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Heart Rate Variability Response to Alcohol, Placebo, and Emotional Picture Cue Challenges: Effects of 0.1 Hz Stimulation

Evgeny G. Vaschillo[1], **Marsha E. Bates**[1,2], **Bronya Vaschillo**[1], **Paul Lehrer**[2], **Tomoko Udo**[1], **Eun Young Mun**[1], and **Suchismita Ray**[1]

[1]Center of Alcohol Studies. Rutgers, The State University of New Jersey, USA

[2]Department of Psychiatry. UMDNJ/Robert Wood Johnson Medical School, USA

Abstract

Heart rate variability (HRV) supports emotion regulation and is reduced by alcohol. Based on the resonance properties of the cardiovascular system, a new 0.1-Hz methodology was developed to present emotional stimuli and assess HRV reaction in participants (N=36) randomly assigned to an alcohol, placebo, or control condition. Blocked picture cues (negative, positive, neutral) were presented at a rate of 5 s on, 5 s off (i.e., 0.1-Hz frequency). SDNN, pNN50, and HF HRV were reduced by alcohol, compared to the placebo and control. The 0.1-Hz HRV index was diminished by alcohol and placebo, suggesting that autonomic regulation can be affected by cognitive expectancy. The 0.1-Hz HRV index and pNN50 detected changes in arousal during emotional compared to neutral cues, and the 0.1-Hz HRV index was most sensitive to negative valence. The 0.1-Hz HRV methodology may be useful for studying the intersection of cognition, emotion, and autonomic regulation.

Better understanding of the ways in which alcohol affects emotional regulation is crucial because the desire to regulate positive and negative emotional states is a fundamental motivation for alcohol and other drug taking in animals and humans at all developmental stages of use (Cooper, Frone, Russell, & Mudar, 1995; Koob & Le Moal, 2001; Labouvie & Bates, 2002). The desire to dampen negative affect in particular is theorized to play a central role inmotivating substance use and relapse in addicted organisms (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Koob & Le Moal, 1997). Psychophysiological methods are useful for studying alcohol effects on emotional regulation sensitively and objectively because they can be tailored to answer dynamic questions about increases in, and dampening of, arousal as they occur in real time. In this study, psychophysiological methods provided useful tools to examine changes in arousal that occurred within the individual in response to stimulus cues that evoked varying emotional states. A novel methodology was employed, based on the resonance properties of the cardiovascular system, to stimulate the cardiovascular systemat its approximate resonance frequency of 0.1 Hz with standardized emotional picture cues (Lang, Bradley, & Cuthbert, 2001) and induce high-amplitude resonance heart rate (HR) oscillations. The effects of alcohol and placebo challenges on intraindividual changes in heart rate variability (HRV) response to emotional cues were measured.

Corresponding author: Evgeny Vaschillo, Ph.D., Center of Alcohol Studies, Rutgers, The State University of New Jersey, 607 Allison Road, Piscataway, NJ 08854; Phone (732) 445-3643; Evaschil@rci.rutgers.edu.

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HR is an integrative and sensitive physiological function that reflects responsivity to internal and external physiological and psychological demand (Berntson et al., 1997). HR is quantified as the sequence of R-R intervals (RRI) of the electrocardiogram (ECG). R-R intervals in healthy people continuously change, reacting to internal and external stimuli and expressing a variety of endogenous rhythms. Studies using standardized picture cues to characterize cardiac response to emotional stimuli have primarily examined phasic HR response to individual pictures (Codispoti, Bradley, & Lang, 2001; Gatchel & Lang, 1973; Lang, Greenwald, & Bradley, 1993; Ritz, Thons, Fahrenkrug, & Drahme, 2005) and identified a triphasic waveform. Here we examined a more enduring psychophysiological response (HRV) to a given emotional cue type, observed over the course of 5 min, to characterize emotional and autonomic states that may be relevant preconditions for alcohol or drug use or other action tendencies. HRV occurs continuously and has a complex wave structure, representing mechanisms of cardiovascular regulation and the influence of modulatory functions that promote cardiovascular adaptability (Giardino, Lehrer, & Feldman, 2000). Reduced HRV corresponds to low efficiency of autonomic control and is associated with reduced social competence in childhood (El-Sheikh, Harger, & Whitson, 2001), increased vulnerability to stress (Giardino et al., 2000), and somatic and emotional illnesses (Friedman & Thayer, 1998; Ingjaldsson, Laberg, & Thayer, 2003; Taylor, Carr, Myers, & Eckberg, 1998). HRV assessment is particularly well suited to probe pharmacological and cognitive effects of alcohol intoxication on autonomic response to emotional cues in the environment because it reflects the interplay between sympathetic and parasympathetic activity available to accomplish regulated emotional responding (Appelhans & Luecken, 2006; Goldberger, 1999; Zhong et al., 2005). It also reflects both direct adaptive responses to environmental stimulation and modulatory responses, such as those mediated by the baroreflexes, that help return the organism to homeostasis (Giardino et al., 2000).

Many individuals hold beliefs that alcohol consumption enhances positive affect and suppresses negative affect (Cooper et al., 1995). The psychophysiology literature conversely shows that acute alcohol intoxication reduces multiple indices of HRV in human (Koskinen, Virolainen, & Kupari, 1994; Levanon, Goss, & Chen, 2002; Reed, Porges, & Newlin, 1999; Rossinen et al., 1997) and nonhuman primates (Bennett et al., 2001), suggesting that intoxication is generally associated with decreased potential for adaptive emotional response (Koskinen et al., 1994; Rossinen et al., 1997). Previous alcohol studies have not manipulated the emotional salience of environmental stimuli during HRV assessment, however, so their results do not speak to the nature or magnitude of alcohol-related reductions in cardiovascular adaptability in response to defined emotional contexts, nor to the apparent inconsistency between subjective alcohol expectancies versus physiological effects on modulation of arousal. The present study systematically varied the emotional arousal and valence of picture cues and compared alcohol's dampening of HRV to a placebo control to help discriminate alcohol's pharmacological effects and directly probe learned behavioral or cognitive expectancy effects of alcohol consumption during different emotional contexts.

0.1Hz Stimulation and Heart Rate Variability Indices

Laboratory manipulations of emotional arousal and valence are likely to be much weaker in salience compared to emotional triggers encountered in the real world. To enhance the sensitivity of assessing the impact of emotional stimuli in an experimental setting, a methodology was developed that combined a 0.1-Hz frequency of stimulus presentation with measurement of a 0.1- Hz HRV index. The novel 0.1-Hz HRV index was compared to three standard HRV indices to examine reactivity to alcohol, placebo, and emotional cue challenges.

