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September 25, 2017

Dear Editors:

We kindly request that you consider the attached manuscript for publication as an original research paper in *Addictive Behaviors*.

The paper describes an experimental methodology used to examine the effects of alcohol consumption on cardioceptive accuracy using a placebo-controlled, double-blind, crossover design. The primary findings were that, for men only, alcohol significantly impaired cardioceptive accuracy relative to a placebo at both low and high levels of arousal, with medium to large effect sizes. These findings, though preliminary, are consistent – at least for men – with the proposed hypothesis linking alcohol consumption and anxiety.

Thank you very much for your consideration. We look forward to hearing from you.

Sincerely,

Ken Abrams, on behalf of my co-authors

Submitted for publication as an original research paper in *Addictive Behaviors*

(September 2017)

Running Head: Alcohol and Heartbeat Perception

The Effects of Alcohol on Heartbeat Perception: Implications for Anxiety

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- The authors report no conflicts of interest.

Abstract

Introduction: It is well established that some individuals self-medicate their anxiety with alcohol. Though much evidence exists that alcohol consumption can be negatively reinforcing, there remains uncertainty regarding what mediates the relationship between alcohol and anxiety. An unexplored possibility is that, for some, alcohol impairs interoceptive sensitivity (the ability to accurately perceive one's physiological state), thereby decreasing state anxiety. Consistent with this, highly accurate heartbeat perception is a risk factor both for elevated trait anxiety and anxiety disorders. However, the direct impact of alcohol on cardioceptive accuracy has not to our knowledge been previously examined. **Methods:** Sixty-one social drinkers came to the lab in groups of 4-6 on two days spaced a week apart. Each participant was randomly assigned to receive alcoholic drinks targeting a BAC of .05% on one testing day and placebo drinks on the other, with the order counter-balanced. On both testing days, participants engaged in a Schandry heartbeat perception task on three occasions: at baseline, after an alcohol absorption period, and after physiological arousal was raised via exercise. **Results:** For men only, alcohol significantly impaired cardioceptive accuracy relative to a placebo at both low and high levels of arousal, with medium to large effect sizes. **Conclusions:** Though preliminary, this finding is consistent with the proposed hypothesis linking alcohol consumption and anxiety, at least for men. Future studies should directly examine whether, among individuals with anxiety disorders, cardioceptive sensitivity mediates the relationship between alcohol consumption and state anxiety.

Keywords: alcohol, interoception, cardioception, state anxiety

The Effects of Alcohol on Heartbeat Perception: Implications for Anxiety

It is well established that, for those prone to anxiety, alcohol often serves as an anxiolytic, leading to self-medication and negative reinforcement. Several hypotheses have been offered for this effect. For example, alcohol binds to $GABA_A$ receptors, leading to neuronal inhibition, sedation, and muscle relaxation (tension-reduction hypothesis; Sher, 1987). Alcohol may also decrease in the apparent self-relevance of anxiogenic cues (self-awareness model; Hull, 1981) and divert attention away from such cues by narrowing attentional capacity (attention-allocation model; Steele & Josephs, 1988). Additionally, alcohol may lower anxiety by providing an externalized excuse for anticipated failure (self-handicapping theory; Tucker, Vuchinich, & Sobell, 1981).

An unexplored possibility, though, is that alcohol reduces anxiety for some by impairing interoceptive sensitivity – awareness of the physiological state of the body as transmitted via afferent neurons (Cameron, 2001; Craig, 2002). Individuals high in interoceptive sensitivity more rapidly notice changes related to autonomic arousal, such as an increased heart rate (Melzig, Holz, Michalowski, & Hamm, 2011). In theory, alcohol may decrease conscious awareness of and the ability to detect somatic sensations. Consistent with this, heightened interoceptive sensitivity has been identified as a risk factor for elevated trait anxiety. Several studies found that trait anxiety positively correlates with accuracy of heartbeat perception (e.g., Richards & Bertram, 2000; Pollatos, Herbert, Kaufmann, Auer, & Schandry, 2007; Karsdorp, Kindt, Rietveld, Everaerd, & Mulder, 2009), though two studies concluded otherwise (DePascalis, Alberti, & Pandolfo 1984; Steptoe & Vogele, 1992).

