Getting to the Heart of Low Sensitivity to Alcohol: Context Moderates Low Cardiovascular Response to Alcohol in Persons With a Family History of Alcohol Use Disorder

Marsha E. Bates, Eun-Young Mun, Jennifer F. Buckman, Evgeny Vaschillo, Bronya Vaschillo, Paul Lehrer, Tomoko Udo, and Laura M. Lesnewich

Background: Low sensitivity to alcohol in persons with a family history of alcoholism (FH+), compared to those without (FH−), contributes to risk for alcohol use disorder (AUD). However, sensitivity of FH+ cardiovascular response to alcohol is not well understood. This gap is significant because cardiovascular processes contribute to emotional regulation and stress response problems theorized to be central to the development and persistence of AUD. This study compared changes in heart rate (HR) and HR variability (HRV) between FH groups after consuming alcohol and control beverages and examined how these changes were moderated by emotional and alcohol-related contexts.

Methods: Young adults (N = 165) with FH+ (n = 110) or FH− (n = 55) each completed 2 sessions, separated by 1 week. They received one of 3 different beverages (alcohol, placebo, and told-no-alcohol) in each session. Electrocardiogram data were recorded during pre–beverage consumption and post–beverage consumption baselines, and then during 4 picture cue tasks (neutral, positive, negative, and alcohol-related). Generalized estimating equations were used to examine differences in cardiovascular reactivity (changes in HR and HRV power at ~ 0.1 Hz) across FH groups, beverage conditions, and picture cue tasks.

Results: A significant beverage condition × cue task × FH interaction effect on HRV was observed. The FH+ group, compared to the FH− group, showed (a) significantly less HRV suppression in specific cue contexts following alcohol, (b) a mixed pattern of more and less HRV suppression across cue contexts following placebo, and (c) a similar HRV reactivity pattern in the told-no-alcohol condition across cue tasks. For HR, there were no significant effects involving FH.

Conclusions: Diminished cardiovascular sensitivity to oral alcohol in FH+ persons varied within a given drinking episode depending on emotional and alcohol-related features of the context, suggesting that environmental characteristics play a role in the expression of low sensitivity to alcohol among FH+ individuals.

Key Words: Heart Rate Variability, Family History of Alcoholism, Low Response to Alcohol, Context, Loading.

LOW SENSITIVITY (LS) to alcohol, also referred to as a low level of response to alcohol, is an observable characteristic associated with at-risk drinking behaviors, increased risk for the development of an alcohol use disorder (AUD), and persistence of problem drinking in persons diagnosed with an AUD (Schuckit et al., 2018; Schuckit et al., 2012a). This reduced sensitivity to acute alcohol intoxication effects has been observed in persons with a family history of AUD (FH+, e.g., Schuckit, 1980; Schuckit, 2009b; Schuckit and Smith, 2000; Schuckit and Smith, 2017; Schuckit et al., 2004) who also are at increased risk for alcohol problems and AUD (Elliott et al., 2012). Although findings have not

From the Division of Life Sciences (MEB, JFB, EV, BV), Department of Kinesiology and Health, School of Arts and Sciences, Rutgers University – New Brunswick, New Brunswick, New Jersey; Center of Alcohol and Substance Use Studies (MEB, JFB, EV, BV, LML), Graduate School of Applied and Professional Psychology, Rutgers University - New Brunswick, Piscataway, New Jersey; Department of Health Behavior and Health Systems (E-YM), School of Public Health, University of North Texas Health Science Center, Fort Worth, Texas; Department of Psychiatry (PL), Robert Wood Johnson Medical School, Rutgers University - New Brunswick, Piscataway, New Jersey; Department of Health Policy, Management, and Behavior (TU), School of Public Health, University at Albany– SUNY, Rensselaer, New York; and Department of Psychology (LML), School of Arts and Sciences, Rutgers University - New Brunswick, Piscataway, New Jersey .

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Reprint requests: Marsha E. Bates, PhD, Center of Alcohol and Substance Use Studies, Rutgers University - New Brunswick, 607 Allison Road, Smithers Hall, Piscataway, NJ; Tel.: (848) 445-3559; Fax: (732) 445-3500; E-mail: mebates@smithers.rutgers.edu

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been entirely consistent (Newlin and Renton, 2010), persons with a FH+ have shown reduced postural sway (Schuckit, 1985; Schuckit et al., 2000), hormone response (Schuckit et al., 1987a; Schuckit et al., 1987b; Schuckit et al., 1988b), electroencephalographic background activity (Ehlers and Schuckit, 1991), and P300 event-related potential latency (Schuckit et al., 1988a) and have self-reported less perceived intoxication, impairment, and mood effects (Quinn and Fromme, 2011) following alcohol consumption, compared to persons without a family history of AUD (FH−). These findings point to the expression of LS across multiple response systems, but physiological indicators of reduced cardiovascular system response to alcohol have not been identified.

We posited that the process of heart rate variability (HRV), variability in the beat-to-beat intervals of the heart as measured by electrocardiogram (ECG), would be useful to characterize the putative LS phenotype. HRV reflects fine-grained, millisecond-by-millisecond adjustments in the time intervals between adjacent heart beats (Task Force of the European Society of Cardiology and the American Society of Pacing and Electrophysiology, 1996). Measured at rest, HRV reflects health status and autonomic activity; a relatively higher level of HRV is a robust biomarker of higher levels of physical and psychological health and resilience (Carnevali et al., 2018; Kemp and Quintana, 2013; McCraty and Shaffer, 2015; Nolan et al., 1998). Measured in response to challenge, changes in HRV reflect autonomic response to stimulation (e.g., by stress, substances, disease) and capacity for resilience (e.g., El-Sheikh et al., 2013; Hamilton and Alloy, 2016; Kim et al., 2018; Ralevski et al., 2019). It further provides a dynamic assessment of emotional responding (Appelhans and Luecken, 2006). Thus, HRV sensitively indexes cardiovascular adaptation in a manner and to a degree that heart rate (number of heart beats per minute) has not (Appelhans and Luecken, 2006; Porges, 2007; Vaschillo et al., 2008). Moreover, HRV maps onto the LS to alcohol phenotype by providing a measurable, in-the-moment response that should reflect an individual's sensitivity to a given stimulus (e.g., alcohol, salient cue exposure).