Various modulatory reflexes represented in HRV are largely mediated by autonomic processes, yet these reflexes and other factors may contribute independently to HRV through central

neural mechanisms (Malpas, 2002). Porges' (2007) conceptualization of the autonomic nervous system (ANS) considers central- peripheral neural feedback "circuits" as the basis for cardiac function regulation. Each feedback loop, due to its resonance property, is a pacemaker for periodic function oscillation. It has been further shown that not only respiratory sinus arrhythmia (RSA) but also resonance properties of the cardiovascular system are sources of HRV (deBoer, Karemaker, & Strackee, 1987; Hammer & Saul, 2005; Legramante et al., 1999; Vaschillo, Lehrer, Rishe, & Konstantinov, 2002; Vaschillo, Vaschillo, & Lehrer, 2006; Vaschillo, Zingerman, Konstantinov, & Menitsky, 1983).

Resonant properties considerably amplify HRV response to stimulation by producing very high amplitudes of HR oscillations if stimuli are presented at resonance frequencies. High-amplitude HR oscillations have been demonstrated with multiple forms of stimulation at a frequency of 0.1 Hz, including paced breathing (Song & Lehrer, 2003; Task Force, 1996; Vaschillo, Vaschillo, & Lehrer, 2004), rhythmical muscle tension (Tiedt, Wohlgemuth, & Wohlgemuth, 1975; Wigertz, 1971), gravitation (orthostatic) tilting (Hamilton, Lindan, & Reswick, 1969), and thermal stimulation (Lindqvist, 1990). The 0.1-Hz HRV index was thus based on the resonance property of the cardiovascular system at a frequency of 0.1 Hz, which has been shown to be associated with baroreflex activity (deBoer et al., 1987; Vaschillo et al., 1983, 2002, 2006). By stimulating the cardiovascular system with emotionally valent stimuli at a frequency of 0.1 Hz, the HRVresponse should be enhanced by the resonance. This methodology thereby simultaneously evaluates autonomic nervous system reaction to various interventions (Nickel & Nachreiner, 2003) and activation of a modulatory reflex -the baroreflex- (Cevese, Gulli, Polati, Gottin, & Grasso, 2001).

The 0.1-Hz HRV index was contrasted with three standard HRV indices. Within the time domain, the standard deviation of normal RRI's (i.e., SDNN) was used to represent the overall level of HRV and to evaluate the general activity of cardiac autonomic regulation (Task Force, 1996). Although previous research has shown that pNN50 correlates highly with HF HRV and the amount of traffic in oscillatory fibers of the cardiac vagus nerve (Berntson et al., 1997; Task Force, 1996), it provides additional information about large-amplitude beat-to-beat changes in HR (i.e., it is the percentage of adjacent RRI that differ by at least 50 ms). Short-term high-amplitude HR changes might be expected by exposing participants to discrete emotionally charged stimuli. Frequency domain HRV indices included HF HRV, calculated using spectral analysis of RRI as a power of the RRI spectrum within the frequency range of 0.15–0.4 Hz and a 0.1-Hz index, described above. HF HRV usually reflects RSA, and thus is also often used as an index of vagus nerve activity (Berntson et al., 1997; Task Force, 1996). HF HRV and other indices of parasympathetically mediated cardiac activity have previously been found to decrease during acute alcohol intoxication (Koskinen et al., 1994; Levanon et al., 2002; Reed et al., 1999) and thus provide useful comparison points for the new 0.1- Hz HRV index.

Hypotheses

Individuals exposed to an alcohol challenge were expected to show decreases in the 0.1-Hz index as well as HRV indices of overall regulation (SDNN), rapid adjustment (pNN50), and parasympathetic modulation (HF HRV and pNN50), compared to those in the control condition. Based on previous findings that alcohol's arousal dampening effects on mean HR are pharmacologically mediated (Greeley & Oei, 1999), it was tentatively expected that the HRV indices would be lower in individuals receiving alcohol compared to placebo. The 0.1-Hz HRV index was expected to be more sensitive than the other HRV indices to intraindividual changes from baseline in response to emotionally arousing picture cues, compared to response to neutral picture cues, because picture cues were presented at a frequency of 0.1 Hz. This frequency was intended to trigger HR resonance that theoretically should enhance the 0.1-Hz

HRV index's sensitivity to emotionally valenced stimulation presented at the same frequency. Further, given that the 0.1-Hz index should reflect both the strength of autonomic reaction (Nickel & Nachreiner, 2003) and regulatory activity (Cevese et al., 2001) elicited by visual cues, it was hypothesized that alcohol's dysregulation of this system should be more evident in response to emotionally arousing compared to emotionally neutral stimuli because arousing stimuli would make greater demands on the system in terms of response intensity and subsequent modulatory demand. We thus predicted an interaction between challenge groups and stimulus blocks in affecting the 0.1-HzHRV index, but not necessarily the traditional HRV measures.

Method

Participants

Thirty-six participants (16 women) were recruited through advertisements in university and community newspapers and bulletin boards. Inclusion criteria were age between 21 and 24 years and English as a first language. Exclusion criteria included a history of psychiatric or neurological disorder or treatment; medical conditions that preclude alcohol administration or confound interpretation of HRV (e.g., diabetes, heart disease); 20% over- and underweight from the ideal for age and gender; consumption of less than four standard alcohol drinks (three drinks for women) per occasion fewer than twice per month in the previous year; alcohol dependence; history of any substance abuse treatment; regular illicit or prescription drug use; lifetime diagnosis of any substance use disorder on the part of the prospective participant's biological mother (to rule out prenatal exposure effects); and, for women, pregnancy. The minimum drinking criteria were specified because we did not wish to expose participants to an alcohol dose substantially greater than their routine self-administered dosage levels in the natural environment.

Participants were randomly assigned to an alcohol, placebo, or control group (n = 12 per group). Those assigned to the alcohol and placebo groups were told that they would consume a beverage containing some amount of alcohol and that the maximum expected blood alcohol concentration (BAC) would be slightly more than the legal limit of intoxication for driving in the United States (i.e., ~90 mg/dl). This target BAC is typical of that found in naturalistic field research on college students following an evening of drinking (Kraus et al., 2005). Control participants were told they would drink orange juice. Participants were asked to report for testing 3 h following a light meal and to refrain from drinking alcohol or taking any drugs for 24 h before the session.

