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Craving, cortisol and behavioral alcohol motivation responses to stress and alcohol cue contexts and discrete cues in binge and non-binge drinkers

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Abstract

Alcohol use disorders are associated with high craving and disruption of stress biology, but their role in behavioral alcohol motivation is less clear. We examined the effects of craving and cortisol responses on behavioral alcohol motivation to stress, alcohol cue and neutral-relaxing context cues, in addition to discrete alcohol cues, in demographically matched binge/heavy (BH) and moderate (MD) social drinkers. Subjects participated in a 3-day laboratory experiment of provocation by three personalized guided imagery contexts and discrete alcohol cues followed by the ‘alcohol taste test’ (ATT) to assess behavioral motivation, as measured by ATT intake. Post-ATT alcohol effects on craving and cortisol responses were also examined. Results indicate BH consumed significantly more alcohol than MD in the ATT. Stress and alcohol cue contexts, relative to neutral, led to significantly greater ATT intake across both groups, which also correlated positively with self-reported alcohol use in past 30 days. Stress and alcohol context and discrete alcohol cues each significantly increased alcohol craving, more so in the BH than MD, and significantly predicted greater ATT intake in BH only. The BH showed significantly lower cortisol responses than MD overall and blunted cortisol responses to cues predicted significantly greater ATT intake in the stress condition for BH and in the alcohol cue condition for MD. Higher ATT intake predicted greater cortisol response and higher craving post-ATT, and these effects were moderated by group status. In sum, findings suggest a role for sensitized context-induced craving and blunted cortisol responses in increased behavioral motivation for alcohol.

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Author Contributions

RS designed, implemented and provided oversight for the study. NN and SB conducted data analysis and SB and RS wrote the manuscript. JGB provided medical oversight and admitted subjects to the Hospital Research Unit. RH helped in data collection and study implementation.

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Keywords

alcohol intake; binge drinking; cortisol; HPA axis; stress; alcohol cues

INTRODUCTION

Excessive alcohol use is a key behavioral cause of morbidity and mortality in the world (Whiteford et al. 2013; Grant et al. 2015). Evidence from population based studies indicate that alcohol related problems and risk for alcohol use disorders (AUDs) are directly related to quantity and frequency of intake (Dawson & Archer 1993; Grant et al. 2003). Binge and heavy alcohol use are associated with higher levels of motivation for alcohol and potentially less control over alcohol use, thereby increasing risk for progression towards hazardous consumption levels (Field et al. 2010; Weafer & Fillmore 2015). Thus, understanding the biobehavioral mechanisms that may underlie motivation for higher levels of alcohol intake may suggest specific processes that contribute to hazardous drinking.

Preclinical studies show that animals allowed to drink episodically to intoxication, such as via ‘drinking the dark’ procedures, develop sensitivity to stress and alcohol cues, which is directly linked to increased alcohol consumption (Lu & Richardson 2014; Colombo et al. 2017). Clinically, we have shown that higher or ‘sensitized’ craving response and blunted hypothalamic pituitary adrenal (HPA) axis responses to individually calibrated and matched stress and alcohol cues are predictive of future relapse in treatment seeking AUD individuals (Sinha et al. 2011b; Seo et al. 2013; Blaine, Seo, & Sinha 2017), and Thomas, Bacon, et al. (2011) showed that acute stress with alcohol priming predicted greater alcohol intake in AUD individuals. Additionally, ecological momentary assessment studies of socially drinking adults shows that greater alcohol exposure is associated with higher craving and greater alcohol intake in daily life (Serre et al. 2015).

Preclinical evidence also indicates that alcohol potently stimulates the HPA axis, but that this response is highly susceptible to adaptation (Lee & Rivier 1997b; Allen, Lee, et al. 2011), with binge and chronic exposure resulting in blunted HPA axis responses, indicative of ‘neuroendocrine tolerance’ (Lee et al. 2015; Fritz & Boehm 2016; Torcaso et al. 2017). Human studies have also reported blunted cortisol response to fixed dose of alcohol administration in binge/heavy (BH) relative to moderate (MD) social drinkers (Waltman et al. 1993; Frias et al. 2000; Lovallo 2006; Thayer et al. 2006; Heilig et al. 2010; Allen, Rivier, & Lee 2011; Söderpalm Gordh & Söderpalm 2011; Mick et al. 2013). This previous work suggests that binge and heavy alcohol consumption results in greater subjective craving and blunted cortisol responses. However, no previous experimental study has assessed whether such increased subjective craving and blunted cortisol in response to stress and alcohol contexts and to discrete cues increases alcohol intake in BH and MD social drinkers.