The value of HRV as a dynamic assessment tool also stems from understanding the underlying processes and mechanisms that regulate it. Respiratory sinus arrhythmia (RSA) and baroreflex signaling are two intrinsic processes of the cardiovascular system that are major sources of HRV (deBoer et al., 1987; Hammer and Saul, 2005; Legramante et al., 1999; Vaschillo et al., 2002; Vaschillo et al., 2006; Vaschillo et al., 1983; Yasuma and Hayano, 2004). Both RSA and baroreflex signaling are sensitive to acute alcohol intoxication and chronic alcohol use behaviors (Buckman et al., 2015; Mun et al., 2008; Ralevski et al., 2019). RSA, the increase and decrease in heart rate, respectively, with inhalation and exhalation, results from the interaction between cardiovascular and respiratory systems (Grossman and Taylor, 2007; Yasuma and Hayano, 2004) and is thought to reflect parasympathetic nervous system activity. Baroreflex signaling is a negative feedback loop between the heart and brain that coordinates heart rate with blood pressure and combines cardiovascular and brain reactivity to generate integrated responses to stress and emotion (Benarroch, 1997; Goldstein, 2001). Low-frequency HRV oscillations near 0.1 Hz frequency (i.e., 0.1 Hz HRV) provide a proxy measure of baroreflex activity (Cevese et al., 2001; Pfurtscheller et al., 2018) at rest and in response to cognitive, emotional, and appetitive challenges (Aasman et al., 1987; Mulder and Mulder, 1981; Mun et al., 2008; Pfurtscheller et al., 2017; Redondo and Del Valle-Inclan, 1992; Vaschillo et al., 2008).

We previously observed that more emotionally engaging visual picture cues (e.g., persons kissing, a snarling dog) elicited significantly elevated HRV reactivity compared to more neutral cues (e.g., a towel) in young adult drinkers (Vaschillo et al., 2008), likely as a part of the body's response to emotional loading. Blood alcohol concentrations (BACs) of ~ 70 to 90 mg/dl significantly reduced 0.1 Hz HRV, as did a placebo beverage, compared to a no-alcohol control beverage. Planned contrasts showed this reduction was statistically significant in the alcohol group, compared to the control group, and occurred in response to negative and positive emotional cues, but not neutral cues. This pattern of results suggests that emotional context influenced alcohol-related cardiovascular suppression of HRV and baroreflex activity. The relation of the drinking context to the expression of LS to alcohol in persons with FH+ is understudied, but appears to be important in view of the differences in cognitive and emotional processing and cue reactivity observed in this population compared to FH− persons (Bennett et al., 1988; Cservenka, 2016; Dager et al., 2013).

In this study, we examined whether 0.1 Hz HRV reactivity to oral alcohol was consistent with a LS phenotype. Healthy, young adult FH+ and FH− drinkers' HRV was measured during a low-demand cognitive task before and after drinking an active dose of alcohol, a placebo dose, or a no-alcohol beverage. Then, context was manipulated by exposing participants to 4 blocks of picture cues that were emotional (i.e., positive, negative, neutral) or alcohol-related. A 2-way interaction was predicted between beverage condition and FH status across all cue types. That is, LS to alcohol in FH+ drinkers was expected to present as weaker suppression of 0.1 Hz HRV reactivity following acute alcohol ingestion compared to FH− drinkers, implying relatively less cardiovascular adaptation to oral alcohol ingestion, and less disruption of communication between the neural network that modulates HRV and cardiovascular feedback to the brain through the baroreflex. We examined a 3-way interaction to explore whether the emotional or alcohol-related nature of the cues affected 0.1 Hz HRV reactivity to acute alcohol and placebo differently as a function of family history status. In other words, we tested whether LS to alcohol in FH+ drinkers was attenuated or strengthened in response to different cue types. Alcohol consumption and cue context effects were examined on heart rate as a secondary outcome for comparison to the previous literature.

MATERIALS AND METHODS

Design

This doubly controlled alcohol challenge study used a within-subjects design with planned missingness and randomization such that each participant was assigned to 2 of the 3 experimental beverage conditions: active alcohol, placebo alcohol, and told-no-alcohol beverage. This planned missingness design (e.g., Graham et al., 2006; Little and Rhemtulla, 2013) was implemented to reduce participant burden, attrition, and expense associated with testing each participant in all 3 beverage conditions (see also Analysis).

Participants

Participants were recruited through university and community advertisements for a study of alcohol effects on response to visual stimuli. To enhance recruitment of FH+ participants, some advertisements specified having a father, brother, or sister who was a heavy drinker. The sample ($N = 165$) included 26 men and 29 women who were FH− for all first- and second-degree relatives (33%), and 53 men and 57 women who were FH+ for alcohol dependence on the part of 1 or more first-degree relatives (67%). This study was approved by the Rutgers University Arts and Sciences Institutional Review Board for the Protection of Human Subjects Involved in Research (Protocol #04-167Rx). Each participant provided signed informed consent prior to the start of each experimental session. At the completion of each session, participants were compensated $50.00 for their time, or a prorated amount if the session was not completed.

Inclusion and Exclusion Criteria

Potential risks associated with the alcohol dose used in this study were minimized by excluding men who did not consume 4 drinks, and women who did not consume 3 drinks, in a drinking episode at least twice per month in the past year. Additional exclusion criteria were self-reports of a lifetime history of any substance dependence, psychotic or neurological disorder or treatment, a past-year history of any other psychiatric diagnosis or treatment, maternal (biological) substance use disorder during pregnancy to help rule out fetal alcohol effects, medical conditions that contraindicated alcohol administration or confounded interpretation of HRV (e.g., diabetes, high blood pressure, heart disease, asthma), an abnormal cardiovascular record or high blood pressure detected in the laboratory, more than 20% over- or underweight from the ideal for gender, height, and body frame (Metropolitan Life Height-Weight Table, 1983), and self-reported weekly use of illicit or prescribed drugs. Women provided a urine sample to screen for exclusion due to pregnancy.