Procedure

The study was completed in one session that lasted approximately 3.5 h. Participants were individually tested in both a picture cue exposure phase and a picture memory phase of the experiment (this article reports the results of the cue exposure phase). Participants in the alcohol condition remained in the laboratory following the experiment until their BAC reached zero. Sessions were begun between 10 a.m. and 2 p.m. to minimize differences in biological circadian rhythms. Participants provided written informed consent, then completed substance use and related questionnaires and a brief version of the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1992). Blood pressure, oral temperature, and a breath estimate of BAC were assessed, and participants were weighed in order to calculate alcohol dose and/or drink volume. Women completed a urine pregnancy test.

Alcohol doses were mixed with orange juice in a ratio of 4 parts mixer to 1 part ethanol. The beverage was divided into three equal drinks, each consumed during consecutive 5-min periods. Thus, all participants consumed three volume-controlled drinks that were either 100%

mixer (told no alcohol = control), placebo (mixer with 100μl ethanol float per each cup and other olfactory alcohol cues), or mixer plus 95% ethanol dose to produce a target BAC of ~90 mg/dl.

The participant was then seated in a comfortable chair located 2.5 m in front of a TV screen in a sound-attenuated, dimly lit room. To collect ECG data, a negative electrode was attached to the upper right arm, a positive electrode to the lower left leg, and a ground electrode to the upper left arm. To record respiration data, belts with sensors were placed around the upper chest and abdomen. Skin conductance, skin temperature, and finger pulse data were also collected from sensors as a part of another study. After performing the first baseline task (B1), the participant consumed his/her condition's beverage. When a BAC level of at least 60 mg/dl was reached (pre-test BAC), or after 10 min in placebo and control conditions, a second baseline task (B2) was completed, and the picture cue exposure tasks began. Post-test BAC was assessed immediately after the picture cue exposure tasks were completed.

Experimental Tasks

During B1 and B2, a low cognitive demand task (“plain vanilla”; Jennings, Kamarck, Stewart, Eddy, & Johnson, 1992) was completed. It involved viewing, on a TV screen, squares that changed color every 10 s and simply counting the number of blue squares. The picture cue exposure tasks included three categories of picture blocks that are the focus of the present study: negative emotional, positive emotional, and neutral, as well as three exploratory picture cue blocks that were not included in the present study (alcohol, marijuana, and polydrug). The presentation order of picture blocks was randomized across participants so that HR reaction to block valence and arousal would not be confounded with the time lapse from beverage consumption (Sayette, 1993b) and so that there would not be systematic effects of viewing any particular block before or after any other block. In each block, one of two matched sets (total 15 pictures) was presented twice; the order of picture presentation within sets was also randomized. We used picture stimuli from the International Affective Picture System (IAPS; Lang et al., 2001) to match positive and negative emotional pictures on standardized arousal ratings that varied systematically in valence. Neutral pictures were of moderate valence and low arousal (Bradley, Cuthbert, & Lang, 1990). Table A1 in the Appendix lists the IAPS identification numbers of the slides that were used.

Each picture was presented for 5 s with a 5-s interpicture interval, resulting in a 0.1-Hz frequency of picture presentation. During the 5-s interpicture interval, participants gave either a liking or an arousal rating (rating order counterbalanced across participants). The interblock time interval was 30 s. A 7-point (1 = *not at all* to 7 = *moderately intoxicated*) subjective intoxication rating scale (Newlin, 1985) was administered at the session's end to validate the beverage condition manipulation. This study was approved by the Rutgers University Institutional Review Heart rate response to alcohol Review Board for the Protection of Human Subjects Involved in Research.

Apparatus and Software

A PowerLab Acquisition System (ADInstruments, Colorado Springs, CO) was used to collect data from ECG, respiration, and picture presentation time marker signals. The data sampling rate for each channel was 1000 times per second. WinCPRS software (Absolut Aliens Oy, Turku, Finland) was used to analyze data. Pictures were presented on a 75-cm LCD TV (View Sonic N3000W) using E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA) to provide a picture presentation schedule with a time setting accuracy of 1 ms, a marker for individual “picture - on” time, and randomization of the picture blocks and pictures within blocks.

Psychophysiological Data Analysis

Analysis of the signals was performed off-line. ECG and respiration data for each 5-min block were analyzed separately. Standard procedures for HRV analysis were used to compute indices for each stimulus block (Cooke et al., 1999; Task Force, 1996; Taylor et al., 1998). Frequency domain analyses were done using Fourier analyses. Cubic interpolation of the non–equidistant waveform of the RRI sequence was completed, and RRIs were resampled at 4 Hz. We calculated the time domain indices of SDNN and pNN50 and frequency domain indices of HF HRV (0.15–0.4 Hz) and the 0.1-Hz HRV index, measured as the maximum amplitude of the RRI spectral power at ~ 0.1 Hz (range between 0.075 and 0.108 Hz). The 0.1-Hz HRV was measured within this narrow range to accommodate individual differences in the specific cardiovascular resonance frequency (Vaschillo et al., 2002, 2006). All HRV indices were transformed using the natural logarithm after adding a constant of one, and no influential outliers remained following the log transformation.

Statistical Analyses

Within-individual change scores for each psychophysiological measure from baseline (B1) to the level within each of the three emotional cue blocks (negative, positive, neutral) were analyzed. This within-individual change approach adjusts for any individual differences in reactivity while performing the low-cognitive demand task (i.e., B1 baseline prior to beverage consumption and picture cue blocks) by subtracting participants' baseline HRV scores from their HRV scores recorded while they were being shown picture cue blocks. Therefore, the resulting HRV change scores reflect changes due to group conditions and picture cue block types, but not due to individual differences in HRV reactivity levels.

We analyzed all HRV indices from the mixed between-subjects (beverage challenge groups: alcohol, placebo, control) and within-subjects (emotional valence of the picture cue blocks: negative, positive, neutral) design using the doubly multivariate repeated measures analysis of variance (ANOVA; Hertzog & Rovine, 1985; Maxwell & Delaney, 2004) to examine whether the effects of experimental groups, picture blocks, and their interaction on reactivity varied across the four different HRV indices (0.1-Hz HRV, HF HRV, SDNN, and pNN50). The doubly multivariate ANOVA is appropriate when more than one dependent variable (i.e., HRV indices) exists at each and every level of the repeated factor (i.e., picture cue blocks) and is advantageous for protection from inflated family-wise Type I error (for a review, see Hertzog & Rovine, 1985). Repeated measures ANOVAs were then conducted to show the pattern of HRV change to picture cue blocks for three beverage challenge groups in greater detail for each HRV index. The sphericity assumption necessary for repeated measures ANOVA was met.

