, after a 5-min resting baseline and again after 5 min of alcohol cue exposure, participants were asked to rate current levels of stress and craving on two, 10-point visual analogue scales (0 = not at all, 9 = extreme). Participants were asked the following: “How stressed do you feel right now?” and “If your favorite alcoholic drink were in front of you, how strong of an urge to drink it would you feel right now?”

Alcohol craving. Subjective alcohol craving was measured with the Penn Alcohol Craving Scale (PACS-10, \( \alpha = .91 \)) (Flannery et al., 2001). Participants used a 7-point scale to indicate craving frequency and intensity over the past week on items like “How often have you thought about drinking or about how good a drink would make you feel?” and “At its most severe point, how strong was your craving?”

Perceived stress. The 10-item Perceived Stress Scale (PSS-10, \( \alpha = .85 \)) was used to assess on a 5-point scale how often (0 = never, 4 = very often) in the past month participants found their lives unpredictable, uncontrollable, and overwhelming (Cohen, Kamarck, & Mermelstein, 1983) and included items like “How often have you felt nervous and ‘stressed’?” and “How often have you felt that you were on top of things?”

Alcohol dependence severity. The AUDIT was used to measure severity of alcohol dependence. This widely used, internally consistent measure (\( \alpha = .80 \)), evidences convergent validity with biomarkers of alcohol consumption and predictive validity for distal consequences of drinking (Allen, Litten, Fertig, & Babor, 1997).

Data Analysis

With regard to the analysis of HRV cue-reactivity, R-R intervals were measured in the raw ECG data using automated routines in Nevrokard aHRV software (Medistar, Stegne, Ljubljana, Slovenia). The R-wave file was then visually inspected to correct mis-identified or omitted R-waves. Kubios 2.0 (BioSignal Analysis and Medical Imaging Group, University of Finland) was used for time-domain analysis of R-R intervals. The square root of the mean squared differences between successive R-R intervals (RMSSD) was selected to estimate parasympathetically mediated HRV. Kubios 2.0 was also used for spectral analysis, applying a fast Fourier transform to extract high-frequency (HF) and low-frequency (LF) HRV in the .15–.40- and .04–.15-Hz frequency bands, respectively, from a de-trended, end-tapered interbeat interval time series (Berntson et al., 1997). HFHRV was used as another index of parasympathetically mediated HRV. The LF/HF ratio was selected to estimate sympathetically mediated changes in HRV (Malliani, 2005; Ori, Monir, Weiss, Sayhouni, & Singer, 1992). Mean HRV was computed for the 5-min baseline and 5-min alcohol cue-exposure periods.

With regard to analysis of skin temperature cue-reactivity, we computed slope values to describe the rate of change in finger temperature over the 5-min alcohol cue-exposure period with the formula

\[
\text{Finger Temperature Slope} = \frac{f(x^*) - f(x^0)}{x^* - x^0}
\]

where \( f(x^0) \) is finger temperature at the beginning and \( f(x^*) \) is finger temperature at the end of the 5-min alcohol cue-exposure period. This slope measure allows us to more precisely represent change over time than examining differences in skin temperature averaged over the 5-min baseline and cue-exposure periods. The unit of measure for slope is Fahrenheit per seconds, but for ease of interpretability, we rescaled the slope measure to Fahrenheit per minute. A negative slope value indicates that temperature decreased over the 5-min alcohol cue-exposure period, whereas a positive slope value indicates that temperature increased over the period.

RT differences on the spatial cueing task were assessed with paired \( t \) tests. Multiple linear regression was utilized to examine
the extent to which alcohol AB predicted changes in HRV parameters (RMSSD, LF/HF ratio), skin temperature slope, and subjective cue-reactivity after controlling for a set of covariates conceptually linked with cue-reactivity (alcohol-use disorder severity, duration in residential treatment, alcohol craving, and perceived stress). To assess reactivity in HRV and skin temperature parameters to cue-exposure, baseline levels were entered into regression equations as covariates. Potential multicollinearity issues were screened by examining the variance inflation factor of each variable. Some values were missing because of random technical difficulties with the psychophysiological cue-reactivity paradigm.