FH and Participant Characteristic Assessment

Family history of AUD was classified using the Family History Assessment Module, a reliable and valid semi-structured interview (Rice et al., 1995). This instrument was developed using diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders (3rd ed., revised, American Psychiatric Association, 1987) for clinicians and nonclinicians to assess for the presence of major psychiatric disorders (e.g., alcohol and drug abuse and dependence, depression, mania, schizophrenia, antisocial personality) among relatives of the informant. In this study, the interviews were administered by advanced clinical psychology doctoral students who were trained to conduct such interviews.

To determine comparability of FH groups on potentially confounding factors, typical quantity per occasion of alcohol use, and typical frequency of alcohol, cigarette, cannabis, and other drug use during the past 30 days was assessed (Buckman et al., 2015). For illicit drugs, such as stimulants, cocaine, psychedelics, and tranquilizers, the total number of drugs tried in lifetime and used in the past 30 days was calculated. The Beck Depression Inventory-II (BDI-II; Beck et al., 1996) and the Beck Anxiety Inventory (BAI; Beck and Steer, 1990) were used to assess negative affective states. The Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) was used to assess mood before and after the experiment. Participant characteristics are shown by FH group in Table 1. There were no significant differences between the FH groups in alcohol and drug use, as is typical in college samples (Elliott et al., 2012), nor in age or symptoms of depression and anxiety.

Stimulus Cues

Emotionally valenced picture cues (negative, positive, neutral) were from the International Affective Picture System (IAPS; Lang et al., 2001). Alcohol-related picture cues were from the Normative Appetitive Picture System (NAPS; Stritzke et al., 2004) and Mun et al., (2008). Six different blocks of picture cues were constructed for each of the 4 cue types: positive (e.g., ice cream sundae, puppy dogs), negative (e.g., snake, man aiming gun), neutral (e.g., pair of shoes, man with bike), and alcohol-related (e.g., mug of beer, woman drinking martini), to mitigate the potential influences of any individual pictures. Each block consisted of a set of 15 unique picture cues of one cue type that was presented twice, for a total of 30 cue presentations per block. The order of pictures was randomized within sets. Highly negative and positive pictures were matched as closely as possible on IAPS standardized ratings of arousal, but varied systematically in valence, while neutral pictures were intermediate in valence and relatively low in arousal (Lang et al., 2001). IAPS picture cue numbers are given in Table S1. The mean standardized affective valence ratings based on the Self-Assessment Manikin methodology (SAM; Lang et al., 2001) on a scale of 1 = *unpleasant*

Table 1. Demographic Characteristics of Participants with a Family History Positive compared to Negative for Alcohol Use Disorders

	FH+ ($n = 110$)	FH− ($n = 55$)	*t*-test/chi-square
Age	21.6 (0.85)	21.5 (0.72)	$t(163) = 0.48$
% female	51.8	52.7	$\chi^2(1) = 0.01$
BDI-II[a]	3.99 (4.15)	4.50 (4.29)	$t(156) = 0.72$
BAI[b]	3.34 (3.85)	3.40 (3.85)	$t(157) = 0.09$
Alcohol use (past 30 days)			
Drinks per occasion	4.99 (2.03)	4.91 (2.13)	$t(163) = 0.24$
Drinking days per week	1.85 (1.26)	1.77 (1.10)	$t(163) = 0.40$
Drug use (% participants reporting use)			
Cigarettes			
Past 30 days	39.1	40.0	$\chi^2(1) = 0.01$
Lifetime	34.6	41.8	$\chi^2(1) = 0.83$
Cannabis			
Past 30 days	25.5	29.1	$\chi^2(1) = 0.25$
Lifetime	50.9	47.3	$\chi^2(1) = 0.19$
Other[c]			
Past 30 days	1.8	5.5	$\chi^2(1) = 1.65$
Lifetime	34.6	38.2	$\chi^2(1) = 0.21$

FH− = family history negative for alcohol use disorders; FH+ = family history positive for alcohol use disorders; BDI-II = Beck Depression Inventory-II; BAI = Beck Anxiety Inventory.

[a]BDI-II, $N = 158$ (FH−, $n = 52$; FH+, $n = 106$) due to missing data because of experimenter error.

[b]BAI, $N = 159$ (FH−, $n = 53$; FH+, $n = 106$) due to missing data because of experimenter error.

[c]Any use of cocaine, club drugs (e.g., ecstasy), opiates, psychedelics, inhalants, or the nonmedically prescribed use of tranquilizers, analgesics, sedatives, stimulants, or over-the-counter medications.

to 9 = *pleasant* were 2.14 (SD = 0.46), 7.27 (SD = 0.51), and 4.89 (SD = 0.40) for negative, positive, and neutral pictures, respectively. The mean standardized arousal ratings (Lang et al., 2001) on a scale of 1 = *calm* to 9 = *aroused* were 6.38 (SD = 0.49), 5.92 (SD = 0.71), and 2.99 (SD = 0.49) for negative, positive, and neutral cues, respectively. Standardized ratings of the alcohol-related pictures were obtained from an independent sample of 100 college student volunteers. The SAM (Lang et al., 2001) was used to generate valence and arousal ratings that were comparable to IAPS ratings. Alcohol picture cues had an average valence rating of 5.11 (SD = 0.31) and an average arousal rating of 4.08 (SD = 0.29).

Procedures

Following an initial telephone screening interview and the family history assessment, each eligible participant was assigned to complete 2 of the 3 beverage conditions (alcohol, placebo, control). The 2 beverage conditions were conducted in 2 separate sessions scheduled approximately 1 week apart. The order of beverage conditions across sessions was counterbalanced across participants. Participants were asked to refrain from alcohol or other drug use (except caffeine and cigarettes) for 24 hours prior to the session and to consume a light meal 3 hours before coming to the laboratory. Sessions were scheduled between 10 AM and 2 PM to minimize circadian variation. Participants provided written informed consent and then completed questionnaires. Blood pressure, temperature, weight (to calculate alcohol dose/drink volume), and a breath estimate of BAC (to assure no alcohol prior to testing) were assessed.