Results

Sample Description and Manipulation checks

The alcohol, placebo, and control groups did not differ in gender composition, age, past month alcohol use, or affective state as assessed by the POMS at the start of the experiment (Table 1). Control participants were significantly more likely to have ever tried marijuana,[1] but not other drugs, than those in other groups. On average, participants drank 4.0 standard alcohol drinks 2.2 times per week in the preceding month (one standard drink = 12 oz. of 5% beer or malt beverage, 5 oz. of 12–17% wine, or 1.5 oz. of 80-proof hard liquor). In the alcohol group, average pre- and posttest BACs showed a relatively narrow range, encompassing the upper

[1]These differences in lifetime “ever tried” are unlikely to have affected autonomic response differences between groups, as regular (weekly) marijuana use was an exclusion criterion in this study and there were no differences in the number of alcohol, placebo, and control subjects who had used marijuana in the past year (n = 4, 4, and 3, respectively).

portion of the ascending limb, peak, and initial portion of descending limb of the blood alcohol curve.

Average subjective intoxication ratings varied significantly across groups, with the alcohol group reporting significantly higher levels of perceived intoxication than did the placebo group, which reported significantly higher levels of intoxication than the control group, which reported no intoxication (Table 1). Thus, the average placebo-induced subjective perception of intoxication was intermediate between the alcohol and no-alcohol control conditions.

An example of HR and Respiration Reaction to 0.1Hz Picture Presentation

Figures 1 and 2 illustrate the resonance frequency approach we applied in this study. Rhythmical presentation of emotionally salient pictures at a frequency of 0.1 Hz was used to impose high-amplitude oscillations in HR at this frequency. Figure 1 shows HR and respiration reactions to 0.1 Hz presentation of emotional pictures in a typical participant. Figures 2a and 2b illustrate typical differences in response to picture blocks of different emotional valences.

Respiration

Because differences in respiration rate can sometimes influence differences in amplitude of RSA independently of vagus nerve traffic (Grossman, Karemaker, & Wieling, 1991), it is often necessary to adjust analyses of HRV measures reflecting RSA (in this study, HF HRV and pNN50) for respiration rate. We first examined whether respiration rate differed between groups and among the three emotional picture blocks. Neither challenge group, $F(2,33) = 1.49$, n.s., picture block, $F(2,66) = 1.13$, n.s., nor their interaction, $F(4,66) = 0.54$, n.s., affected respiratory rate. Average respiration rate during picture presentations ($M = 0.32$, $SD = 0.05$ Hz, ~ 19 breaths per minute) did not differ significantly from that during the B1 task ($M = 0.28$, $SD = 0.06$ Hz, ~17 breaths per minute). Similarly, respiratory frequency was not a statistically significant covariate of change in HF HRV in the repeated measures ANOVA. Thus, changes in HRV in response to beverage and picture cue manipulations were not explained by changes in respiratory frequency, and no adjustments for respiration rate were made in analyses of the various HRV indices.

Doubly Multivariate Repeated Measures ANOVA and Planned Contrasts of HRV Indices

Doubly multivariate repeated measures ANOVA were used to examine whether effects of experimental groups, picture blocks, and their interaction on reactivity differed across the four HRV indices (0.1-Hz HRV, HF HRV, SDNN, and pNN50). Interaction effects between experimental groups and HRV indices, between picture blocks and HRV indices, and between experimental groups, picture blocks, and HRV indices were tested. There were statistically significant interaction effects between HRV indices and picture blocks (Wilk's $\Lambda = .55$, $F[8,26] = 2.66$, $p < .05$), and between HRV indices and experimental groups (Wilk's $\Lambda = .39$, $F[8,60] = 4.50$, $p < .01$) on reactivity. These results indicate that effects of picture cue blocks and experimental groups on HRV reactivity were measured differently across the four indices. The three-way interaction effect between the HRV indices, groups, and picture blocks was not significant (Wilk's $\Lambda = .66$, $F[16,52] = 0.76$, n.s.), suggesting that the four indices did not differ in the pattern of differences between experimental groups crossed with picture cue blocks.

Differences between indices in response to picture cue blocks—Planned contrasts were used to determine whether the 0.1-Hz index detected effects of picture cue blocks differently than other indices. With respect to differences between negative compared to neutral picture cue blocks, the 0.1-Hz HRV index showed significantly greater contrasts than HF HRV (Wilk's $\Lambda = .73$, $F[1,33] = 11.92$, $p < .01$), SDNN (Wilk's $\Lambda = .65$, $F[1,33] = 18.00$, $p < .01$), and pNN50 (Wilk's $\Lambda = .77$, $F[1,33] = 10.05$, $p < .01$). With respect to positive compared to neutral picture cue blocks, the 0.1-Hz HRV index was statistically different from SDNN (Wilk's

$\Lambda = .85$, $F[1,33] = 5.91$, $p < .05$), but not from HF HRV (Wilk's $\Lambda = .90$, $F[1,33] = 3.66$, $p = .06$) nor pNN50 (Wilk's $\Lambda = .93$, $F[1,33] = 2.56$, $p = .12$). The specific nature of these differences is addressed in the following repeated measures ANOVAs of each index.

Differences between indices in response to experimental group effects—Next, we examined whether the 0.1-Hz HRV index was the source of the significant interaction effects between groups (alcohol, placebo, control) and HRV indices. The contrast results indicated that the 0.1-Hz HRV index was not statistically different from HF HRV (Wilk's $\Lambda = .86$, $F\ (2, 33) = 2.72$, $p = .08$), SDNN (Wilk's $\Lambda = .89$, $F\ (2, 33) = 2.08$, $p = .14$), or pNN50 (Wilk's $\Lambda = .86$, $F\ (2, 33) = 2.70$, $p = .08$) indices in detecting group effects. The above significant omnibus interaction effect between HRV indices and experimental groups thus could be attributed to differences between pNN50 and SDNN (Wilk's $\Lambda = .60$, $F\ (2, 33) = 10.88$, $p < .01$), between pNN50 and HF HRV (Wilk's $\Lambda = .81$, $F\ (2, 33) = 3.93$, $p < .05$), and between SDNN and HF HRV (Wilk's $\Lambda = .78$, $F\ (2, 33) = 4.53$, $p < .05$), indicating that three other HRV indices were differentially sensitive to experimental group conditions.