Therefore, in the present study, we experimentally assessed behavioral alcohol motivation as measured by alcohol intake in an adapted version of the well-established alcohol taste test (ATT) (Marlatt, Demming, & Reid 1973; Caudill & Marlatt 1975; Marlatt, Kosturn, & Lang 1975), and as utilized by previous research to assess alcohol motivation (Thomas, Bacon, et

al. 2011). The ATT was conducted after exposure to personalized imagery of stress, alcohol and neutral-relaxing contexts that was followed by discrete alcohol cues (Fig. 1). Context on each day was induced using our well-validated personalized guided imagery laboratory procedures which individually calibrate personal stressful events and have been shown to reliably provoke stress-induced and cue-induced craving in those with and without substance use disorders (Fox et al. 2005; Fox et al. 2007; Sinha et al. 2007; Chaplin et al. 2008; Sinha et al. 2009; Sinha 2009b; Seo et al. 2011; Fox et al. 2010; Sinha et al., 2011a; Seo et al. 2013; Milivojevic et al. 2017). Finally, subjective craving and cortisol responses were also assessed post-ATT to examine both context and alcohol intake effects on these responses. A multilevel modeling approach was used to assess dynamic changes in craving and cortisol during the experiment and their relationship to alcohol motivation. We hypothesized that stress and alcohol contexts as well as discrete cues would each increase subjective craving and predict higher ATT intake relative to neutral-relaxing contexts. Furthermore, we hypothesized that blunted cortisol responses in stress would be predictive of greater ATT intake, particularly in the BH group. Finally, we hypothesized that after the ATT (Phase II), higher ATT intake would predict greater cortisol levels and reveal differences in subjective craving between the BH and MD groups.

METHODS AND MATERIALS

Screening and intake procedures

Participants were recruited from the greater New Haven area via flyers, radio and social media advertisements calling for individuals who 'liked beer'. Participants were healthy, nonsmoking, non-substance using, beer drinking men and women (aged 18–45) who completed medical, demographic, substance abuse and interview-driven psychiatric health assessments, including the Structured Clinical Interview for the Diagnostic and Statistical Manual IV-TR (First et al. 1996), Cahalan Quantity Frequency Variability Index (QFVI) (Cahalan, Cisin, & Crossley 1969), the Family Tree Questionnaire (Vogel-Sprott, Chipperfield, & Hart 1985) and the Alcohol Use Disorders Identification Test (AUDIT) (Babor et al. 2011). Participant drinking history was determined on the basis of their responses to several interviews and self-report questionnaires, including an alcohol intake screening that assessed past and current 30 days drinking using items from the Addiction Severity Index, drug use section (McLellan et al. 1992), as well as current alcohol intake on the QFVI and the AUDIT. If there were unexplained discrepancies across the Addiction Severity Index, drug use section, the QFVI and AUDIT, volunteers were excluded from further participation. All participants endorsed beer as their most frequently consumed beverage. MD and BH group status was characterized using the National Institute of Alcoholism and Alcohol Abuse (NIAAA) criteria for hazardous drinking, with 8 or more drinks/week in women and 15 or more drinks/week in men with weekly binge drinking episodes (five or more drinks in men; four or more drinks in women per drinking episode) for BH group. The MD group comprised those who reported less than 8/week for women and less than 15/week for men with no episodes of binge drinking (NIAAA 2012). Participants were excluded if they were cigarette smokers, met current DSM-IV-TR *dependence* criteria for alcohol, current DSM-IV-TR criteria for any substance use or psychiatric disorders, or if they were taking any medications. Participants underwent breath

alcohol testing, carbon monoxide testing and urine toxicology screens to confirm the self-reported sobriety at each study appointment and no participant was positive for any substance use at admission to the study. Participants received a physical examination by the admitting physician (JBG) to ensure all participants were in good health. Participants provided written informed consent and the study was approved by the Human Investigation Committee of the Yale University School of Medicine.

Script development and imagery training

Imagery script development was conducted before the laboratory challenges, as per methods described in previous studies (Sinha et al. 2000; Sinha et al. 2003; Fox et al. 2005; Sinha 2009a). Briefly, the stress imagery script was based on participants' descriptions of a recent personally stressful event which made them 'sad, mad, or upset', combined with little control over the situation in the moment, and that was experienced as 'most stressful'. 'Most stressful' was determined by assessing perceived stress on a 10-point Likert scale where 1 = not at all stressful and 10 = the most stress they felt in the past year. Individual calibration of stressful situations was conducted by only accepting situations rated as 8 or above as appropriate for script development. Stressful situations involving alcohol or drugs were not allowed. The alcohol cue scripts were developed by participants identifying a recent situation that included alcohol-related stimuli and subsequent alcohol use. Alcohol-related situations that were associated with negative affect or psychological distress were not allowed. A neutral-relaxing, non-physiologically arousing and non-alcohol-related script was developed from the participants' description of a personally relaxing situation. Participants were also provided with training in progressive relaxation and mental imagery in a 40-minute session prior to experiment sessions as described below. The procedures for the training are outlined in the imagery training manual (Sinha & Tuit 2012) and in previous work (Sinha 2009a). Briefly, the progressive muscle relaxation procedure involves learning to monitor the tension in specific muscle groups by first tensing each muscle group, then releasing the tension, while directing attention towards the differences felt during tension and relaxation.