Results

Spatial Cueing Task

On the spatial cueing task, mean accuracy of target detection was 97.2% ± 0.4%. Mean RT to target probes replacing neutral cues was 585.3 ± 123.9 ms, whereas mean RT for target probes replacing alcohol cues was 587.7 ± 120.8 ms. The mean difference in RT to target probes replacing alcohol cues and neutral cues was not statistically significant according to a paired t test, t(53) = .96, p = .34. Inspection of the raw data revealed that 30 participants had an AB < 0, indicative of a bias away from alcohol cues (M = −14.78 ± 13.33 ms), whereas 25 participants had an AB > 0, indicative of a bias toward probes replacing alcohol photos (M = +17.30 ± 22.63 ms). For descriptive purposes, we divided sample intro groups of persons with AB toward alcohol (alcohol approach group) and AB away from alcohol (alcohol avoidance group).

Effects of the Cue-Reactivity Paradigm on Subjective and Psychophysiological Cue- Reactivity

Paired t tests indicated that participation in the stress-primed alcohol cue-reactivity paradigm was associated with significant increases in stress and alcohol craving, t(54) = 4.81, p < .001, and t(54) = 4.49, p < .001, respectively. We computed a difference score by subtracting baseline from alcohol cue-exposure levels of stress and craving to calculate subjective cue-reactivity indices. Pearson product–moment correlations were used to examine associations between AB group and subjective cue-reactivity. Alcohol AB was not significantly associated with cue-elicted increases in stress or craving. We also used multiple linear regression to predict subjective cue-reactivity from alcohol AB, controlling for alcohol-use disorder severity, duration of treatment, alcohol craving, and perceived stress. In these multivariate analyses, alcohol AB remained a nonsignificant predictor of cue-elicted changes in stress and craving.

There were no significant mean effects1 of the cue-reactivity paradigm on HRV parameters or finger temperature slope (p > .10). Visual inspection of the raw data revealed variability in HRV and finger temperature responses to the cue-reactivity paradigm. Some participants exhibited a cue-elicted increase in HRV indices and skin temperature, whereas others exhibited decreases in these parameters. This suggested there might be individual differences that explain the variance in reactivity. Subsequently, we implemented individual difference analyses to explore which factors might explain the heterogeneity in psychophysiological cue-reactivity across the sample. These analyses were ex post facto and exploratory in nature.

Alcohol AB Predicts HRV Cue-Reactivity

We ran a series of multiple regression models to examine the association of alcohol AB with HRV parameters, controlling for a set of clinically relevant covariates. Descriptive statistics of study variables are reported in Table 1 and regression parameters are reported in Table 2. First, we tested a multiple regression model where alcohol AB, baseline RMSSD, alcohol-use disorder severity, duration of treatment, alcohol craving, and perceived stress were entered simultaneously as possible predictors of RMSSD during alcohol cue-exposure. In this model, alcohol AB (β = .12, p = .04, ƞ2 = .10), alcohol craving (β = −.12, p = .03, ƞ2 = .12), and baseline RMSSD (β = .90, p < .001, ƞ2 = .88) were significant predictors of RMSSD during cue-exposure.

Next, we tested a multiple regression model where the aforementioned variables were entered simultaneously as predictors of HFHRV during alcohol cue-exposure. In this model, alcohol AB (β = .23, p = .03, ƞ2 = .11) and baseline HFHRV (β = .70, p < .001, ƞ2 = .53) were the only statistically significant predictors of HFHRV during cue-exposure, indicating that alcohol AB accounted for a significant portion of variation in HFHRV reactivity after controlling for the influence the clinically relevant variables listed above.

Lastly, we tested a multiple regression model predicting LF/HF during alcohol cue-exposure from alcohol AB, controlling for baseline LF/HF and the same set of covariates listed above. In this model, alcohol AB was the only statistically significant predictor of LF/HF during alcohol cue-exposure (β = −.59, p < .001, ƞ2 = .40).

For descriptive purposes, we depict HRV responses by the dichotomized AB variable (approach and avoidance groups) in Figure 1.