Interoceptive sensitivity appears related not only to sub-clinical anxiety but also to anxiety disorders. Individuals with social anxiety disorder and generalized anxiety disorder report hypervigilance for somatic sensations (Gregor & Zvolensky, 2008; Anderson & Hope, 2009), and interoceptive sensitivity may play an even greater role in the development and maintenance of panic disorder (PD). When quietly monitoring their own heartbeats, those with PD are more accurate than infrequent panickers and individuals with specific phobias or depression (Ehlers & Breuer, 1992; Ehlers, Breuer, Dohn, & Fiegenbaum, 1995; van der Does, van Dyck, & Spinhoven, 1997). Further, a meta-analysis employing 10 studies with 609 combined participants revealed a medium effect size (d=0.52) for heartbeat perception accuracy between those with PD and healthy controls (Domschke, Stevens, Pfleiderer, & Gerlach, 2010).

Individuals with PD often catastrophically appraise normal cardiovascular sensations, associating them with imminent threat (Barlow, 1988; Beck, Emery, & Greenberg, 1985; Clark, 1986). For example, an elevated heart rate might be viewed as signifying an impending heart attack. Such interpretations, in turn, increase the intensity of physical sensations, leading to a vicious circle that may end in panic. In addition, physical sensations may serve as conditioned stimuli for anxiety, further potentiating panic and maintaining PD (learning theory; Bouton, Mineka, & Barlow, 2001). In short, heightened interoceptive sensitivity may increase the risk for PD by amplifying the base of physical sensations that have the potential to be viewed as threatening (Domschke et al., 2010).

Present Study

The present study aims to provide a proof-of-concept test of the hypothesis that alcohol impairs interoceptive sensitivity. If supported, future studies could aim to examine whether, among those with anxiety disorders, interoceptive sensitivity mediates the relationship between alcohol consumption and anxiolysis. We focus on heartbeat perception, as stimuli arising from the cardiovascular system are especially likely to cause marked distress for those with anxiety disorders and, at times, be catastrophically misinterpreted. As examples, the most common fear among patients with PD as measured by the Body Sensations Questionnaire is having a heart attack (Chambless, Beck, Gracely, & Grisham, 2000), 89% of patients with PD complain of palpitations (Fleet, Dupuis, Marchand, Burelle, Arsenault, & Beitman, 1996), and as many as 25% of patients referred to cardiac clinics with atypical chest pains or palpitations receive a diagnosis of PD (Fleet et al., 1996). We predict that the pharmacologic effects of alcohol will impair cardioception just as alcohol impairs other forms of perception, such as depth perception and proprioception (Kunchulia, Pilz, & Herzog, 2012; Stock, Mückschel, & Beste, 2015; Wegner & Fahle, 1999).

A related issue is whether alcohol impairs interoception at low and/or high levels of physiological arousal. For those with PD, this question would examine when in the vicious cycle, if at all, alcohol diminishes interoceptive sensitivity and hence disrupts the cycle. Past studies have induced physiological arousal via exercise and found that doing so increases interoceptive performance for both individuals with PD and healthy controls (Antony, Brown, Craske, Barlow, Mitchell, & Meadows, 1995; Schandry & Specht, 1981). Further, increases in heart rate positively correlate with increased cardioceptive sensitivity in non-anxious participants (Katkin, Morell, Goldband, Bernstein, & Wise,

1982). These findings make sense given that faster, stronger heartbeats should be more salient. Still, a study that induced arousal via caffeine in infrequent panickers and healthy controls failed to find a relationship between arousal level and interoception (Zoellner and Craske, 1999). In the present study, we measure cardioception both at rest and following exercise to examine whether alcohol differentially affects heartbeat perception at low vs. high levels of arousal.

With respect to sex differences, there is some evidence that men have greater interoceptive sensitivity than women, especially at higher levels of physiological arousal (Ehlers, Mayou, Sprigings, & Birkhead, 2000). For example, men learn to detect their heartbeats faster than do women (Katkin, 1985), and arousal induced via exercise promotes interoceptive accuracy more so in men than in women (Katkin, 1985). Explanations offered for this sex difference include the greater bodyweight of men (Jones, 1994) and the stronger adrenergic response to exercise by men, leading to greater cardiac output and arterial blood pressure and hence stronger cardiovascular sensations to detect (Katkin, 1985). Given these findings and the greater prevalence of alcohol use disorder in men (Wilsnack, Vogeltanz, & Wilsnack, 2000), we explored the possibility that sex would moderate the relation between alcohol consumption and interoception.