The participant was seated 2.5 meters from the front of a TV screen in a sound-attenuated, dimly lit room. Ag-AgCl ECG electrodes were placed on the right arm (active), left arm (ground), and left leg (active) to continuously record an electrocardiogram (ECG) using a Powerlab Acquisition system (ADInstruments, Colorado Springs, CO) with a sampling rate of 1,000 Hz. Respiration was assessed by placing 2 respiration strain gauge belts around the participant's chest and abdomen.

Each participant completed the first baseline task prior to consuming a beverage (prebeverage baseline cue task = B1). The baseline task was a standardized low-demand "vanilla" task (Jennings et al., 1992) wherein variously colored rectangles were presented sequentially at the rate of 1 rectangle per 10 seconds (i.e., 0.1 Hz) and the participant was asked to silently count the number of blue rectangles. This task was used, rather than an uncontrolled resting baseline, to equate cognitive load effects on cardiovascular signaling across participants (Jorna, 1992; Sloan et al., 1994) and to provide a baseline HRV value that has better between- and within-subject repeatability across sessions (Jennings et al., 1992). The 0.1 Hz presentation rate of the baseline task provided a rigorous comparison to the picture cue tasks wherein stimuli also were presented at 0.1 Hz.

Next, the participant consumed one of the 3 experimental beverages, alcohol, placebo, or told-no-alcohol control, depending on his or her assigned beverage condition in that session. In both the alcohol and placebo condition sessions, participants were told that their beverage contained some amount of alcohol and that the maximum BAC that they could expect would be near the legal limit for driving in the United States. In the told-no-alcohol control condition, participants were told that their beverage contained no alcohol. Alcohol doses to achieve a target peak BAC of approximately 90 mg/dl were calculated based on body weight (0.90 ml/kg for men, 0.78 ml/kg for women) and combined with a mixer (orange, cranberry, and lime juice) in a ratio of 4 parts mixer to one part alcohol (95% ethanol). Each volumetric beverage was either 100% mixer (i.e., told no alcohol and received no alcohol), mixer with 100 μl ethanol float per cup and alcohol wiped around the cup rim for olfactory cues (i.e., told alcohol and received placebo), or mixer plus alcohol (i.e., told alcohol and received alcohol). The beverage was divided into 3 equal drinks, and each drink was consumed during a consecutive 5-minute interval. When BAC reached ~ 60 mg/dl on the ascending limb of the BAC curve (or after 5 minutes in placebo and control conditions), the participant performed a second baseline vanilla task (postbeverage baseline cue task = B2), immediately followed by the 4 picture cue exposure tasks (blocks of positive, negative, neutral, and alcohol-related cues).

The participant viewed 4 blocks of picture cues types (i.e., the 4 cue tasks); each block contained only 1 cue type (i.e., alcohol-related, positive, negative, or neutral). The specific block seen was one of 6 different blocks per picture cue type that had been constructed. To guard against potential habituation or carryover effects from viewing cue blocks in a specific order, the presentation order of the 4 cue tasks was counterbalanced across participants using 24 patterns of task orders generated with SAS Proc Plan (SAS Institute, Cary, NC, USA). Participants always saw different blocks of cues in Sessions 1 and 2. For all tasks, each picture cue was presented for 5 seconds with a 5-second interstimulus interval (ISI), resulting in a 0.1 Hz frequency of picture cue presentation to amplify cardiovascular response and increase measurement sensitivity (e.g., Vaschillo et al., 2008).

During each ISI within a particular cue set (two 15-cue sets per block), the participant gave either a valence or an arousal rating using the SAM method (Lang et al., 2001), with the order of valence and arousal ratings counterbalanced across participants (i.e., during one set, participants gave valence ratings for the cues, and during the other set, participants gave arousal ratings). Each cue task lasted for 5 minutes with a 30-second intertask interval. Participants viewed a total of 120 pictures in each session (4 blocks of 30 pictures) for a total of 20 minutes. Then, BAC was measured again.

The conditions of the current study were completed in approximately 2.5 hours. Afterward, additional measurements were obtained as part of different study aims, including paced breathing (Udo et al., 2013) and memory tasks (Nguyen-Louie et al., 2016). Finally, a 7-point (1 = *not at all* to 7 = *moderately intoxicated*) subjective intoxication rating scale (Newlin, 1985) was completed to validate the beverage condition manipulation. In the alcohol condition, participants were in the laboratory for a total of about 5.5 hours (until their BAC = 0); in other conditions, about 3.5 hours.

Approximately 1 week following Session 1, the participant returned to the laboratory for Session 2 and was reconsented; procedures were identical to Session 1 with the exception of the beverage condition assignment. The intertrial and intertask intervals were identical for all participants throughout the study, and all participants completed the procedures in exactly the same order in each session.

Psychophysiological Measures

ECG and respiration data were exported to WinCPRS software (Absolute Aliens Oy, Turku, Finland) to process beat-to-beat RR intervals (RRIs) of the ECG and perform spectral (i.e., Fourier) analysis of the successive RRIs (Cooke et al., 1999; Taylor et al., 1998). Cubic interpolation of the nonequidistant waveform of the RRI sequence was completed, and RRIs were resampled at 4 Hz. For each of the six 5-minute tasks (pre- and postbeverage baselines, neutral cues, negative cues, positive cues, and alcohol cues), the 0.1 Hz HRV index was calculated as the maximum amplitude of the RRI spectral power (e.g., Buckman et al., 2010; Mun et al., 2008; Vaschillo et al., 2008) within a narrow range surrounding the 0.1 Hz frequency (0.076 to 0.107 Hz). The 0.1 Hz HRV index is thought to reflect individual differences in the amplitude of baroreflex responsivity to stimulation, with higher baseline values and reactivity to breathing interventions indicating better functioning (Vaschillo et al., 2002; Vaschillo et al., 2006). HR was calculated as the mean number of beats per minute within each of the 5-minute tasks.