1 The association between AB group on RMSSD reactivity to stress-primed alcohol cues was tested with a 2 (AB group: approach bias group, avoidance bias group) × 2 (time: baseline, alcohol cue-exposure) repeated-measures ANOVA. Although there was no main effect of time, F(1, 46) = 2.48, p = .12, or group F(1, 46) = .67, p = .42, there was a significant interaction between AB group and time, F(1, 46) = 5.04, p = .03. This interaction effect indicated that persons in the alcohol approach group had a significantly different HRV reaction to stress-primed alcohol cue exposure than persons in the alcohol avoidance group. Follow-up paired t tests indicated that persons in the alcohol approach group experienced a mean increase in HRV from baseline through alcohol cue exposure, t(18) = −2.07, p = .05. In contrast, persons in the alcohol avoidance group did not experience significant change in HRV from baseline through alcohol cue exposure, t(28) = .62, p = .54. See Figure 1 for a depiction of differences in HRV reactivity between alcohol approach and avoidance groups. The association between AB group on skin temperature slope during alcohol cue-exposure was tested with one-way ANOVA. Alcohol approach-avoidance group significantly predicted skin temperature slope during alcohol cue-exposure, F(1, 31) = 10.50, p = .003, such that on average, persons with alcohol approach bias exhibited increasing skin temperature during cue-exposure, whereas persons with alcohol avoidance bias exhibited decreasing in skin temperature during cue-exposure. There were no significant Group × Time interactions on the HFHRV of LF/HF variables.
Table 1
Clinical and Psychophysiological Characteristics of a Sample of Alcohol-Dependent Adults in Residential Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months in residential treatment</td>
<td>22.24 (3.58)</td>
</tr>
<tr>
<td>Alcohol craving - PACS</td>
<td>5.00 (4.83)</td>
</tr>
<tr>
<td>Alcohol dependence severity - AUDIT</td>
<td>32.36 (5.56)</td>
</tr>
<tr>
<td>Perceived stress - PSS-10</td>
<td>16.81 (6.38)</td>
</tr>
<tr>
<td>Baseline stress</td>
<td>.83 (1.49)</td>
</tr>
<tr>
<td>Stress after alcohol cue exposure</td>
<td>1.87 (2.44)</td>
</tr>
<tr>
<td>Baseline craving</td>
<td>1.42 (1.58)</td>
</tr>
<tr>
<td>Craving after alcohol cue exposure</td>
<td>2.58 (2.81)</td>
</tr>
<tr>
<td>Baseline RMSSD</td>
<td>38.66 (33.93)</td>
</tr>
<tr>
<td>RMSSD during alcohol cue exposure</td>
<td>40.71 (35.29)</td>
</tr>
<tr>
<td>Baseline HFHRV</td>
<td>24.95 (18.63)</td>
</tr>
<tr>
<td>HFHRV during alcohol cue exposure</td>
<td>25.26 (16.24)</td>
</tr>
<tr>
<td>Baseline LF/HF Ratio</td>
<td>2.28 (2.38)</td>
</tr>
<tr>
<td>LF/HF Ratio during alcohol cue exposure</td>
<td>2.92 (3.85)</td>
</tr>
<tr>
<td>Baseline finger temperature slope</td>
<td>.03 (2.24)</td>
</tr>
<tr>
<td>Finger temperature slope during alcohol cue exposure</td>
<td>–.02 (.17)</td>
</tr>
</tbody>
</table>

Note. PACS = Penn Alcohol Craving Scale; AUDIT = Alcohol Use Disorders Identification Test; PSS-10 = Perceived Stress Scale 10; RMSSD = square root of the mean squared differences between successive R-R intervals; HRV = heart rate variation; LF and HF = low and high frequency, respectively.

Alcohol AB Predicts Skin Temperature Cue-Reactivity

We estimated a multiple regression model (see Table 2) to examine the association of alcohol AB with finger temperature slope during alcohol cue-exposure, controlling for duration of residential treatment, alcohol-use disorder severity, alcohol craving, and perceived stress. Regression parameters are reported in Table 2. In this model, alcohol AB ($\beta = .40$, $p = .04$, $\eta^2 = .32$) and alcohol craving ($\beta = .40$, $p = .03$, $\eta^2 = .16$) significantly predicted finger temperature slope during cue-exposure.