Repeated Measures ANOVAs of Changes in Individual HRV Indices

The doubly multivariate analyses were followed by four repeated measures ANOVAs to examine the detailed pattern of change in each HRV index individually (see Table 2). Figure 3 shows changes from baseline (B1 task) in response to the negative, positive, and neutral picture cues for the three experimental groups and their 95% confidence intervals for each of the four indices. The horizontal line at zero indicates no change in HRV from baseline to picture cues, and values above and below the zero line indicate increases and decreases, respectively, in HRV in response to emotional picture cues. Figure 3 shows that the 0.1- Hz HRV index generally showed elevated levels during exposure to picture cues, whereas other HRV indices generally decreased.

Among the four HRV indices, the 0.1-Hz HRV index and pNN50 were both sensitive to differences among picture cue blocks, explaining 24% and 11% of the variances, respectively (see Table 2 and Figure 3). Compared to neutral stimuli, negative picture cue blocks led to the largest increase in the 0.1-Hz HRV index, explaining 34% of the variance; positive picture valence contributed to a smaller, but significant, change in both of these indices (an increase and a decrease, respectively, in the 0.1-Hz HRV index and pNN50). These results were in line with the planned contrast results following the doubly multivariate ANOVA, in which the 0.1-Hz HRV index was different from other indices in response to negative picture blocks, whereas it was not different from pNN50 (or HF HRV) in response to positive picture cue blocks.

The 0.1-Hz HRV index, HF HRV, SDNN, and pNN50 were each sensitive to between–group differences, explaining 16%, 28%, 34%, and 46%of the variances, respectively. As illustrated in Figure 3, each index showed a significantly lower response in the acute alcohol intoxication condition, compared to the level shown by the control group. With respect to alcohol versus placebo challenge group contrasts, HF HRV, SDNN, and pNN50 indices were all significantly lower in the alcohol than in the placebo group, suggesting that these indices reflect primarily pharmacological effects of alcohol on dampened autonomic response. There was no statistically significant difference, however, between the alcohol and placebo groups as measured by the 0.1-Hz HRV index. As shown in Figure 3, the magnitude of 0.1-Hz HRV reduction following placebo was nearly identical in magnitude to that caused by the alcohol, suggesting that the 0.1 Hz index is sensitive to cognitive or behavioral effects of expecting alcohol.

The interaction effect between picture blocks and beverage challenge groups was not statistically significant. However, omnibus hypothesis testing can be insensitive to small and medium-sized effects (Hertzog & Rovine, 1985). Therefore, we examined differences in HRV

in response to the picture blocks across groups using planned comparisons (last six rows of Table 2). The three standard indices were generally depressed by alcohol during exposure to both arousing and neutral picture cues, whereas the 0.1-Hz HRV index was significantly suppressed in response to emotionally arousing cues but not to neutral picture cues. The 0.1-Hz index, but not the others, showed suppression in response to arousing cues in the placebo condition. Thus, alcohol uniformly diminished most HRV response to picture cues, regardless of emotional content. In contrast, the 0.1-Hz index displayed a dampened increase in response only to emotionally valenced stimuli, and this dampened increase was observed both in the alcohol and placebo conditions.

Discussion

This study examined four HRV indices of autonomic reactivity in response to picture cues that varied in emotional arousal and valence during alcohol challenge, placebo challenge, and control conditions. All the HRV indices were dampened by alcohol to varying extents, whereas only pNN50 and the 0.1-Hz index showed differentiated response to emotionally arousing cues. The 0.1-Hz HRV index was the most sensitive to changes in response to negatively valenced picture cues and uniquely sensitive to cognitive expectancy effects of alcohol.

Mechanism for sensitivity of the 0.1 Hz index in this study

We propose that the 0.1-Hz HRV index showed particular sensitivity to emotional content and placebo challenge because the picture cues were presented at 0.1 Hz, the resonance frequency of the cardiovascular system. This is consistent with the idea that the 0.1-Hz index simultaneously assessed both the individual's response to the stimulus and a modulatory (homeostatic) process, mediated by the baroreflex system that is simultaneously activated whenever the autonomic nervous system is stimulated (Eckberg & Sleight, 1992). Thus, a stimulus-induced increase in blood pressure triggers a baroreflex-induced decrease in HR, which, through mechanical action, causes blood pressure to decrease, which, in turn, causes HR to increase. Delay in the baroreflex system caused by inertia and blood vessel plasticity thus produces oscillations in both HR and blood pressure at a frequency close to 0.1 Hz. These oscillations increase in amplitude when the system is stimulated, either by external triggers (e.g., the picture stimuli in the current study or thermal stimulation; Lindqvist, 1990) or by endogenous processes, such as slow breathing (Lehrer et al., 2003; Vaschillo et al., 2006). Consistent with this model, it is known that HR rhythms close to 0.1 Hz are highly associated with baroreflex activity (Cevese et al., 2001).

It is thus likely that resonance effects of the 0.1-Hz frequency of stimulus presentation were shaped by the HR response characteristics to the picture stimuli. Others have studied phasic HR response to each IAPS picture cue separately (Bradley & Lang, 2000; Codispoti et al., 2001; Gatchel & Lang, 1973; Lang et al., 1993), and found that responses to individual stimuli tended to last approximately 10 s and to have a triphasic waveform, consisting of a small initial HR deceleration, a larger midinterval acceleration, and a final deceleration. We hypothesize that when, as in the present study, a stimulus appears every 10 s, the stimulus presentation frequency synchronizes with stimulus-induced HR reactions and increases the HRV reaction. In other words, each new stimulus was presented (and caused initial HR deceleration) just as the triphasic HR response to the previous stimulus was about to end its final deceleration phase (see Figure 1b), thus producing high-amplitude HR oscillations at 0.1 Hz, particularly when the stimuli were emotionally arousing. The large 0.1-Hz effect size for negative-affect stimuli may have resulted because the accelerative leg of the triphasic response tends to best discriminate the picture valence (Gatchel & Lang, 1973; Lang et al., 1993).