Analysis

Generalized estimating equations (GEE) were used to examine data from the ECG recording that was repeated in the baseline and cue tasks, which were then repeated in 2 beverage sessions. GEE models are well suited for repeated or nested data that are highly correlated, and can be applied to data with planned missingness, as in the current experiment wherein each participant completed only 2 of the 3 conditions (Ghisletta and Spini, 2004). GEE models were analyzed using SPSS (SPSS Inc., Chicago, IL) to examine cardiovascular reactivity in response to cue exposure across the beverage conditions. The mean 0.1 Hz HRV and HR reactivity scores were assessed using change scores from B1, the prebeverage baseline task. The 0.1 Hz HRV index was first log-transformed, as is standard practice for normalizing frequency-domain HRV indices (Shaffer and Ginsberg, 2017), and change scores were subsequently calculated. Mean change scores were normally distributed, and thus, an identity link was specified for both outcome measures. An unstructured correlation structure and robust standard errors were specified.

We analyzed 2 models separately for 0.1 Hz HRV and mean HR. First, main-effects–only models were analyzed. Family history (FH+, FH−), task (B2, neutral, positive, negative, alcohol picture cue blocks), beverage condition (alcohol, placebo, control), beverage session order (first, second), and sex (female, male) were used as time-invariant fixed effects. Change in respiration frequency was included as a time-varying covariate for the HRV analysis because respiration frequency may affect HRV. Respiration was not included in the HR model so that results could be compared to previous acute alcohol administration studies of HR, which did not control for respiration. Next, all 2-way and 3-way interaction effects were tested in the second models: beverage condition × task, family history × task, beverage condition × family history, and beverage condition × family history × task interaction effects. The 3-way interaction tested whether LS to alcohol among FH+ individuals varied across task, and all lower-order interactions were included, as their inclusion is necessary to correctly interpret the 3-way interaction effect.

RESULTS

The family history groups did not differ statistically in terms of the average BAC, negative or positive affective state, or subjective arousal or valence ratings of picture cues. These results are summarized in Tables S2–S6. Participants' ratings of intoxication at the end of the session were used as a placebo manipulation check. Average subjective intoxication ratings varied significantly across beverage conditions, with the participants in the alcohol condition reporting higher levels of perceived intoxication (mean ± standard deviation: 4.6 ± 1.3, Session 1; 4.7 ± 1.4, Session 2) than those in the placebo condition (2.6 ± 1.2, Session 1; 2.1 ± 1.0, Session 2). The control group reported no intoxication.

0.1 Hz HRV Reactivity

Table 2 shows the results of the GEE model analyses for HRV (top) and HR (bottom). The main-effects–only model indicated that there were significant mean 0.1 Hz HRV differences across beverage conditions, gender, and tasks. 0.1 Hz HRV reactivity was significantly suppressed in the alcohol condition and, to a lesser extent, in the placebo condition, compared to the control condition. Women exhibited higher levels of 0.1 Hz HRV reactivity than did men. 0.1 Hz HRV reactivity to all picture cues was significantly higher than 0.1 Hz HRV reactivity during the postbeverage baseline task (B2); reactivity was significantly higher in response to the negative cues than to the positive, neutral, and alcohol cues, which did not vary from one another. Finally, higher respiration frequencies were significantly associated with lower 0.1 Hz HRV reactivity responses.

In the interaction model, there was a significant beverage condition × task interaction effect. Figure 1 shows that alcohol, compared to the placebo and control beverages, substantially suppressed 0.1 Hz HRV reactivity at B2 and blunted reactivity to the picture cue blocks.

There was a significant 3-way beverage condition × task × family history interaction effect. Figure 2 shows changes in the 0.1 Hz HRV index across tasks for FH+ and FH− individuals during alcohol, placebo, and control beverage conditions. In the told-no-alcohol control condition, post hoc mean comparisons indicated that the FH groups were relatively equivalent (i.e., no significant FH group differences) across tasks, with HRV reactivity in both groups being elevated significantly in response to picture cues, and especially negative picture cues, relative to the B2 task. In the alcohol condition, the FH+ group showed significantly less HRV suppression compared to the FH− group at B2 and in response to the emotional and alcohol cues, but not the neutral cues. Following placebo, the FH+ group

Table 2. Generalized Estimating Equations Model Fit

	Main-effects models			Interaction-effects model		
	X^2	*df*	*p*	X^2	*df*	*p*
Change in 0.1 Hz HRV						
Intercept	103.69	1	0.00	98.02	1	0.00
Sex	5.88	1	0.02	2.09	1	0.15
Session Order	0.29	1	0.01	0.49	1	0.49
Task	325.09	4	0.00	247.28	4	0.00
Beverage	28.89	2	0.00	22.09	2	0.00
Family History	0.58	1	0.45	0.01	1	0.94
Respiration Frequency	9.65	1	0.00	11.82	1	0.00
Beverage × Family History				1.36	2	0.51
Task × History				3.24	4	0.52
Beverage × Task				18.15	8	0.02
Beverage × Task × Family History				18.48	8	0.02
Change in HR						
Intercept	239.27	1	0.00	240.80	1	0.00
Sex	0.05	1	0.83	0.00	1	0.97
Session Order	7.66	1	0.01	11.58	1	0.00
Task	166.63	4	0.00	180.26	4	0.00
Beverage	96.25	2	0.00	126.47	2	0.00
Family History	0.01	1	0.93	0.00	1	1.00
Beverage × Family History				0.64	2	0.73
Task × Family History				1.30	4	0.86
Beverage × Task				18.26	8	0.02
Beverage × Task × Family History				10.58	8	0.23

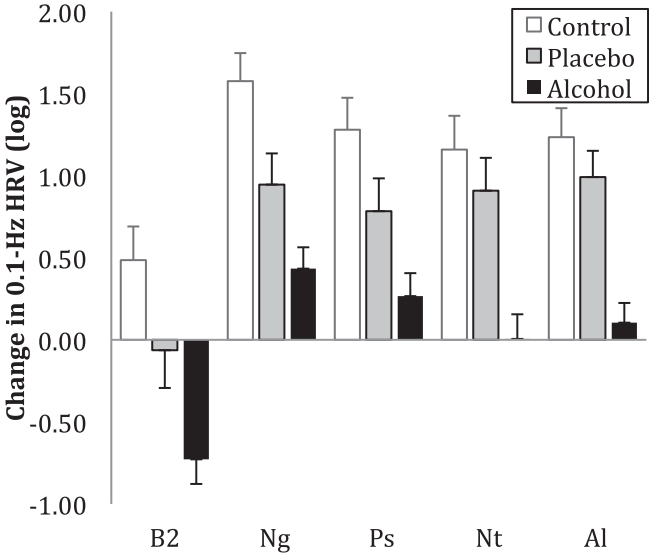

Fig. 1. Changes in the 0.1 Hz HRV index (from predrinking baseline task) across tasks during alcohol, placebo, and control conditions. Least square means and standard errors. B2 = postdrinking baseline; Ng = emotionally negative picture cue block; Ps = emotionally positive picture cue block; Nt = emotionally neutral picture cue block; and Al = alcohol-related picture cue block.

showed enhanced HRV suppression at B2, but reduced suppression in response to negative and alcohol cues, compared to the FH− group.