Discussion

Study results indicated that alcohol AB as measured by a spatial cueing task was significantly positively associated with parasympathetically mediated HRV and finger temperature during stress-primed alcohol cue-exposure and inversely was associated with sympathetically mediated HRV during cue-exposure. To our knowledge, this study is the first to demonstrate significant relationships between alcohol AB, HRV, and skin temperature among persons diagnosed with alcohol dependence participating in an affect-modulated cue-reactivity paradigm.

Higher levels of alcohol AB were associated with greater parasympathetically mediated HRV (i.e., RMSSD and HFHRV) during stress-primed alcohol cue-exposure. This finding may be explained by the neurovisceral integration model (Thayer & Lane, 2000), which holds that HRV reflects the activation of circuits within the central autonomic network that subserve the regulation of attention (Thayer, Hansen, Saus-Rose, & Johnsen, 2009). During exposure to attention-demanding, motivationally salient stimuli, the PFC and ACC exert downstream influences on HRV (Lane et al., 2009). These influences are thought to be mediated by circuits extending from cortical structures to parasympathetic preganglionic projections from the nucleus ambiguous and dorsal motor nucleus of the vagus that output on the sinoatrial node of the heart (Bertnson et al., 1997). As such, the positive association between alcohol AB and parasympathetic HRV cue-responses may reflect neurocognitive processing of cues associated with reward. Indeed, rats in an appetitive conditioning paradigm exposed to a conditioned stimulus associated with the “reward expecting state” exhibited significant increases in high-frequency, vagally mediated HRV (Inagaki, Kuwahara, & Tsubone, 2005). Alternatively, the observed pattern of HRV reactivity may indicate the presence of severe perturbations from visceral homeostasis that require robust parasympathetic regulation via intensive vagal activation. It is possible that study participants exhibiting alcohol approach biases were highly reactive and perturbed by stress-primed alcohol cues and as such may have exhibited greater central autonomic network activation when processing appetitive stimuli (reflected in increased parasympathetically mediated HRV) than persons who were less affected by such cues.

In contrast, lower levels of alcohol AB were associated with reduced parasympathetically mediated HRV and a higher LF/HF ratio in response to stress-primed alcohol cue-exposure. One possible interpretation is that participants who tended to avoid looking at alcohol cues during the spatial cueing task may have had a learned aversion to alcohol and consequently diverted their attention when presented with photographs of alcohol during the cue-reactivity paradigm. Attentional avoidance may have led to less stimulus exposure and consequently, less cognitive processing of alcohol cues as reflected by attenuated HFHRV reactivity. Although initial, rapid attentional orienting to an emotional cue may initiate neural computations in subcortical regions mediating incentive salience attributions, later diversion of attention away from the cue may reduce higher-order, elaborative processing, which is theorized to promote fully conscious appetitive responses (Kavanagh, Andrade, & May, 2005).

However, our finding of significant increases in subjective stress and craving during alcohol cue-exposure irrespective of alcohol AB seems to argue against this interpretation. The lack of association between AB and craving during the cue-reactivity paradigm might be explained by social desirability bias (Marissen, Franken, Hendriks, & van den Brink, 2005), as participants were in treatment and may not have been forthcoming with reports of craving.

Notably, the relations between AB and RMSSD craving on the one hand, and craving and RMSSD on the other hand, were in opposite directions. Several theories suggest that AB and craving are positively related constructs. Although a recent meta-analysis confirms this association (Field et al., 2009), the correlation is low, indicating that although they are associated, AB and craving are distinct constructs that might be differently related to RMSSD. This could be interpreted as a dissociation between self-reported measures and psychophysiological findings. We observed such dissociation in our data for all the psychophysiological measures except for skin temperature. Dissociation between self-reported craving and psychophysiological cue-reactivity data has been reported by others (e.g., Carter & Tiffany, 1999) and might reflect the fact that craving measures are biased due to limitations associated with self-report measures such as demand characteristics and social desirability (e.g., Marissen et al., 2005). In this context,
it is interesting that Marissen et al. (2006) found that AB was a better predictor of relapse than self-reported craving. Another explanation could be that our measurement of craving was not optimal. Studies indicate that certain self-report measures of craving (e.g., Alcohol Urge Questionnaire; Bohn, Krahn, & Staehler, 1995) perform better than others (see Drobes & Thomas, 1999).