Method

Participant Selection

Individuals aged 21-65 who were in "good health" were recruited through flyers and ads placed in local newspapers. We excluded a) those with conditions for which alcohol consumption would be inadvisable, including pregnant or breastfeeding women, individuals taking medications for which alcohol consumption is contraindicated, those

with a history of alcohol use disorder, and teetotalers; b) those with cardiac or other physical conditions for which engaging in aerobic physical activity would be inadvisable; and c) those who could impair the internal validity of the study, including individuals with pacemakers, peripheral neuropathy, or congenital analgesia and individuals not fluent in English. Additionally, those taking psychiatric medications "as needed" were required to abstain from such medications for three days prior to both sessions. Approval for the study was granted by the Carleton College Institutional Review Board.

Apparati

To collect heartbeat data, we utilized Polar H7 Bluetooth Smart Heart Rate Sensors with adjustable-length chest straps (Polar, Kompele, Finland), iPad Mini 2s (Apple, Cupertino, CA) to receive the heart rate data via Bluetooth, and a custom-made app titled BeatBeacon developed by Stephen Grinich (Northfield, MN) that detects, records, and exports heartbeat data.

For the group aerobic exercise activity, we utilized 25"L x 11"W x 8"H plastic aerobic steps.

Measures

Alcohol Use Disorder Identification Test (AUDIT). The AUDIT (Saunders & Aasland, 1987) is a 10-item self-report measure widely employed to screen for hazardous or harmful alcohol use. Responses are scored from 0 to 4, with total scores of 16 or greater considered to reflect high levels of alcohol problems (Babor, Biddle-Higgins, Saunders, & Monteiro, 2001). The measure is considered to have favorable internal consistency, test-retest reliability, and criterion validity (Reinert & Allen, 2007).

Anxiety Sensitivity Index-3 (ASI-3). The ASI-3 (Taylor et al., 2007) is an 18-item self-report measure of anxiety sensitivity (the fear of arousal-related sensations). Respondents receive a total score as well as three factor scores (Physical, Cognitive, and Social Concerns). The measure and its subscales have demonstrated high levels of reliability and validity (Farris, Dibello, Allan, Hogan, Schmidt, & Zvolensky, 2015).

State-Trait Anxiety Inventory-Trait Form (STAI-T). The STAI-T (Spielberger, Gorsuch, Lushnee, Vagg, & Jacobs, 1983) requires respondents to rate 20 anxiety-related symptoms with reference to how they feel in general. Items are rated from 1 (*not at all*) to 4 (*very much so*) on a Likert scale. Psychometric evaluation has shown the STAI-T to be a reliable and valid measure of trait anxiety (Spielberger et al., 1983).

State-Trait Anxiety Inventory-State Form (STAI-S). The STAI-S (Spielberger et al., 1983) assesses anxiety-related symptoms with reference to how the individual feels at the moment (e.g., ‘‘I feel calm’’ and ‘‘I am worried’’). Its 20 items are rated on a Likert scale from 1 (*not at all*) to 4 (*very much so*). Psychometric evaluation has shown the STAI-S to be a reliable and valid measure of state anxiety (Spielberger et al., 1983).

Confidence. Following each heartbeat perception task, participants indicated how confident they were that their perceived number of heartbeats was fairly close (“within a couple heartbeats”) to their actual number of heartbeats using a five-point Likert scale ranging from 1 (*not confident at all*) to 5 (*extremely confident*; modified from Zoellner & Craske, 1999).

Procedure

Overview. Participants, in groups of 4-6, came to the lab on two separate days spaced approximately seven days apart. Each participant was randomly assigned to

receive on one testing day alcoholic drinks targeting a BAC of .05% and on the other testing day alcoholic drinks targeting a BAC of .005%, with the order counter-balanced. On both testing days, participants engaged in a heartbeat perception task on three occasions: 1) at baseline, 2) after an alcohol consumption/absorption period, and 3) following a brief period of cardiovascular exercise.

Initial Screening. Trained research assistants (RAs) screened by telephone individuals who had responded to study ads. To assess for a high level of alcohol problems, RAs administered the AUDIT, with a total score greater than 15 or an alcohol dependence subscale score greater than 3 serving as exclusion criteria (Babor et al., 2001). RAs additionally assessed individuals' medical history using a semi-structured interview. Final decisions on eligibility were made during team meetings led by the first author based on the criteria described earlier.

Eligible individuals were provided by phone and mail with pre-session instructions, which were designed to minimize variance in exercise as well as the consumption of food, beverages, and substances that can affect heart rate and the absorption of alcohol. Specifically, participants were instructed to (a) not drink alcohol for 24 hours prior to study sessions, (b) not consume caffeine for 12 hours prior to sessions, (c) not exercise for two hours prior to sessions, (d) eat a light meal one hour prior to sessions and then nothing further (besides water) until the completion of each session, (e) inform us if they took any psychoactive medications during the three days prior to a session (so it could be rescheduled or cancelled), and (f) if a smoker, smoke as usual until the start of the sessions and then not at all until the completion of each session.