HR Reactivity

There were significant main effects of beverage condition, task, and session on mean HR. HR increased the most in the alcohol condition, followed by the placebo condition, and then the control condition (Table 2). The HR responses to all picture cue types were greater than the HR responses to B2. HR responses to negative cues were less than to positive, neutral, and alcohol picture cues, which were not statistically different from one another. Mean HR responses were also greater during the first session, compared to the second session.

In the second HR model with interaction effects, there was a significant beverage condition × task interaction effect. No other interaction effects were significant. Figure 3 shows adjusted means and standard errors. Post hoc mean comparisons revealed that in all beverage conditions, participants showed the highest HR responses to positive, neutral, and alcohol cues. In the control condition, alcohol cues elicited

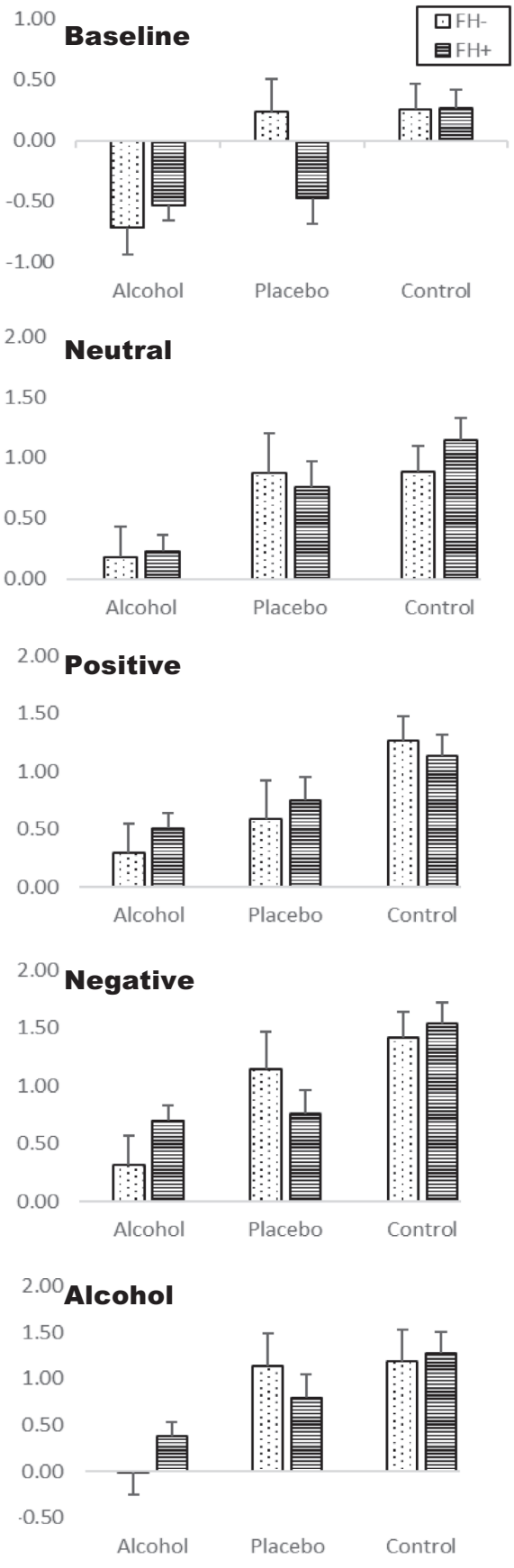

Fig. 2. Changes in the 0.1 Hz HRV index (from predrinking baseline task) across tasks for family history–positive (FH+) and family history–negative (FH−) individuals during alcohol, placebo, and control conditions. Least square means and standard errors. A time-varying covariate, change in respiration frequency, was adjusted at 0.11. B2 = postdrinking baseline; Ng = emotionally negative picture cue block; Ps = emotionally positive picture cue block; Nt = emotionally neutral picture cue block; and Al = alcohol-related picture cue block.

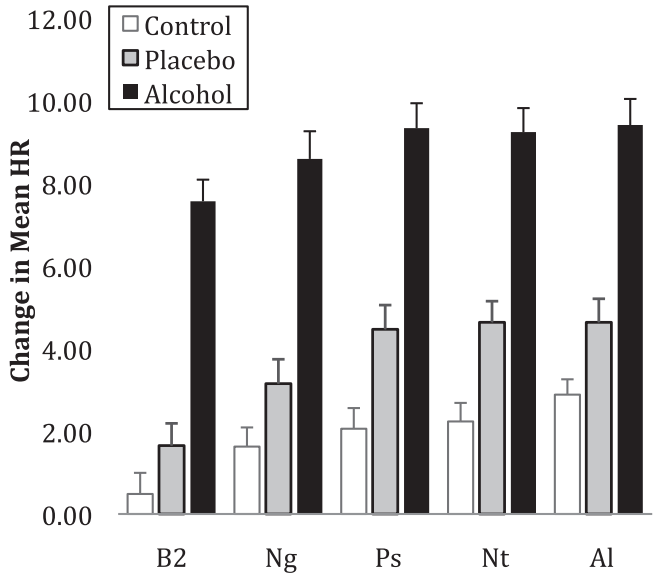

Fig. 3. Changes in mean HR (from predrinking baseline task) across tasks during alcohol, placebo, and control conditions. Least square means and standard errors. B2 = postdrinking baseline; Ng = emotionally negative picture cue block; Ps = emotionally positive picture cue block; Nt = emotionally neutral picture cue block; and Al = alcohol-related picture cue block.

the most HR reactivity of all cue types. In both placebo and control conditions, HR response to negative cues was significantly lower than to positive, neutral, and alcohol cues, although higher than B2. Overall, HR reactivity to different cue types was somewhat less differentiated in the alcohol condition than it was in other conditions.