Experimental procedures

Participants were admitted for a 3-day, 2-night stay at the Yale Center for Clinical Investigation-Hospital Research Unit located at the Yale New Haven Hospital, to ensure an alcohol-free state and a controlled environment during the experiment. Upon admission on day 1, subjects were trained in progressive muscle relaxation and guided imagery as per our previous work and as outlined in the personalized imagery procedures training manual (Sinha & Tuit 2012). On each day, participants were brought into the testing room at 2:00 PM, after eating a light lunch at noon. A heparin-treated catheter was inserted by the research nurse in the antecubital region of the participant's non-preferred arm. A 45-minute adaptation period followed. Next, baseline plasma samples were drawn and subjective alcohol craving was assessed. Participants then underwent 20 minutes of progressive relaxation after which a second set of baseline plasma samples were drawn and subjective alcohol craving was assessed. Next, participants were provided with headphones and exposed to the 5-minute personalized guided imagery script of either their stress, alcohol cue or neutral-relaxing scenarios, one per day in a randomized and counterbalanced order.

Participants were given the following instructions: ‘Close your eyes and imagine the situation being described, ‘as if ‘ it were happening right now. Let your body and mind get completely involved in the situation, doing what you would do in the real situation’. Immediately following imagery exposure on each day, participants were presented with discrete alcohol cues in the form of a tray of two 12-Oz beer mugs filled with chilled beer and a glass of water with ice. Next, participants underwent a modified version of the ATT (Marlatt et al. 1973), and the following instructions were given to each participant: ‘There are 2 glasses in front of you, each containing beer. You are to taste each beer and tell us whether you think they are the same or different. You can drink as much as you need to make your decision. If you are correct, you will be paid \$10. You have 10 minutes to decide’. The amount of beer consumed on each experimental day (intake) was recorded as an implicit measure of behavioral motivation for alcohol (ATT alcohol intake). On all 3 days, both mugs contained the same type of Bud Light beer (Anheuser–Busch), which has an alcohol content of 4.2%. Craving and cortisol assessments were made at repeated timepoints throughout the session (Fig. 1). All measures prior to ATT were specified as Phase I and post-ATT assessments were grouped as Phase II of the experiment.

Dependent measures

Alcohol craving—To assess craving, participants were asked to rate the intensity of their desire to use alcohol at that moment using an 11-point visual analog scale in which 0 = ‘not at all’ and 10 = ‘extremely high’. Assessments were made prerelaxation and post-relaxation baseline, following imagery exposure, following discrete alcohol cue, following the ATT, and every 15 minutes for an hour afterward (Fig. 1).

Measurement of cortisol—Plasma samples (4 ml) were collected at the same eight consecutive timepoints as craving (Fig. 1). All plasma samples were collected in heparinized tubes that were immediately placed on ice after drawing. Within 30 minutes of collection, the blood was centrifuged at 4°C and the plasma was pooled and aliquoted for cortisol assays. All tubes were stored at –70°C and analyzed using standard radioimmunoassay procedures as reported previously (Sinha et al. 2011b).

Alcohol taste test alcohol intake as a measure of implicit behavioral motivation

Each of the two beers consisted of 375 ml of 4.2% alcohol, allowing for ATT alcohol intake to be up to 750-ml maximum on each day.

Data analyses

All statistical analyses were performed using R software (R Core Team, 2013, Vienna, Austria) and all figures were created with GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, USA).

Multilevel linear mixed effect models (ML-LME) were utilized, with an unstructured variance/covariance matrix structure (that makes less assumptions about the data) in all models, to examine: (1) whether within-person and between group changes in craving or cortisol response to stress, alcohol and neutral contexts, and discrete alcohol cues in the pre-ATT phase predicted greater ATT intake (Phase I) and (2) whether the level of ATT intake

predicted craving or cortisol changes post-ATT (Phase II). The ML-LME modeling was performed with three within-person factors—Phase, Condition and repeated Timepoints and Subjects as a Random effect. Phase, Condition and Timepoints were coded as within subject fixed factors, and Drinking Group served as a between subjects fixed factor, with baseline craving/cortisol as covariates in the pre-ATT Phase I analyses. Within-person craving and cortisol responses were assessed as time-varying factors leading to alcohol intake. In post-ATT analyses, the ATT alcohol intake served as a within-person random factor, and cortisol levels and craving served as the continuous dependent variables. Day order was also included in all analyses to account for any linear effects of condition order in the experiment.