Pre-Drink Phase

First session. Participants, in groups of up to six, arrived for each of their two study sessions at a set time and were greeted by two RAs who were blind (and would remain blind) to beverage condition. All participant activities occurred in a 20'x20' room without clocks. Participants were asked to provide informed consent and then silence and remove time-keeping devices (phones and watches).

Participants then completed forms that assessed compliance with pre-session instructions. Those who complied were instructed to wear a dampened heart rate monitor attached to a chest strap. Following this, participants completed a set of questionnaires that assessed trait characteristics, including demographics, frequency of aerobic exercise, trait anxiety (STAI-T and ASI-3), and state anxiety (STAI-S).

Participants then engaged in a practice Schandry heartbeat perception task (HPT) (Schandry, 1981). After being instructed to stand at an assigned spot, participants were advised to silently count heartbeats during an interval between two tones without taking their pulse. The length of this interval was 51 seconds, though this was not announced. Afterward, participants recorded the number of heartbeats counted and indicated on a scale how confident they were that the estimate was within a few heartbeats of the actual number of heartbeats. No feedback on the accuracy of these estimates was provided to participants.

After answering questions participants began the "pre-drink" HPTs, which consisted of four trials (Wolk, Sutterlin, Kock, Vogele, & Schulz, 2014). For each trial participants stood at an assigned spot, silently counted heartbeats between two tones, and recorded heartbeats counted and confidence level. For this set of HPTs and all others during the study, the (unannounced) durations between the two tones for the four trials

were, in random order, 24, 32, 39, and 45 seconds.

Second session. The second session pre-drink phase was similar to the first, except that trait characteristics were not assessed and the practice HPT was not performed.

Drink Phase. The drink phase took place immediately following the pre-drink HPTs. An RA advised participants: "As you will recall from the Consent Form, you will be given two drinks - vodka sours - containing alcohol. The amount of alcohol you receive will differ on the two study sessions, but the two drinks combined on a given session will not target a blood alcohol concentration over .05%."

Participants individually – not as a group – were randomly assigned to consume alcohol or a placebo during their first session and the other beverage during their second session. The non-blind RA who made the drinks was never in the same room as the participants. Rather, the blind RAs who interacted with participants simply retrieved the drinks from a back room.

When in the alcohol condition, all participants consumed drinks that were of the same strength but varied in volume as a function of weight and sex. More specifically, participants consumed two drinks over 20 minutes consisting of a 3:1 lemonade (made with Country Time lemonade mix and tonic water) to vodka mixture that targeted a BAC of .05% (Fisher, Simpson, & Kapur, 1987). When in the placebo condition, all participants consumed two drinks over 20 minutes consisting of straight lemonade, with a few drops of vodka placed on top to evoke the smell and taste of vodka and to target a nominal BAC of .005% (Abrams, Kushner, Lisdahl Medina, & Voight, 2001). The volume of the placebo drinks matched those in the alcohol condition.

During the 20-minute drink phase and 25-minute absorption period afterward, emotionally-neutral scenes from a nature film (*Planet Earth*, 2007) were shown.

Post-Drink Phase. Following the absorption period, participants completed the STAI-S and engaged in the "post-drink" HPTs. As before, for each of four trials, participants stood at an assigned spot, counted heartbeats between two tones, and recorded heartbeats counted and confidence level.

Exercise Phase. During the exercise phase, participants alternated between brief aerobic tasks and heartbeat perception trials, doing each four times. For the aerobic task, a series of tones 1.5 seconds apart guided participants to step onto (high tone) or down from (low tone) their aerobic step. Following each aerobic task, participants completed a heartbeat perception trial, again by standing at an assigned spot, counting heartbeats between two tones, and recording heartbeats counted and confidence level. The durations of the four aerobic tasks were, respectively, 3, 3, 2, and 1.5 minutes. (Pre-study testing revealed increasingly shorter durations were needed to achieve approximately the same elevated heart rate.) Following the four block trial of HPTs, participants again completed the STAI-S.

Concluding Activities

Following the exercise phase of the second session, participants were then asked to indicate which set of drinks (first vs. second session) they believed was stronger and the degree to which it was stronger. At the conclusion of both sessions, participants were paid for their participation and then picked up by a friend, provided a taxi voucher to travel home, or (for students) escorted back to their campus housing.