DISCUSSION

Lower physiological and subjective responses to acute oral alcohol have been associated with increased risk for the development of AUD. Although multiple physiological and subjective indicators of LS to alcohol are overrepresented in FH+ and other high-risk samples, cardiovascular indicators of LS previously have not been identified. We compared the FH+ and FH− groups of young adult drinkers on an index of 0.1 Hz HRV reactivity to alcohol challenge to capture a dynamic, real-time process of body–brain communication within different emotional and alcohol-related contexts. A primary contribution of this study was to provide initial evidence that the expression of cardiovascular LS to alcohol in persons with FH+ is dependent in part on the emotional and appetitive visual characteristics of the environment.

The pattern of HRV main effects in the GEE model was generally consistent with previous findings regarding alcohol and emotional context effects on 0.1 Hz HRV reactivity (Vaschillo et al., 2008). That is, HRV reactivity was suppressed by an acute dose of oral alcohol that gave rise to BACs near the legal limit of intoxication in the United States; an alcohol placebo beverage also decreased HRV reactivity, but to a lesser extent. HRV reactivity was significantly greater in response to picture cues compared to the postbeverage baseline task, with negative cues evoking greater reactivity, compared to the other cue types. The significant 2-way interaction between cue task and beverage condition pointed to the contribution of context to both the physiological effects of alcohol and alcohol expectancy effects on cardiovascular regulation.

The significant 3-way interaction involving cue task, beverage, and family history status suggested that the moderating role of context on HRV reactivity to alcohol and placebo beverages varied by FH status. To explain this further, in the control (told-no-alcohol) beverage condition, the family history groups responded rather similarly, showing the anticipated increases in 0.1 Hz HRV reactivity in response to picture cues, and especially to those that were emotionally valenced and alcohol-related (Mun et al., 2008; Vaschillo et al., 2008). In the alcohol condition, the FH+ group evidenced significantly less alcohol-related suppression of 0.1 Hz reactivity, indicative of a LS response, in some contexts. LS to alcohol in the FH+ group was observed shortly after drinking (B2 postbeverage baseline) and was most pronounced when task content was emotionally negative and alcohol-related (Fig. 2). In the placebo condition, the FH+ group showed the opposite pattern: enhanced suppression of HRV at B2 and in response to negative emotional and alcohol-related cue tasks compared to the reactivity of the FH− group. In contrast, the FH− group's reactivity was relatively unaffected by the placebo beverage, except in emotionally valenced contexts. In the context of the other picture cues, both FH groups' HRV reactivity levels following the placebo beverage were intermediate between their alcohol and control levels. Thus, FH+ cardiovascular reactivity appeared to be uniquely sensitive to the expectancy effects compared to the FH− group in some contexts (e.g., baseline, negative emotional loading), but showed little differentiation in other contexts. The 3-way interaction test involving contextual loading cautions against overinterpreting specific context effects. Yet, these differentiated responses highlight the value of assessing alcohol sensitivity in varying cognitive, emotional, and appetitive environments to begin to understand contextual influences on the expression of LS to alcohol and the operation of alcohol expectancy.

LS to Alcohol, Risk, and Context

Low sensitivity to alcohol has been associated with negative alcohol-related consequences (Schuckit et al., 2008; Wetherill and Fromme, 2009) and used to predict the prospective development of AUD (Schuckit and Hesselbrock, 1994; Schuckit and Smith, 1996; Schuckit and Smith, 2000; Schuckit and Smith, 2001; Schuckit et al., 2007a; Trim et al., 2009). In line with well-established evidence that people often drink alcohol to modify emotional states and decrease inhibition (e.g., Cooper et al., 1995; Labouvie and Bates, 2002; Patrick and Schulenberg, 2011), LS to alcohol

effects on cardiovascular regulation could promote risk by increasing the amount of alcohol needed to achieve desired effects of drinking, such as increased sociability and disinhibition and decreased negative affect (Schuckit, 2009a; Schuckit, 2009b; Schuckit et al., 2007b). From an integrated brain–body perspective (Buckman et al., 2018), the decreases in HRV that have been observed in multiple laboratories following oral alcohol ingestion (reviewed in Ralevski et al., 2019) would serve to alter communication between the cardiovascular system and the brain areas involved in cardiovascular regulation (Benarroch, 1997; Goldstein, 2001). These brain areas, collectively referred to as the central autonomic network, include neural relay and integration areas extending from nuclei in the brainstem, through midbrain to extended limbic and prefrontal regions that participate in cognitive, emotional, and behavioral control. It follows that, consistent with a low cardiovascular sensitivity to alcohol, reduced communication between cognitive control and behavioral activation systems through the baroreflex loop (Kandel et al., 2000) during states of acute intoxication may promote increased consumption of alcohol to achieve functional goals of drinking.

Yet, the effects of LS to alcohol appear to be nuanced, with other evidence suggesting potential protective functions of low alcohol sensitivity, for example, in reducing regretted, alcohol-related sexual encounters in women (Hone et al., 2017) and protecting from hangover depending on the level of alcohol consumption (Piasecki et al., 2012). This complexity suggests that the mechanisms through which lower sensitivity to alcohol biases drinking behavior to achieve affective and behavioral goals, or through other pathways, will require a more inclusive conceptualization that takes into account additional personal and environmental factors. The present results suggest that the potential expression of lower cardiovascular sensitivity by FH+ persons following drinking was modulated by contextual features in the environment that were negatively charged or alcohol salient. Importantly, this implies that even within the same person, physiological sensitivity to acute alcohol may vary within a drinking occasion dependent on changes in the environment.