Given the fact that alcohol AB was found to be statistically unrelated to craving, the observed relationship between alcohol AB and psychophysiological cue-reactivity may reflect differences in attentional strategy than in appetitive drive for alcohol. In light of the long photo presentation duration during the spatial cueing task and cue-reactivity paradigm, participants had time to first orient to and process the alcohol cue, then decide to avoid the alcohol image, and finally to reorient attention to the neutral cue. In this regard, the comparatively suppressed HFHRV response and exaggerated LF/HF ratio observed among persons with AB away from alcohol cues may result from strategic attempts to avoid focusing on the photos in the presence of an underlying (and perhaps unconscious) appetitive motivation toward alcohol. This cognitively demanding effort might require attentional hypervigilance, as the individual must actively monitor whether his or her attention has inadvertently become engaged by the alcohol cue, and if so, then reorient attention back to the neutral cue. In support of this interpretation, sustained attention tasks evoking effortful states of attentional hypervigilance are associated with suppression of HFHRV responses (Hansen, Johnsen, & Thayer, 2003), and performing mentally stressful tasks under conditions of high cognitive load (e.g., the Stroop Color Word Conflict Test) is associated with increases in LF/HF ratio (Delaney & Brodie, 2000; Seong et al., 2004).

Furthermore, finger temperature during cue-exposure was found to be positively associated with alcohol AB. This result is congruent with findings of significantly increased skin temperature among smokers exposed to visual images of cigarette smoking (Tong, Bovbjerg, & Erblich, 2007) and cocaine users in a drug treatment program exposed to cocaine images (Kilgus, Pumariega, & Rea, 2009). Yet, other cue-reactivity studies have identified decreased skin temperature during substance cue-exposure (for a review, see Carter & Tiffany, 1999), a finding that accords with our own result of decreased finger temperature among persons with avoidance biases. It is possible that these discrepancies observed in previous studies might be explicated by attentional factors. It may be that for those individuals with an attentional bias toward alcohol cues, sustaining attention on the cue for 2000 ms is associated with an unchecked appetitive approach motivation, resulting in increased skin temperature. This interpretation is bolstered by a meta-analysis of autonomic function in emotional experience that found increases in skin temperature (as well as increased HRV) during exposure to visual stimuli related to the anticipation of pleasure (Kreibig, 2010). In contrast, participants with an attentional bias away from alcohol cues may have had the urge to drink yet attempted to avoid the stimulus triggering the appetitive response; such approach-avoidance conflicts can cause anxiety (Roth & Cohen, 1986), an emotional state that has been associated with decreases in skin temperature across a host of studies (Kreibig, 2010). Furthermore, emotional suppression is
associated with increased sympathetic activation and decreased finger temperature (Gross, 1998; Gross & Levenson, 1997), and studies have linked suppression with attenuated HRV responses among alcohol-dependent individuals (Garland, Carter, Ropes, & Howard, 2012; Ingjaldsson et al., 2003). These findings lend support to the interpretation that among alcohol-dependent individuals, attentional avoidance of alcohol cues is a cognitively demanding attentional strategy associated with sympathetic dominance of the cardiovascular system (Gross, 2002).