RESULTS

The sample of 25 nonsmoking, moderate social drinkers (MD) was demographically matched to 28 nonsmoking, binge-heavy social drinkers (BH) at a group level during recruitment in age, years of education, IQ, sex, race, number of first-degree relatives with AUDs and days since they last consumed alcohol (Table 1). As expected, the two groups differed significantly in number of drinking days in the past month, the total amount of alcohol consumed in the past month and usual and maximum amount of alcohol consumed per drinking episode.

Baseline group differences: craving

There were no condition by day effects on baseline craving, $F(2,474) = 0.053$, $P = \text{ns}$. BH drinkers showed higher basal craving than MD [BH mean: 1.02 (0.2), MD mean: 0.53 (0.11), $P < 0.05$]. This group difference existed 45 minutes after IV insertion and remained significant after progressive relaxation, [BH mean: 0.9 (0.1), MD mean: 0.36 (0.07), $P < 0.05$]. Baseline craving levels were significantly related to days since last drink, $F(1,117) = 4.7$, $P < 0.05$, such that longer abstinence was associated with greater craving. Baseline craving also positively predicted ATT alcohol intake, $F(1,157) = 10.9$, $P < 0.001$. Thus, all further analyses included baseline craving as a covariate.

Baseline group differences: cortisol

There were no condition by day effects on baseline cortisol, $F(2,474) = 0.62$, $P = \text{ns}$. Higher basal cortisol levels were seen for BH relative to MD [BH mean: 8.16 (0.3), MD mean: 7.22 (0.38), $P < 0.01$]. This group difference existed 45 minutes after IV insertion, but became nonsignificant after progressive relaxation, $F(1,156) = 0.02$, $P = \text{ns}$. Baseline cortisol levels were not related to days since last drink, $F(1,157) = 0.01$, $P = \text{ns}$, but negatively predicted ATT alcohol intake, $F(1,156) = 5.07$, $P < 0.05$. All further analyses included baseline cortisol as a covariate.

Group and condition differences in alcohol taste test intake

A significant main effect of Drinking Group, $F(1,53) = 12.42$, $P < 0.01$, was found for ATT intake, indicating that the BH group consumed more alcohol in each of the three experimental conditions than the MD group (Fig. 2a). A significant main effect of Condition, $F(2,414) = 13.96$, $P < 0.001$, also indicated that across both groups, stress and

alcohol cue relative to neutral-relaxing cue conditions was associated with greater ATT intake (Fig. 2b). The Drinking Group $\times$ Condition interaction was not significant. Furthermore, ATT intake (averaged across all 3 days) correlated significantly with self-reported alcohol intake in past 30 days on the Cahalan QFVI, $F(1,48) = 10.52$, $R^2 = 0.18$, $P < 0.01$, (Fig. 2c), thereby validating the ATT in the experiment as an index of real world drinking levels.

Phase I pre-alcohol taste test results

All significant main effects and interaction effects are presented in Table 2. When three-way interactions were significant, we do not discuss the two-way interactions as recommended by Tabachnick & Fidell (2007).

Effects of imagery and discrete alcohol cues on subjective craving—There was a significant Group $\times$ Timepoint interaction, $F(2,318) = 11.46$, $P < 0.0001$, resulting from the MD group showing increases in craving following stress and alcohol cue-relative to neutral context (P s < 0.05), and then further significant increases in craving with discrete cues in each condition (P s < 0.05), while the BH group showed greater craving following stress and cue-induced imagery with no additional increases at the discrete cue timepoint in the stress and alcohol cue contexts (P s < 0.05 , Fig. 3a,b). A Condition $\times$ Timepoint interaction, $F(4,318) = 14.93$, $P < 0.0001$, resulted from significant increases in craving after presentation of discrete beer cues across both groups in the neutral-relaxing condition ($P < 0.05$), but greater increases in craving in stress and alcohol cue relative to neutral from baseline to imagery ($P < 0.05$), and imagery to discrete cues timepoints ($P < 0.05$).

Effects of provoked craving on alcohol taste test alcohol intake—A Craving $\times$ Condition $\times$ Group effect was observed, $F(2,411) = 4.09$, $P < 0.05$, resulting from the BH group showing greater stress/discrete cue-induced alcohol craving being associated with greater ATT alcohol intake, $F(1,26) = 16.43$, $P < 0.01$, and greater neutral/discrete cue-induced craving associated with greater ATT intake, $F(1,26) = 11.7$, $P < 0.01$, effects not seen in the MD group: $F(1,23) = 1.58$, $P = \text{ns}$ for the stress condition and the $F(1,23) = 1.62$, $P = \text{ns}$ for the neutral condition. Craving in the alcohol cue condition was not related to ATT intake in either group, $F(1,26) = 2.05$, $P = \text{ns}$ for the BH group and $F(1,23) = 0.62$, $P = \text{ns}$ for the MD group (Fig. 3c,d).