Because 0.1-Hz HR oscillations are strongly affected by the HR component of the baroreflex, we theorize that the 10-s triphasic response interacted with baroreflex effects on HR at this

frequency, thus causing the high-amplitude 0.1-Hz response in this study. We have previously shown that high-amplitude HR oscillations at an approximate 0.1-Hz frequency produced by paced breathing result from baroreflex stimulation (Lehrer et al., 2003; Vaschillo et al., 2002). From this perspective, the resonance property in HRV at 0.1 Hz is provided by activity of the HR baroreflex (Cevese et al., 2001; Vaschillo et al., 1983, 2002, 2006). In this study, the picture presentations acted similarly to paced breathing in the previous studies, by stimulating the baroreflex system at its resonance frequency. The baroreflex would then amplify the initial HR deceleration in response to the next salient stimulus because it occurred approximately 10 s after the preceding one. This theory is offered tentatively because, to prove that large HRV oscillations sensitively discriminated intraindividual changes in emotional response and placebo responses in this study, it is necessary to present the pictures at other frequencies as well, compare the amplitude of response, and measure beat-to-beat blood pressure. This has been demonstrated for paced breathing interventions (Song & Lehrer, 2003; Vaschillo et al., 2006), but not for paced emotional picture stimulation.

Effects of Emotionally Arousing Picture Cues

The 0.1-Hz HRV index and pNN50 showed significantly larger increases over baseline in response to emotionally arousing picture cues, compared with emotionally neutral pictures. The 0.1- Hz HRV index increased more in response to pictures with negative emotional valence, whereas the 0.1-Hz HRV index and pNN50 showed equivalent effect size responses to positive pictures. We think it is likely that, due to our methodology, pNN50 captured some resonance effects of 0.1-Hz stimulation as reflected in steep beat-to-beat changes in the low frequency range. When not measured under resonance conditions, pNN50 is typically more related to HF HRV and sometimes is interpreted as an alternative measure of vagus nerve activity (Berntson et al., 1997) because in resting conditions, the steepest beat-to-beat changes usually occur in respiratory sinus arrhythmia. This was not the case in the current study, where HF HRV did not discriminate arousal or valence of stimulus cues. The sensitivity of pNN50, particularly to pictures eliciting negative emotions, may be somewhat lower than that of the 0.1-Hz HRV index because the latter more directly measures the effects of simulation at 0.1 Hz.

Effects of Alcohol and Placebo Challenges

Compared to the control condition, alcohol significantly decreased all HRV indices, consistent with previous research (e.g., Bennett et al., 2001; Koskinen et al., 1994; Lehrer & Taylor, 1974; Li, Deng, & Xie, 2006; Weise, Krell, & Brinkhoff, 1986). The pNN50 index, in particular, showed a large effect size in discriminating alcohol group effects from control and placebo in the current study, likely reflecting a decrease in vagus nerve activity (Levanon et al., 2002; Reed et al., 1999).We further found that alcohol significantly reduced pNN50, SDNN, and HFHRV compared to placebo challenge. This is consistent with past research examining placebo effects on mean HR and suggests that much autonomic response dampening by alcohol is due to alcohol's pharmacological actions (Greeley & Oei, 1999).

Unlike the other indices, the 0.1-Hz HRV index was diminished by placebo to a similar extent as alcohol challenge, suggesting that the belief that alcohol had been consumed affected autonomic reactivity and/or modulation as measured by this index. Prominent accounts of alcohol's effect on ANS indicators of emotional response have focused on alcohol's direct pharmacological effects on limbic brain structures or indirect effects mediated through alcohol's pharmacological effects on cortical structures that support attention allocation or information processing (Lang, Patrick, & Stritzke, 1999; Sayette, 1993a; Steele & Josephs, 1988). Our results further suggest that the central autonomic network may initiate cardiac adjustments (reflected in the 0.1-Hz index) in response to arousing stimuli when participants believe that they have consumed alcohol. This placebo effect could conceivably be mediated

by the bidirectional feedback pathways between the ANS and cortical structures of the central nervous system (CNS; e.g., Thayer & Lane, 2000) that support higher-order cognitive processes such as learned expectancies regarding alcohol effects. If placebo effects on the 0.1-Hz HRV index are replicated, this index may be a promising and accessible indicator of coordinated CNS/ANS emotional regulatory activity that is susceptible to cognitive manipulation.

Changes in Response to Picture Cues among Alcohol and Placebo Challenge Groups

Although individuals report that they are motivated to drink alcohol to both enhance positive, and diminish negative, affect (Cooper et al., 1995; Labouvie & Bates, 2002), most alcohol theory and research has focused on negative affective states and alcohol's stress-reducing properties (Greeley & Oei, 1999). To our knowledge, this is the first study to examine alcohol effects on HRV in response to arousing stimuli of both positive and negative emotional valence, as well as neutral stimuli. Alcohol reduced HF HRV, pNN50, and SDNN in response to all picture blocks, indicating a general blunting of autonomic responsivity that was independent of the arousal value or valence of cues. In contrast, the planned contrasts provided evidence for selective emotional dampening effects of alcohol and placebo on 0.1 Hz HRV responses to negative and positive cues, compared with neutral ones. These findings support the hypothesis that the 0.1 Hz index would be especially sensitive to dysregulation by alcohol in response to emotionally salient stimuli, as environmental challenges would elicit stronger reactions than neutral stimuli and increase need for autonomic modulation. Caution is warranted because the omnibus *F* tests for interaction effects between groups and stimulus types were not statistically significant, yet the effect sizes were medium, supporting the idea that the 0.1 Hz presentation of emotionally salient stimuli, together with the 0.1 Hz index, may provide a sensitive method for studying pharmacological and cognitive effects of alcohol on emotional experience in the lab.

Using an alternative assessment of emotional response to IAPS picture cues, Donahue, Curtin, Patrick, and Lang (2007) found that an alcohol dose comparable to the one used here suppressed potentiation of the eyeblink component of the startle response to negative emotional picture cues. At the same time, alcohol did not reduce the typical diminution of startle in response to positive pictures, suggesting that alcohol selectively reduces emotional response to negative stimuli. Donahue et al. studied phasic reactions to individual picture cues; we induced tonic emotional states, which may have contributed to the difference in results. Sensitivity to positive emotional cues may also Heart rate response to alcohol 855 have been enhanced in this study because the 0.1-Hz stimulus presentation methodology increased response magnitude, due to resonance effects. To our knowledge, simultaneous changes in HRV and eyeblink startle have not been studied in response to emotional stimuli, although this may be a fertile area for future study given evidence that resting HRV modulates startle magnitude to emotionally valenced pictures and may be related to startle sensitivity (Ruiz-Padial, Sollers, Vila, & Thayer, 2003).