The present study was limited in several respects. First, its cross-sectional design precludes causal inferences. Without experimental induction of an attentional strategy (e.g., training participants to attend or avoid attending to alcohol cues), we cannot ascertain whether the alcohol approach and avoidance biases exhibited by participants in the present study are the cause, correlate, or consequence of the psychophysiological responses observed. In addition, despite reports that persons with alcohol-use disorders exhibit AB toward drinking-related cues, the mean alcohol AB for our sample was not statistically significantly different than zero. Inspection of individual differences revealed that the sample was divided into persons with AB toward alcohol cues and those with AB away from such cues. One might expect to observe such heterogeneity among alcohol-dependent inpatients in long-term residential treatment, who tend to exhibit wide variation in their response to treatment. On the other hand, the nonsignificant mean AB in this study may result from our use of a spatial cueing task, which differed somewhat from typical tasks used to measure alcohol AB. Though, the construct validity and sensitivity of this spatial cueing task was established by a prior study that identified a significant positive correlation between alcohol AB as revealed by this task and level of alcohol consumption (Garland, Boettiger, Gaylord et al., 2011).

In addition, given the extended period of abstinence from alcohol among study participants, current study findings may not be generalizable to current drinkers or persons early in recovery from alcohol dependence. Also, our HRV results may be confounded because we were unable to control for respiration rate in our analyses (Grossman & Taylor, 2007), although there is substantial debate in the literature regarding the importance of such corrections (e.g., Denver, Reed, & Porges, 2007). The modest sample size and presence of missing data may have resulted in underpowered analyses, leading to our inability to detect significant effects of the cue-reactivity paradigm on psychophysiological indices. Alternatively, the absence of a “main” effect could be due to the fact HRV and skin temperature responses were significantly different for persons with bias toward and away from alcohol cues.

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
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<tbody>
<tr>
<td><strong>Multiple Linear Regression Models Predicting Psychophysiological Cue Reactivity Among Alcohol-Dependent Patients</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>RMSSD during alcohol cue exposure</strong></th>
<th><strong>B</strong></th>
<th><strong>SE B</strong></th>
<th><strong>β</strong></th>
<th><strong>t</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline RMSSD</td>
<td>0.94</td>
<td>0.06</td>
<td>.90**</td>
<td>16.55</td>
</tr>
<tr>
<td>Alcohol AB</td>
<td>0.23</td>
<td>0.11</td>
<td>.12</td>
<td>2.11</td>
</tr>
<tr>
<td>Alcohol dependence severity</td>
<td>−0.31</td>
<td>0.39</td>
<td>−0.04</td>
<td>−0.79</td>
</tr>
<tr>
<td>Duration of residential treatment</td>
<td>1.40</td>
<td>0.76</td>
<td>0.10</td>
<td>1.85</td>
</tr>
<tr>
<td>Craving (PACS)</td>
<td>−0.94</td>
<td>0.41</td>
<td>−0.13</td>
<td>−2.29</td>
</tr>
<tr>
<td>Perceived stress (PSS-10)</td>
<td>0.31</td>
<td>0.34</td>
<td>0.05</td>
<td>0.90</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>HFHRV during alcohol cue exposure</strong></th>
<th><strong>B</strong></th>
<th><strong>SE B</strong></th>
<th><strong>β</strong></th>
<th><strong>t</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HFHRV</td>
<td>0.60</td>
<td>0.09</td>
<td>.70**</td>
<td>6.74</td>
</tr>
<tr>
<td>Alcohol AB</td>
<td>0.21</td>
<td>0.10</td>
<td>.23</td>
<td>2.19</td>
</tr>
<tr>
<td>Alcohol dependence severity</td>
<td>−0.34</td>
<td>0.35</td>
<td>−0.11</td>
<td>−0.98</td>
</tr>
<tr>
<td>Duration of residential treatment</td>
<td>0.15</td>
<td>0.67</td>
<td>0.02</td>
<td>0.23</td>
</tr>
<tr>
<td>Craving (PACS)</td>
<td>−0.06</td>
<td>0.36</td>
<td>−0.02</td>
<td>−0.15</td>
</tr>
<tr>
<td>Perceived stress (PSS-10)</td>
<td>−0.23</td>
<td>0.30</td>
<td>−0.09</td>
<td>−0.78</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>LF/HF ratio during alcohol cue-exposure</strong></th>
<th><strong>B</strong></th>
<th><strong>SE B</strong></th>
<th><strong>β</strong></th>
<th><strong>t</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LF/HF ratio</td>
<td>0.42</td>
<td>0.22</td>
<td>0.24</td>
<td>1.90</td>
</tr>
<tr>
<td>Alcohol AB</td>
<td>−0.13</td>
<td>0.03</td>
<td>−0.59**</td>
<td>−4.78</td>
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<tr>
<td>Alcohol dependence severity</td>
<td>0.07</td>
<td>0.10</td>
<td>0.08</td>
<td>0.63</td>
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<tr>
<td>Duration of Residential Treatment</td>
<td>−0.03</td>
<td>0.19</td>
<td>−0.02</td>
<td>−0.14</td>
</tr>
<tr>
<td>Craving (PACS)</td>
<td>−0.10</td>
<td>0.10</td>
<td>−0.12</td>
<td>−0.95</td>
</tr>
<tr>
<td>Perceived stress (PSS-10)</td>
<td>0.13</td>
<td>0.08</td>
<td>0.21</td>
<td>1.58</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Finger temperature slope during alcohol cue-exposure</strong></th>
<th><strong>B</strong></th>
<th><strong>SE B</strong></th>
<th><strong>β</strong></th>
<th><strong>t</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol AB</td>
<td>0.10</td>
<td>0.03</td>
<td>.56**</td>
<td>3.35</td>
</tr>
<tr>
<td>Alcohol dependence severity</td>
<td>−0.08</td>
<td>0.09</td>
<td>−0.15</td>
<td>−0.85</td>
</tr>
<tr>
<td>Duration of residential treatment</td>
<td>0.14</td>
<td>0.19</td>
<td>0.12</td>
<td>0.75</td>
</tr>
<tr>
<td>Craving (PACS)</td>
<td>0.20</td>
<td>0.09</td>
<td>.35**</td>
<td>2.17</td>
</tr>
<tr>
<td>Perceived stress (PSS-10)</td>
<td>−0.03</td>
<td>0.08</td>
<td>−0.06</td>
<td>−0.35</td>
</tr>
</tbody>
</table>