We previously characterized reductions in HRV and other cardiovascular changes on the ascending limb of the blood alcohol curve as real-time cardiovascular adaptations to alcohol challenge in healthy young drinkers such as the current sample (Buckman et al., 2015). These cardiovascular adaptations would be expected to alter interoceptive processes (Verdejo-Garcia et al., 2012) that relay visceral information about increasing blood alcohol concentrations to the brain to bring about awareness of the phenomenal experience of intoxication, including the need to slow or increase drinking rate depending on the reason for alcohol use. The present findings suggest that LS to alcohol in FH+ individuals may mute this interoceptive feedback loop in contexts that are emotionally negative and alcohol-related. Potential genetic moderators of physiological sensitivity to alcohol, such as family history of AUD, thus may bias drinking behavior in a complex manner depending not only on the personal motivations and reasons for drinking highlighted in the previous literature, but also on interaction with the environment. A previous series of consensus papers considered how progress might be made in identifying well-defined alcohol risk phenotypes for robust study across human and animal models (Crabbe et al., 2010). The LS phenotype was thought to hold promise, but at that time, there was no evidence that the cardiovascular system participated. The present results suggest that it would be useful to perform parallel animal studies to probe cardiovascular mechanisms further to determine whether alcohol's dampening effects on HRV in different contexts share genetic influence with other systems implicated in the LS phenotype.

The present study did not find a significantly higher HR response to alcohol in the FH+ compared to the FH− group. Although heightened cardiovascular sensitivity to alcohol effects has been observed in other high-risk populations of drinkers (e.g., Newlin and Renton, 2010; Newlin and Thomson, 1990), such effects appear to reflect alcohol's reward and reinforcement value, rather than the LS phenotype, per se (e.g., Crabbe et al., 2010). Studies designed to capture simultaneous alcohol effects on different cardiovascular and neural processes within the individual are needed. Informative designs further would include tasks that characterize a person's active regulation of cognitive and emotional responses during acute alcohol intoxication. Previous alcohol administration studies have identified differences in neural reactivity during emotional and cognitive processing tasks, as well as differences in cerebral blood flow, between those who did and did not express LS to alcohol (Paulus et al., 2012; Schuckit et al., 2012b; Tolentino et al., 2011). Study of alcohol sensitivity at multiple, concurrent system levels would inform how reduced and heightened alcohol sensitivity of different system processes correlate within individuals to affect the expression of risk in different environments.

Strengths and Limitations

This study had a number of strengths, including the within-subjects experimental design (Quintana and Heathers, 2014), appropriate representation of women (McHugh et al., 2018), placebo and told-no-alcohol control beverages, and similarity between the family history groups in age, current drinking practices, other drug use, mood, and depression and anxiety symptoms that could confound the interpretation of group differences in alcohol sensitivity. HRV was measured precisely with short-term ECG recordings and operationalized with a quantitative index, although reliability of the 0.1 Hz index could not be assessed in this sample because participants were not tested in the same beverage condition in the 2 sessions. We note that the reliability of HRV indices has been found to vary substantially across different populations of subjects and data collection

methodologies. In contrast to some clinical populations, in healthy populations such as the present, multiple other HRV measures collected under stationary conditions in controlled laboratory paradigms have shown good-to-moderate reliability levels (reviewed in Sandercock et al., 2005). Further study of the reproducibility of between-person differences and within-person changes in the 0.1 Hz HRV index is needed.

The generality of the present results also is limited to young adults who were primarily college students and did not report a history of alcohol or drug use disorder or treatment. Nondrinkers and light drinkers were excluded to reduce risk associated with the active alcohol dose administered. Thus, the participants in this study did not represent the full spectrum of alcohol use behaviors nor risk in either FH+ or FH− populations. Nonetheless, the present sample was comprised of ostensibly healthy young adult drinkers, and thus, the identification of context-dependent differences specific to family history status may suggest a robust underlying phenomenon that could be better detected across the full spectrum of drinkers. Risk conferred by LS to alcohol, of course, will not be realized in many FH+ or other high-risk persons, and risk may be expressed at different developmental stages depending upon other co-occurring risk processes, both internal and in the environment. This experiment did not assess concordance between reduced cardiovascular response to acute alcohol and other systems implicated in putative LS phenotypes. For example, our subjective intoxication assessment was a single item asked as a placebo manipulation check at the end of the experimental session when BACs were low in the alcohol condition. Thus, this assessment was not comparable in complexity or timing to the subjective intoxication assessments that have been the focus of previous LS research (Quinn and Fromme, 2011).

Importantly, the use of standardized picture cues in a constrained laboratory setting to examine alcohol effects within emotional and alcohol-related drinking contexts was a highly artificial proxy of everyday drinking episodes wherein people respond to personally relevant emotional and appetitive cues. Replication studies are needed to test these results in ecologically valid drinking contexts. Recent technological advancements in the mobile and telemetric assessment of physiological signals may be used to provide a stronger test of the expression of LS to alcohol effects in the natural environment. Future laboratory-based studies would benefit from including simultaneous assessment of multiple cardiovascular and neural processes to further elaborate the role of neurocardiac signaling in the LS phenotype.

CONCLUSIONS

The present findings suggest that the cardiovascular system participates in the LS phenotype in FH+ persons and that their likelihood of reduced HRV response to alcohol is moderated by the context in which it occurs. Specifically, this study found that oral alcohol suppressed HRV less in FH+ individuals than their FH− counterparts predominantly when contextual cues were emotionally negative or alcohol-related. These results, if replicated, highlight the role of emotional and appetitive contexts in LS phenotype expression.

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CONFLICTS OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. International Affective Picture System (IAPS) cue numbers.

Table S2. Average blood alcohol concentration (BAC) estimates in the alcohol group before (pre) and after (post) picture cue exposure by family history group.

Table S3. Analysis of variance of family history and beverage condition effects on affective state in session 1.

Table S4. Analysis of variance of family history and beverage condition effects on affective state in session 2.

Table S5. Repeated-measures analysis of variance of family history, beverage condition, and cue type effects on subjective ratings of cue valence.

Table S6. Repeated-measures analysis of variance of family history, beverage condition, and cue type effects on subjective ratings of cue arousal.