Limitations and directions for future research

The present results need to be considered within the study's limitations. The relatively modest sample size compromised statistical power of the omnibus interaction tests, so that evidence for differential 0.1-HzHRVresponse to emotional arousal following alcohol and placebo challenges was based on univariate contrasts and measures of effect size. Replication research with larger samples is needed to confirm these findings. There is also a limit on subjective perceptions of intoxication following an alcohol placebo challenge (Martin, Earleywine, Finn, & Young, 1990), so that HRV response to placebo in this study was linked to subjective perceptions of intoxication that were only about half the magnitude of those obtained in the alcohol group. Further, the participants in this study were young social drinkers, and the results may not generalize to older aged persons who vary in terms of background levels of

cardiovascular regulation and chronicity of drinking experience or to young adults who are very light or infrequent drinkers. Finally, substantial individual differences exist in ANS responsiveness to stress, as well as to other negative and positive emotional experience (Lacey & Lacey, 1970), and it will be important for future research to capture underlying psychological and other sources of this heterogeneity.

In summary, the findings suggest that a 0.1-Hz stimulus presentation, used together with a 0.1-Hz HRV index, may be a sensitive methodology for future research aimed at better understanding the effects of alcohol, placebo, and emotional cues in the environment on emotional arousal and modulation. We demonstrated that the 0.1-Hz HRV index is sensitive to emotionally valenced stimuli and cognitive expectancy effects of alcohol, compared to other measures, by testing directly (doubly multivariate repeated measures ANOVA) and by demonstrating better predictive validity (repeated measures ANOVA). In addition, we showed the convergent and discriminant validity of the new index by demonstrating that, as expected, the 0.1-Hz HRV index decreased for those in the alcohol challenge condition as did the other HRV indices (convergent validity), and that the 0.1- Hz HRV index showed elevated responses in response to picture cues, whereas other HRV indices showed reduction (discriminant validity). Thus, the new 0.1-Hz HRV index demonstrated a differentiated autonomic reaction pattern to emotional pictures following alcohol and placebo challenges that is different from those of more traditional HRV indices. Further research is needed on the relationship of alcohol placebo challenge to changes in HRV because understanding of the susceptibility of autonomic response to placebo challenge may hold promise for identifying neurobiological mechanisms of behavioral change that are cognitively or behaviorally mediated and may enhance our understanding of mechanisms of emotional regulation that support alcohol use.

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Appendix I: IAPS Picture ID Identification Numbers

Set 1			Set 2		
Neutral	**Negative**	**Positive**	**Neutral**	**Negative**	**Positive**
2215	1070	1710	2200	1300	2050
2221	2683	2630[1] (4210)	2480	3000	2216
2440	2730	4500[1] (4220)	2570	3130	4510[1] (4180)
5120	3010	4607[2]	5130	3140	4660[2]
5500	3100	4608[2]	5520	3530	4680[2]
7000	3500	4626	7010	6210	5621
7040	6260	5470	7025	6230	5629
7050	6300	5910	7031	6312	7200
7090	6313	7270	7060	6350	7330
7100	6821	8030	7080	6415	7502
7224	9050	8170	7150	6570	8080
7705	9410	8185	7234	9250	8180
7110	9635.1	8190	7700	9420	8370
9210	9800	8200	9070	9570	8470

Set 1			Set 2		
Neutral	**Negative**	**Positive**	**Neutral**	**Negative**	**Positive**
9360	9810	8490	9090	9910	8501

Note: IAPS = International Affective Picture System (from Lang et al., 2001). Participants were randomly assigned to either Set 1 or Set 2.

[1] Erotic pictures that were different for each gender. Parentheses indicate pictures for males.

[2] Pictures of erotic couples.

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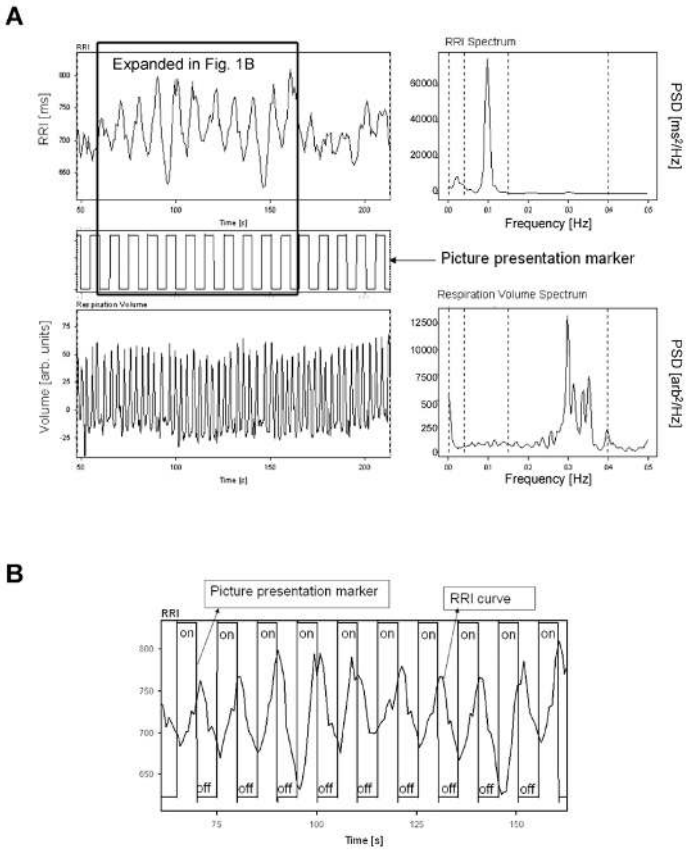

Figure 1.

An example of heart rate reactions to positive picture presentations at 0.1 Hz. A. Picture presentations at 0.1 Hz elicit high amplitude RRI oscillations at 0.1 Hz, but do not affect respiratory rhythm. B. Heart rate responses synchronize with the rhythm of picture presentations. RRIs gradually increase for ~ 5 s following stimulus onset, then gradually decrease for ~ 5 s.