Effects of imagery and discrete alcohol cues on cortisol—A significant main effect of Group, $F(1, 53) = 4.95$, $P < 0.05$, indicated a more blunted cortisol response in the BH relative to MD group across conditions. A significant Group $\times$ Timepoint interaction, $F(2,315) = 4.43$, $P < 0.05$, resulted from the MD group showing significant reductions in cortisol at the discrete cue timepoint relative to the post imagery timepoint across conditions ($P < 0.05$), but the BH group showing no differences between baseline to imagery ($P < \text{ns}$) or from imagery to discrete cue timepoints across conditions ($P < \text{ns}$), (Fig. 4a,b).

Effects of cortisol responses on alcohol taste test intake—An overall significant main effect of Cortisol on ATT intake was observed, such that lower or more blunted cortisol responses predicted higher ATT intake, $F(1,432) = 13.25$, $P < 0.001$. A three-way interaction

of Cortisol $\times$ Group $\times$ Condition, $F(2,409) = 12.05$, $P < 0.0001$, was also significant. In MD drinkers, blunted cortisol levels in the alcohol cue/discrete cue condition predicted higher ATT intake, $F(1,70) = 10.47$, $R^2 = 0.13$, $P < 0.01$, whereas for the BH drinkers, blunted cortisol response to stress/discrete cues condition was associated with greater ATT intake, $F(1,82) = 10.04$, $R^2 = 0.11$, $P < 0.01$, (Fig. 4c,d).

Phase II post-alcohol taste test results

Effects of alcohol taste test intake on post-alcohol taste test craving—There was a main effect of ATT intake on post-ATT craving, $F(1,133) = 8.13$, $P < 0.01$, indicating higher ATT intake predicted greater craving, and a main effect of post-ATT Timepoint, $F(4,622) = 5.15$, $P < 0.001$, which showed that craving decreased over time across groups (Fig. 5a). However, a significant Drinking Group $\times$ post-ATT Timepoint $\times$ ATT intake interaction, $F(4,622) = 4.12$, $P < 0.01$, was also found, resulting from the higher ATT intake in the BH group predicting greater craving through the +30 timepoint (P s < 0.05), but no such effects of higher ATT intake affecting craving over time in the MD group (P s = ns). This effect is further illustrated in figure 5b, which was created by conducting a median split of the ATT intake amount into high and low subgroups within each Drinking Group.

Effects of alcohol taste test intake on post-alcohol taste test cortisol—A significant main effect of ATT intake on cortisol responses post-ATT was observed, $F(1,131) = 6.77$, $P < 0.05$, such that higher ATT intake predicted greater - post-ATT cortisol responses. There was also a significant interaction of ATT intake $\times$ Timepoint, $F(4,612) = 5.76$, $P < 0.001$, on cortisol responses post-ATT, resulting from higher ATT intake predicting greater cortisol responses at the +30 timepoint relative to +15 and +45 timepoints (P s < 0.05 , Fig. 5c). This effect was influenced by a trend level interaction between Drinking Group $\times$ ATT alcohol intake, $F(1,131) = 3.40$, $P = 0.0675$, explained by low levels of ATT alcohol intake predicting higher cortisol responses in the MD group ($P < 0.05$), while this relationship was not significant in the BH group ($P < ns$). This effect is illustrated in figure 5d which was created by conducting a median split of the ATT intake amount into high and low subgroups within each Drinking Group.

DISCUSSION

This study examined the role of context (personalized stress, alcohol cues or neutral-relaxing imagery) and discrete cue exposure on subjective alcohol craving, cortisol responses and behavioral alcohol motivation (as measured by alcohol intake in the ATT), in a well characterized, nonsmoking, group of moderate non-binging (MD) and binge/heavy (BH), non-AUD drinkers. We also assessed whether dynamic context and discrete cue-related changes in craving and cortisol predicted ATT intake, and whether ATT intake, in turn modulated post-intake cortisol and craving responses. We found that BH relative to MD drinkers consumed more alcohol in the ATT and that stress and alcohol cues relative to neutral-relaxing condition led to greater ATT intake across both groups. Findings also indicated that stress and alcohol cue contexts, along with discrete alcohol cues, significantly increased alcohol craving, more so in BH than MD drinkers, and stress and discrete cue-induced craving increases were predictive of alcohol intake in the BH group only. The BH

group showed blunted cortisol responses across conditions relative to the MD group, and blunted cortisol responses were predictive of higher alcohol intake overall across groups and conditions; but more specifically lower cortisol responses in the stress condition for the BH and in alcohol cue condition for the MD were each significantly predictive of greater ATT alcohol intake. Finally, greater ATT intake predicted post-alcohol cortisol rises, with higher alcohol intake related to greater cortisol increases over timepoints, and more sustained post-alcohol cravings in the BH relative to the MD groups. These findings suggest that higher subjective craving and disrupted cortisol responses to stress and alcohol cues are significant responses that may contribute to increased alcohol intake. Relevance of these experimental findings were further supported by the positive and significant association between ATT intake and self-reported recent number of alcoholic drinks consumed by participants in the past 30 days.