Data Analytic Approach

Several variables were measured during four trials for each combination of drink type (alcohol and placebo) and phase (pre-drink, post-drink, and exercise), including actual number of heartbeats, perceived number of heartbeats, and confidence level in perceived number of heartbeats. For these variables, values for each set of four trials were averaged, resulting in six scores per participant.

For each block of four heartbeat perceptions tasks, cardioceptive accuracy was calculated with the following formula: $(1/4)\sum(1 - \frac{|\text{actual heartbeats} - \text{reported heartbeats}|}{\text{actual heartbeats}})$. The result is an index that ranges from 0 to 1, with 1 indicating perfect accuracy of heartbeat detection (Werner, Jung, Duschek, & Schandry, 2009, Wolk et al., 2014). This resulted in each participant having six cardioceptive accuracy scores – one for each combination of drink type and phase.

Continuous measures compared at three time points per session were analyzed with a 3 (time) x 2 (drink type) x 2 (sex) mixed-design ANOVA. Significant 3-way interactions were further explored via a 3 (time) x 2 (drink type) repeated-measures ANOVA for men and, separately, for women. Non-significant 3-way interactions were followed by an examination of the *time x drink* 2-way interaction for significance. Significant 2-way interactions were further explored via 2 (time) x 2 (drink type) repeated-measures ANOVA comparing the pre-drink and post-drink time points and, separately, comparing the pre-drink and post-exercise time points.

Two-tailed tests were used for all analyses. When providing effect sizes, we utilized the following benchmarks (Cohen, 1988): For Cohen's d, small=0.2, medium=0.5, large=0.8. For partial eta squared (η_p^2), small=0.02, medium=0.13, large=0.26.

Results

Participant Characteristics

Sixty-eight individuals were recruited for the study and participated in at least one session. However, two individuals were unable to complete the protocol during their first session (in one case due to dizziness during the exercise phase, and in the other case due to the inability to refrain from touching one's wrists during cardioception tasks) and were not rescheduled. One other individual completed the first session but failed to follow pre-session instructions for the second session and was not rescheduled. Heartbeat data for four others failed to transmit to the receiving device (iPad) for one full session, leaving 61 viable participants. This final group consisted of 26 men and 35 women with a mean age of 22.0 years (SD=3.73). With respect to race/ethnicity, 41 individuals (67.2%) identified as White, 10 (16.4%) as Asian, 5 (8.2%) as Black, 3 (4.9%) as Hispanic, and 2 (3.3%) as Other.

Participant characteristics stratified by sex with respect to age, relative body weight, alcohol consumption, trait anxiety, and exercise are provided in Table 1. As can be seen, on average, men had higher BMIs and reported exercising more hours per week than women. Differences between means for other variables were not significant. On a measure of trait anxiety (STAI-T), the full sample closely resembled a large community sample (Crawford, Cayley, Lovibond, Wilson, & Hartley, 2011) and, on a measure of anxiety sensitivity (ASI-3), participants on average scored similarly to a large community sample on the full scale as well as on the three subscales (Petrocchi, Tenore, Couyoumdjian, & Gragnani, 2014).

Table 1

Participant Characteristics by Sex

	Men (*n*=26)		Women (*n*=35)				
Variable	*M*	*SD*	*M*	*SD*	*t*	*p*	*d*
Age	21.4	0.64	22.3	4.88	0.95	.35	.24
Body Mass Index (kg/m^2)	25.9	6.22	22.9	4.14	2.23	.04*	.59
Drinking occasions per month	8.16	5.48	5.94	3.40	1.93	.06	.50
Drinks per drinking occasion	3.92	2.53	3.10	1.80	1.47	.15	.38
AUDIT	6.69	3.16	5.49	2.74	1.59	.12	.41
STAI-T	36.3	10.0	39.9	11.2	1.29	.20	.34
ASI-3 Total	12.2	10.1	13.9	9.52	0.67	.51	.17
Physical Concerns subscale	2.19	2.82	3.43	3.64	1.44	.16	.37
Cognitive Concerns subscale	2.96	4.41	3.09	3.49	0.12	.90	.03
Social Concerns subscale	7.08	4.65	7.40	4.24	0.28	.78	.07
Hours aerobic exercise per week	6.18	3.86	4.29	3.17	2.07	.04*	.54

Notes: * = $p < .05$. AUDIT = Alcohol Use Disorder Identification Test. STAI-T = State-Trait Anxiety Inventory-Trait Form. ASI-3 = Anxiety Sensitivity Index-3.