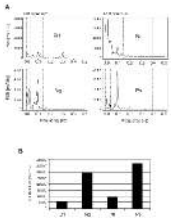

Figure 2.
An example of heart rate reactions to blocks of emotionally salient and neutral pictures. A. RRI spectra for the Baseline task (B1), and Neutral (Nt), Positive (Ps), and Negative (Ng) picture cue presentation blocks. B. Powers of the RRI spectra at 0.1 Hz (0.1 Hz HRV indices) for each block. PSD = Power Spectrum Distribution.

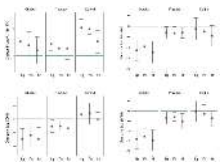

Figure 3.
Mean changes from baseline (B1) in response to negative, positive, and neutral picture stimulus types for three experimental groups and their 95% confidence intervals for the 0.1 Hz HRV index and other indices. The horizontal line at zero indicates zero change in reactivity from baseline to emotional picture cues, and values above the zero line indicate increases in reactivity from baseline to emotional picture cues.

Table 1

Participant Characteristics by Challenge Condition

	Alcohol (n = 12)	Placebo (n = 12)	Control (n = 12)	Overall (N = 36)	Chi-Square/F Statistics
Age in years	22.0 (1.23)	21.8 (0.87)	21.7 (0.98)	21.8 (0.98)	F (2, 33) = .36
Female (%)	41.7	50.0	41.7	44.4	χ^2 (2) = .23
Alcohol use (past 30 days)					
Quantity (per occasion)[1]	4.7 (3.3)	3.0 (1.5)	4.4 (3.3)	4.0 (2.9)	F (2, 33) = 1.20
Frequency (per week)	2.1 (1.3)	1.6 (1.0)	2.8 (2.5)	2.2 (1.7)	F (2, 33) = 1.57
Lifetime use of other drug use (% of participants who ever used)					
Cigarettes	75.0	75.0	58.3	69.4	χ^2 (2) = 1.05
Marijuana	58.3	66.7	100.0	75.0	χ^2 (2) = 6.22*
Cocaine	16.7	16.7	25.0	19.4	χ^2 (2) = .35
Ecstasy/Club-drugs	16.7	25.0	33.3	25.0	χ^2 (2) = .88
Other[2]	25.0	33.3	50.0	36.1	χ^2 (2) = 1.69
POMS (pre-test) [3]	-1.75 (5.48)	-0.42 (6.82)	1.75 (9.21)	-0.14 (7.27)	F (2, 33) = .70
BAC (pre-test)	0.077 (0.025)	0.000 (0.000)	0.000 (0.000)	---	---
BAC (post-test)	0.070 (0.012)	0.000 (0.000)	0.000 (0.000)	---	---
Subjective ratings of intoxication (post-test)	4.45[4] (1.81)	2.55[5] (0.82)	1.00 (0.00)	---	F (2, 31) = 26.94*

Notes. Numbers in parentheses indicate standard deviations.

[1] Average number of standard drinks per occasion;

[2] Sum of opiates, hallucinogens, inhalants, the non-medically prescribed, tranquilizers, analgesics, sedatives, stimulants, and over-the-counter medications;

[3] POMS (Profile of Mood States; McNair et al., 1992) scores range from −20 to 100, with positive scores indicating negative mood and negative scores indicating positive mood;

[4] 4.45 indicates between easily noticeable to slightly intoxicated;

[5] 2.55 indicates between barely noticeable to slightly noticeable; BAC = Blood Alcohol Concentration.

* $p < .05$.

Table 2

Repeated-measures ANOVA and Univariate Planned Contrasts for the 0.1 Hz HRV Index and Other HRV Indices

Overall Effect	**0.1 Hz HRV**			**HF HRV**			**SDNN**			**pNN50**		
Contrast	***df***	***F* or *t***	η_p^2	***df***	***F* or *t***	η_p^2	***df***	***F* or *t***	η_p^2	***df***	***F* or *t***	η_p^2
Stimulus Effects	2, 66	10.56**	.24	2, 66	2.33	.07	2, 66	1.75	.05	2, 66	4.03*	.11
Negative vs. Neutral	1, 33	16.79**	.34	1, 33	3.81	.10	1, 33	1.09	.03	1, 33	4.54*	.12
Positive vs. Neutral	1, 33	7.59**	.19	1, 33	3.64	.10	1, 33	4.13*	.11	1, 33	8.47**	.20
Group Effects	2, 33	3.19*	.16	2, 33	6.52**	.28	2, 33	8.41**	.34	2, 33	13.88**	.46
Alcohol vs. Control [1]	1, 33	-2.09*		1, 33	-3.17**		1, 33	-4.11**		1, 33	-4.92**	
Alcohol vs. Placebo [1]	1, 33	.18		1, 33	-3.08**		1, 33	-2.03*		1, 33	-4.08**	
Within-subjects by Between-subjects Interaction Effects												
Stimulus × Group	4, 66	1.68	.09	4, 66	1.49	.08	4, 66	.29	.02	4, 66	.69	.04
Group Effects on Each Stimulus Type												
Negative: Alc. vs. Con.[1]	1, 33	-2.32*	.14	1, 33	-3.61**	.28	1, 33	-4.15**	.34	1, 33	-4.74**	.41
Negative: Alc. vs. Pla.[1]	1, 33	.38	.00	1, 33	-3.03**	.22	1, 33	-2.16*	.12	1, 33	-3.61**	.28
Positive: Alc. vs. Con.[1]	1, 33	-2.33*	.14	1, 33	-2.46*	.16	1, 33	-3.46**	.27	1, 33	-4.66**	.40
Positive: Alc. vs. Pla.[1]	1, 33	.43	.01	1, 33	-2.21*	.13	1, 33	-1.46	.06	1, 33	-4.04**	.33
Neutral: Alc. vs. Con.[1]	1, 33	-1.20	.04	1, 33	-2.72**	.18	1, 33	-3.12**	.23	1, 33	-4.03**	.33
Neutral: Alc. vs. Pla.[1]	1, 33	.25	.00	1, 33	-3.30**	.25	1, 33	-1.67	.08	1, 33	-3.51**	.27

Notes. All physiological indices were log transformed. All analyses met the assumption of sphericity, and univariate tests of the within-subjects effect were reported. Alc. = Alcohol group; Pla. = Placebo group; Con. = Control group.

* $p < .05$,

** $p < .01$

[1] *t* tests; $t^2 = F$ with $df = 1$; η_p^2 = partial eta squared; η^2 = .01, .06, and .14, respectively, for small, medium, and large effect sizes for ANOVA (Cohen, 1988).