We found higher basal cortisol and craving levels in the BH relative to MD drinkers. Active drinking is known to increase basal cortisol levels (Wand & Dobs 1991), and higher basal craving has also been reported in binge drinkers and in actively drinking AUD patients (Lindgren et al. 2015; Naqvi et al. 2015). We previously reported that higher basal cortisol is related to more blunted responses to stress in AUD individuals relative to controls (Sinha et al. 2009) and suggested that HPA axis disruption may serve as a marker of alcohol relapse and continued use (Sinha et al. 2011b). The current findings indicate that similar disruption may exist in BH drinkers, even prior to the development of AUDs (Blaine & Sinha 2017). Furthermore, higher craving ratings in BH relative to MD drinkers in response to stress and alcohol contexts and in response to discrete cues after neutral context cues, suggests that these contexts and cues have greater incentive salience in the BH relative to the MD group, consistent with the incentive sensitization theory that posits that higher levels of alcohol consumption lead to greater incentive salience of drug and drug-related stimuli, including stress-related contexts (Robinson & Berridge 2000). The higher craving ratings are also consistent with previous preclinical studies on context-induced and cue-induced drug seeking and reinstatement (Shaham, Erb, & Stewart 2000; Crombag et al. 2008) and studies of incentive salience over the course of recent binge drinking (Field & Duka 2002; Field & Eastwood 2005). However, while the personalized stress imagery method has consistently been shown to increase alcohol and drug craving levels in individuals with AUD (Sinha 2009a), it should be noted that other approaches of stress provocation have not reported increased stress-induced craving levels (Thomas, Randall, et al. 2011).

While it is no surprise that BH drinkers consume significantly more beer than MD drinkers, it is important to note that in the current experiment, unlike in a fixed dose study, motivation for alcohol was assessed *implicitly* using the ATT, as has been done in previous research with AUD individuals (Thomas, Bacon, et al. 2011). Furthermore, as shown by others (de Wit et al. 2003; Thomas, Bacon, et al. 2011; Magrys et al. 2013), we also found that stress and alcohol cue contexts relative to neutral-relaxing contexts led to significantly greater ATT intake across both groups, but at higher levels in the BH group. Utility of the ATT in assessing implicit behavioral alcohol motivation in the laboratory has been previously established (Jones et al. 2016; Thomas, Bacon, et al. 2011), and previous studies utilizing the ATT are also consistent with current study's results that participants' alcohol

consumption in the laboratory is associated with their self-reported alcohol use in real world (Leeman, Corbin, & Fromme 2009; Leeman et al. 2013).

Remarkably, we found that blunted cortisol responses in stress and alcohol contexts and cues was predictive of greater ATT intake. Furthermore, for the BH group, greater blunted responses in the stress condition, but for MD greater blunted cortisol in the alcohol cue condition, was each associated with significantly higher alcohol intake, respectively. Blunted cortisol responses have been reported in response to stress and alcohol cues in AUD patients (Wrase et al. 2006; Sinha et al. 2009) and also in response to fixed dose of alcohol in BH relative to MD drinkers (King et al. 2006). Moreover, this blunted cortisol response to stress is predictive of relapse in those with AUDs and is seen in preclinical models of stress-induced reinstatement (Sinha 2001; Koob & Kreek 2007; Higley et al. 2011; Sinha et al. 2011b). One may speculate that blunted cortisol responses to stress predicted higher alcohol intake in BH drinkers as an attempt to normalize their HPA axis dysregulation, (i.e. higher basal cortisol and blunted response to stress) in the service of adaptation and allostasis. The findings also indicate that across groups blunted cortisol is associated with alcohol motivation and that in BH drinkers, stress cues take on the same relevance of alcohol cues for MD drinkers, so BH drinkers may already be showing an altered stress response to alcohol cues. Thus, our findings complement the well-known effects of binge and high alcohol intake on neuroendocrine tolerance (Richardson et al. 2008; Lu & Richardson 2014; Blaine et al. 2016), and further suggest that these blunted cortisol responses have motivational significance and play a role in increasing alcohol motivation and intake.

When interpreting the cortisol findings, it is important to consider the effect of the normal diurnal cortisol rhythm. The 3-day experiment was conducted in a controlled environment of the research hospital setting and in the afternoon when cortisol levels are naturally declining. In the context of these declining cortisol levels, we found the MD group to show sustained cortisol levels from baseline to after imagery, and then a significant drop after discrete cues in the stress and alcohol cue conditions. On the other hand, the BH drinkers showed no sustained cortisol response post-stress or post-alcohol cue imagery and instead their cortisol responses showed a flattened slope with no differences across timepoints, similar to that reported in moderate–severe AUDs (Adinoff et al. 2003; Gianoulakis, Dai, & Brown 2003; Badrick et al. 2008; Boschloo et al. 2011; Ruttle et al. 2015).