Manipulation Check

We examined whether participants were able to effectively stay blind to drink condition. At the conclusion of the second session, participants were asked to compare the strength of their drinks during the first session to the strength of their drinks during the second session, with possible scores ranging from 1 (drinks during the first session were much weaker) to 5 (drinks during the first session were much stronger), with 3 (the drinks were about the same strength) in the center. Average scores were slightly below 3 for both groups (for placebo-first group, M=2.63, SD=1.26; for alcohol-first group, M=2.93, SD=1.19), with the difference non-significant, t(59)=0.78, p=.44 and the effect size small, d=.16. These results suggest that participants were largely unsuccessful at subjectively differentiating between the drink strengths.

Zero-Order Correlations

Table 2 lists zero-order correlations between trait variables and baseline cardioceptive accuracy (defined as the average level of cardioceptive accuracy across all pre-drinking trials in the two sessions). As expected, measures of trait anxiety (STAI-T, ASI-3 and its three subscales) were positively correlated with each other and negatively correlated with the frequency of aerobic exercise. Neither baseline cardioceptive accuracy nor the standardized measure of alcohol use/abuse (AUDIT) were significantly associated with any other measure.

Table 2

Zero-Order Correlations Among Baseline Variables

Variable	1	2	3	4	5	6	7
1. AUDIT							
2. STAI-T	.00						
3. ASI-3 Total	.04	.64***					
4. ASI-3 PC Subscale	.00	.46***	.84***				
5. ASI-3 CC Subscale	.07	.55***	.84***	.64***			
6. ASI-3 SC Subscale	.04	.58***	.83***	.54***	.49***		
7. Hours Aerobic Exercise/Week	.21	-.38**	-.31*	-.34**	-.33*	-.15	
8. BL Cardioceptive Accuracy	.12	.04	.12	.09	.02	.19	.15

Notes: * = p < .05; ** = p < .01, ***=p<.001. AUDIT = Alcohol Use Disorder Identification Test. STAI-T = State-Trait Anxiety Inventory-Trait Form. ASI-3 = Anxiety Sensitivity Index-3. PC = Physical Concerns. CC= Cognitive Concerns. SC = Social Concerns. BL = Baseline.

The Effects of Drink Type on Outcome Measures

Actual and perceived number of heartbeats. A 3-way, mixed-design ANOVA examining the effects of time, drink type, and sex on actual number of heartbeats revealed that the 3-way interaction was not significant, $F(2,114)=.88$, $p=.42$, $\eta_p^2=.015$, but that the two-way, time x drink interaction term was, $F(2,114)=23.96$, $p<.001$, $\eta_p^2=.30$; see Figure 1. The effect size for the latter was large. Alcohol led to a higher heart rate relative to placebo drinks both while quietly standing, $F(1,58)=21.18$, $p<.001$,

η_p^2=.32 and following exercise, F(1,58)=33.89, p<.001, η_p^2=.37, with a large effect size in both cases.

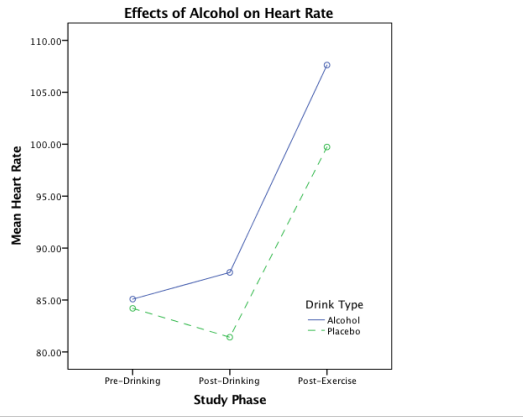

Figure 1. The Effects of Alcohol and Exercise on Heart rate. The Time x Drink Type interaction is significant, *p*<.001, η_p^2=.30.

For perceived number of heartbeats, neither the three-way interaction term (time x drink type x sex), F(2,118)=1.79, p=.17, η_p^2=.029 nor the two-way, time x drink type interaction term was significant, F(2,118)=1.56, p=.21, η_p^2=.026. That is, perceived number of heartbeats was not differentially affected by drink type across the three time points, and effect sizes were low.

Cardioceptive accuracy and confidence. A 3-way, mixed-design ANOVA examining the effects of time, drink type, and sex on cardioceptive accuracy (the primary outcome measure of this study) revealed a significant 3-way interaction, F(2,114)=3.14, p=.047, η_p^2=.052. A follow-up 2-way, repeated-measures ANOVAs indicated that the 2-way interaction of time and drink was significant for men, F(2,50)=7.01, p=.002, η_p^2=.22, though not women F(2,64)=.43, p=.66, η_p^2=.013; see Figure 2. For men, alcohol impaired cardioceptive accuracy relative to a placebo both while quietly standing, F(1,25)=5.86,

p=.023, and also following exercise, F(1,25)=15.11, p=.001, with medium to large effect sizes (η_p^2=.19 and .38, respectively).