Note. AB = attentional bias; PACS = Penn Alcohol Craving Scale; AUDIT = Alcohol Use Disorders Identification Test; PSS-10 = Perceived Stress Scale 10; RMSSD = square root of the mean squared differences between successive R-R intervals; HRV = heart rate variation; LF and HF = low and high frequency, respectively. Boldface indicates statistically significant (p < .05) parameters.

*p < .05.  **p < .01.  ***p < .001.
was not counterbalanced, and participants were not allowed to return to baseline between the stress cue and alcohol cue exposure periods. In consequence, the present study cannot disentangle changes in HRV and skin temperature evoked by stress from changes in these parameters evoked by exposure to alcohol cues. Therefore, it is not possible to conclusively interpret the physiological responses observed in the present study, and study findings cannot be generalized to alcohol cue-reactivity contexts where stress cues are absent. To redress these limitations, future research should replicate present study findings in a larger, randomly selected sample of recently abstinent alcohol-dependent persons undergoing a counterbalanced cue-reactivity paradigm, using eye tracking technology to establish gaze patterns that could support or disconfirm our interpretations of the attentional strategies employed by study participants.

Although both alcohol AB and cue-reactivity have been associated with treatment outcomes (Cox, Hogan, Kristian, & Race, 2002; Fadardi & Cox, 2009; Garland, Franken, & Howard, 2012; Garland, Gaylord, Boettiger, & Howard, 2010; Grüsser et al., 2004; Schoenmakers et al., 2010) and may be subserved in part by common neurobiological structures (Ingjalddson et al., 2003; Thayer & Lane, 2000), surprisingly little is known about how these two processes interact to contribute to the pathogenesis and maintenance of alcohol dependence. The present study suggests that alcohol AB is linked with physiological cue-reactivity and that different attentional strategies are associated with distinct profiles of autonomic responses that may ultimately be found to index or confer additional risk for alcohol dependence relapse.

References
Field, M., Schoenmakers, T., & Wiers, R. W. (2010). Cognitive processes...


ATTENTIONAL BIAS AND CUE-REACTIVITY


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