In Phase II, higher ATT intake significantly predicted increased cortisol levels. Thus, our findings support previous work that shows alcohol intake, including priming drinks, stimulates the HPA axis and results in increased cortisol levels (Gianoulakis 1998; King et al. 2006; Lovallo 2006; Richardson et al. 2008; Thomas, Bacon, et al. 2011). In this study, cortisol levels decreased over time in the MD group, but higher alcohol intake by the BH drinkers led to more sustained cortisol levels over time. The preclinical literature indicates that glucocorticoids released in response to alcohol consumption enhance the development of mesolimbic dopaminergic sensitization to alcohol (Blaine & Sinha 2017), but other preclinical research (Lee & Rivier 1997a; Allen, Lee, et al. 2011; Lu & Richardson 2014), as well as current findings, suggest that there may be neuroendocrine tolerance with binge and chronic alcohol intake, such that perhaps more alcohol may be needed to provide alcohol reward stimulation, as may be the case in the BH drinkers. Thus, over time and with

repeated binges, BH drinkers may show an upregulated basal stress axis and blunted cortisol mobilization in response to stress both of which may be associated with increased craving and motivation for alcohol intake.

On the other hand, with no further opportunity to consume alcohol, post-alcohol intake craving dropped across both groups. These findings are consistent with previous research which shows that perceived availability of a drug is a key factor in increasing subjective craving for that drug (Smart 1977; Wertz & Sayette 2001; Kuntsche, Kuendig, & Gmel 2008; Wilson et al. 2008). BH drinkers' consumed more alcohol and remarkably, their craving remained significantly higher and dropped much less than MD drinkers over time, despite no further opportunity to consume more alcohol. In fact, the more alcohol BH drinker's consumed, the higher their craving remained, whereas no such relationship existed for the MD drinkers. Thus, ATT alcohol intake appeared to satiate the MD drinkers, but not the BH drinkers.

In summary, the current findings utilized an experimental approach to assess the role of stress and alcohol contexts and discrete cues on craving, cortisol and ATT intake in BH and MD drinkers. Dynamic changes in craving and cortisol in these contexts and with discrete cues was found to significantly affect ATT intake, which in turn affected levels of cortisol and craving post alcohol intake. Although these results have important implications for role of salient contexts, craving and cortisol in alcohol intake, our findings should be considered within the context of certain limitations. First, it is important to note that within the BH group, none of these participants met criteria for AUDs at the time of the study and it is unknown which, if any, would go on to develop AUDs. Additionally, although we carefully obtained drinking histories on separate days and across measures prior to MD and BH classification, no biochemical verification of current alcohol use was performed. Next, our ability to interpret these findings is limited by the laboratory context of the experiment. Dynamic modeling of these relationships in the laboratory was necessary to examine interactive effects of stress and alcohol contexts and cues on craving and cortisol responses to affect behavioral alcohol motivation (ATT intake) in a controlled experimental context, but our experiment lacks ecological validity and requires replication in a real-world setting. Nonetheless, our results show that higher and more sensitized stress and alcohol cue-induced cravings, but and blunted cortisol responses, are each predictive of greater alcohol intake, particularly in the BH social drinkers and suggest that these responses may play a role in increased alcohol motivation and loss of control of drinking.

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Figure 1.

Two phase experimental study procedures. A two-phase experiment assessed the effects of environmental context (induced by stress, alcohol cue and neutral imagery) and discrete alcohol cues (tray of two beers and cup of ice water) on subjective craving, cortisol and implicit behavioral motivation for alcohol via the alcohol taste test (ATT) in Phase I, and ATT alcohol intake effects on craving and cortisol in Phase II

Figure 2.

Group, Condition and Recent Drinking effects on AAT intake. (a) BH drinkers showed higher AAT intake than MD drinkers across conditions (P 's < 0.001). (b) Greater AAT alcohol intake was found in the stress (P < 0.05) and alcohol cue (P < 0.05) relative to the neutral-relaxing conditions across both groups. (c) The amount of alcohol consumed during the AAT was positively associated with the self-reported number of alcoholic drinks consumed in the last month on the Cahalan QFVI (P < 0.01). *Note:* * P < 0.05, ** P < 0.01, *** P < 0.001, values reported in (a) and (b) are mean + standard error (M + SE)

Figure 3.