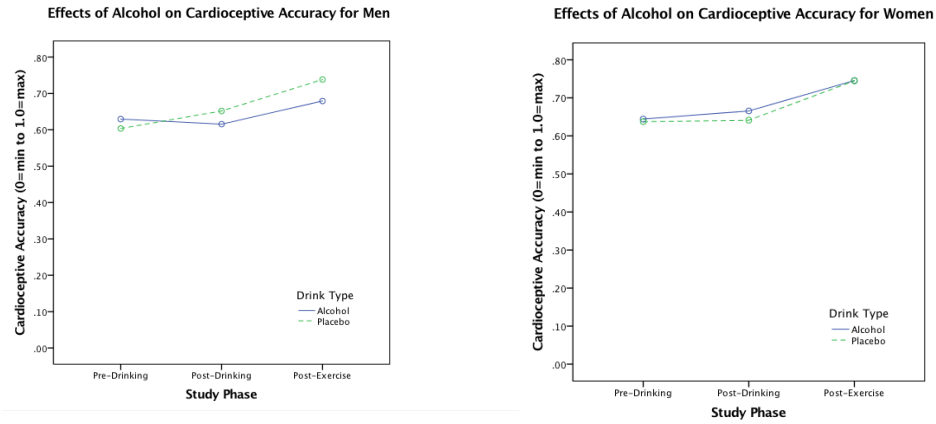

Figure 2. The Effects of Alcohol and Exercise on Cardioceptive Accuracy for Men and Women. For men, the Time x Drink Type interaction is significant, *p*=.002, η_p^2=.22.

For confidence in perceived number of heartbeats, neither the three-way interaction term (time x drink type x sex) nor the two-way, time x drink type interaction term were significant [F(2,118)=1.84, p=.16, η_p^2=.030 and F(1,118)=.028, p=.97, η_p^2<.001, respectively]. That is, confidence level was not differentially affected by drink type across the three time points.

Anxiety. Because the procedure did not include anxiogenic components and study participants were not selected for high anxiety, we did not expect drink type to affect state anxiety level (STAI-S). Consistent with this prediction, neither the three-way interaction term (time x drink type x sex), F(2,110)=1.86, p=.13, η_p^2=.033 nor the two-way, time x drink type interaction term was significant, F(2,110)=.51, p=.88, η_p^2=.002.

Discussion

We examined whether two alcoholic beverages would affect cardioception in social drinkers as well as the extent to which sex and arousal level would moderate the

results. Our primary finding is that, for men only, alcohol impaired cardioceptive accuracy relative to a placebo both while quietly standing (low arousal condition) and following exercise (high arousal condition), with medium to large effect sizes. This finding is partially consistent with past studies in which moderate doses of alcohol compromised other forms of perception, such as depth perception and proprioception, in both men and women (Kunchulia et al., 2012; Stock et al., 2015; Wegner & Fahle, 1999).

Our finding of a sex difference in interoception in some ways builds on past literature; for example, men on average have greater interoceptive sensitivity (Ehlers et al., 2000; Katkin, 1985). Of note, this sex difference has yet to be explained satisfactorily, though hypotheses ranging from differences in cardiac volume, body fat distribution, and motivation have been posited (Ehlers et al., 2000). Additionally, both experimental (Abrams, Kushner, Lisdahl, & Vought, 2002) and survey research (Bolton, Cox, Clara, & Sareen, 2006) have shown that men are more likely to self-medicate clinical anxiety symptoms than are women. On the other hand, past studies have not found sex differences in the effects of alcohol on perception, once BAC is controlled for (e.g., Wait, Welch, Surgate, & Hineman, 2009). Unfortunately, the processes underlying the sex effect cannot be elucidated within the present data set. Future studies should assess whether this effect is replicable and, more generally, seek to better understand the processes that underlie it.

We also found that, collapsing across sex, alcohol led to a higher heart rate relative to placebo drinks in both the low and high arousal conditions, with large effect sizes. Our finding that a moderate amount of alcohol acutely raised heart rates is consistent with past findings (e.g., Howes & Reid, 1986; Ireland, Vandongen, Davidson,

Beilin, & Rouse, 1984). Possible explanations include that, by effecting vasodilation and the entry of calcium into cardiac myocites, alcohol fosters sympathetic activation and inhibits parasympathetic activity (Howes & Reid, 1986; Koskinen, Virolainen, & Kupari, 1994; Ryan & Howes, 2002).

Our finding that interoceptive sensitivity improves with higher levels of arousal induced by exercise is consistent with past studies (Antony et al., 1995; Schandry & Specht, 1981) and can be explained by the stronger afferent signals transmitted to the insula. It remains to be determined if our primary study finding that alcohol impairs cardioception for men at both low and high levels of arousal extends to individuals with PD.

Providing a possible mechanism for our primary finding, alcohol is known to affect areas of the brain responsible for interoceptive awareness. The neural correlates of interoception include the dorsal posterior insular, anterior insular, prefrontal, and cingulate cortices, and ventromedial thalamus (Craig, 2002; Craig & Craig, 2009; Critchley, Wiens, Rothstein, & Dolan, 2004). Two studies using neuroimaging to specifically examine cardioception in humans indicated heightened activation of the anterior insular cortex, cingulate cortex, and thalamus during cardioception compared to a control auditory task (Critchley et al., 2004; Pollatos et al., 2007). Additionally, the activity and gray matter volume of the right anterior insula correlates with the performance in this cardioception task (Critchley et al., 2004). Acute alcohol consumption in rats reduces activity measured through c-Fos expression in thalamic nuclei and the insular cortex (Jaramillo, Randall, Frisbee, & Basheer, 2016) and alcohol

use also reduces the functional connectivity of the anterior insula in humans (Gorka, Phan, & Childs, 2017).

Integrating old and new studies, there now exists evidence that, for men, alcohol impairs cardioception (present study) and that cardioception is associated with clinical anxiety (Domschke et al., 2010). Future studies should build on the present one by examining if alcohol similarly impairs interoceptive accuracy among individuals with PD and, if so, interoceptive accuracy mediates the relationship between alcohol consumption and panic symptoms.

Should evidence emerge for a mediating role of alcohol, specific treatments for co-morbid alcohol use and anxiety disorders among individuals high in interceptive sensitivity could be tested. For example, though cognitive-behavioral therapy does not directly affect cardioception (Antony, Meadows, Brown, & Barlow, 1994; Ehlers & Breuer, 1992), biofeedback could serve as a healthier alternative to drinking and allow individuals to observe inaccuracies in their perceptions of somatic symptoms and gain a sense of control over certain cardiovascular processes (Story & Craske, 2008). Additionally, beta-blockers block beta-adrenergic receptors and hence prevent cardiovascular (sympathetic) arousal. Though most studies to date have shown mixed or negative results regarding the efficacy of beta-blockers in the treatment of anxiety disorders (Hayes & Schulz, 1987; Munjack, et al., 1989), it is possible they could specifically assist co-morbid patients high in interoceptive sensitivity.

Study Limitations

The present study has several notable limitations. First, though the within-subject design of the study increased power, the number of participants who completed both

sessions with viable data (N=61) was relatively small. Second, the sample lacked both geographic and age diversity, and as such results should be generalized with caution. Third, we examined the effects of a moderate amount of alcohol on cardioception. It is unclear if the administration of a higher amount of alcohol would result in similar findings. Similarly, though perception of an elevated heart rate tends to be especially salient during panic attacks (Fleet et al., 1996), it would be informative to examine the effects of alcohol on other viscerоceptive processes, such as blood pressure and gastrointestinal activity.

Fourth, because the study design did not include a lab visit in which no beverages were served, we are unable to draw conclusions about the impact of alcohol *expectancies* on cardioception. That is, our findings relate only to the pharmacologic effects of alcohol. Fifth, as discussed earlier and because the study was designed as proof-of-concept, we did not select participants based on a history of anxiety disorders, thereby limiting the generalizability of the findings and necessitating replication employing individuals with PD.

Conclusions

This is the first study of which we are aware to demonstrate that alcohol consumption impairs cardioception in men. Future studies should examine whether the findings extend to individuals with anxiety disorders. The ultimate aim of this line of research is to elucidate whether interoceptive accuracy mediates the relationship between alcohol consumption and panic so that prevention and treatment of the co-morbid condition can be optimized.

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Statement 2: Contributors

The first four authors (KA, KC, SJ, SK) designed the study and wrote the protocol. All seven authors participated in data collection. The first and fourth authors (KA, GB) conducted the statistical analyses. The first author (KA) wrote the first draft of the manuscript and all seven authors contributed to and have approved the final manuscript.

Statement 3: Conflict of Interest

All seven authors declare that they have no conflicts of interest.

Statement 4: Acknowledgements

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