Craving responses to cues and alcohol intake. (a) Craving was higher in response to stress and alcohol cues than to neutral imagery (P s < 0.01). MD drinkers show a greater craving in response to alcohol cue imagery and stress cue imagery than to neutral (P s < 0.001). In all conditions, craving increased for the MD group with the presentation of the discrete cue, the beer tray (P < 0.05). (b) BH relative to MD drinkers showed higher overall alcohol craving, P < 0.01, and significantly higher craving levels in response to alcohol cue and stress imagery (P s < 0.05) than to neutral imagery that is not further increased with the presentation of the discrete cue. For BH drinkers, craving in the neutral condition increased in response to the beer tray, P < 0.001. (c) Higher craving did not lead to greater alcohol intake in MD drinkers. Regression lines for MD drinkers are stunted by the small range of craving scores. (d) For BH drinkers, craving in response to the stress/discrete cue and neutral-relaxing/discrete cue conditions led to significantly higher alcohol intake in those conditions (P s < 0.001). *Note:* * P < 0.05, ** P < 0.01, *** P < 0.0001, values reported in (a) and (b) are M + SE

Figure 4.

Cortisol responses to cues and alcohol intake. (a) MD drinkers show no change in cortisol from baseline to imagery and then reduction after the presentation of the discrete alcohol cue in all conditions ($P < 0.05$). (b) BH drinkers show an overall blunted cortisol response relative to MD drinkers ($P < 0.001$). BH drinkers showed no differences in cortisol responses to imagery across conditions and no further changes after discrete cue presentation. (c) Blunted cortisol responses to alcohol cues led to high alcohol intake in MD drinkers, ($P < 0.01$). (d) Blunted cortisol levels in the stress condition led to higher alcohol intake in BH drinkers ($P < 0.01$). *Note:* This experiment occurred in the afternoon, when cortisol levels are naturally dropping due to the diurnal cycle. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.0001$, values reported in (a) and (b) are $M \pm SE$

Figure 5.

Effect of alcohol intake on craving and cortisol levels (Phase II)(a) Craving decreased over the hour post-ATT in all participants, but remains significantly higher in the BH group than the MD group ($P < 0.01$). (b) Craving decreased with higher alcohol intake in MD drinkers but dropped less and was sustained with increasing alcohol intake in the BH drinkers ($P < 0.01$). (c) Cortisol levels initially increased in all participants in response to alcohol intake, but more quickly and to higher levels in BH drinkers than MD drinkers ($P < 0.001$). (d) Greater alcohol consumption was associated with lower levels of cortisol in MD drinkers but was not associated with a lower cortisol levels for BH drinkers over time ($P < 0.01$). Additionally, (b) and (d) use a median split for illustration purposes, but craving and cortisol were measured as continuous variables in all analyses. *Note:* * $P < 0.05$, ** $P < 0.01$, *** $P < 0.0001$, values reported are M + SE.

Table 1

Sample demographics and drinking characteristics

<i>Demographic variable</i>	<i>Binge/heavy (N =28)</i>	<i>Moderate (N =25)</i>
Age	27.6 (6.9)	30 (8.4)
Sex (% male)	79%	76%
Race (% Caucasian)	71%	84%
Education	15.6 (2.2)	15.5 (1.9)
Shipley intelligence quotient (IQ)	115.2(6)	114.2(7.8)
Number of alcohol dependent first degree relatives	0.52 (0.7)	0.52 (0.71)
Days since last drink	3(2.5)	3(2)
Years of regular drinking	8.3 (6.6)	5.5 (4.7)
Drinking days/past month [*]	13 (6.5)	6.5 (5.3)
Total amount consumed/past month ^{**}	63.7 (39.6)	15.8 (12.8)
Cahalan QFI usual number of drinks ^{***}	5.07(2.9)	2.08 (0.9)
Cahalan QFI max number of drinks ^{***}	9.1 (4.2)	4.6 (2)

Participants were nonsmokers and non-substance users.

^{*}
 $P < 0.05$.

^{**}
 $P < 0.01$.

^{***}
 $P < 0.0001$.

Table 2

Summary of significant effects among craving, cortisol and alcohol intake

Model	Effect	df	F	p	Direction
Phase I: pre-ATT craving	Group	153	11.46	0.001	BH > MD
	Condition	2106	17.20	<0.0001	Stress and alcohol > neutral
	Timepoint	2318	93.23	<0.0001	Imagery and discrete cue > baseline
	Group × Timepoint	2318	11.46	<0.0001	MD imagery < discrete cue, BH imagery = discrete cue
	Condition × Timepoint	4318	14.93	<0.0001	Neutral imagery < discrete, stress and alcohol imagery = discrete cue
Phase I: pre-ATT cortisol	Group	1253	4.95	0.03	MD > BH
	Timepoint	2315	34.47	<0.0001	Baseline > imagery > discrete cue
	Group × Timepoint	2315	4.43	0.01	MD imagery > discrete cue, BH imagery = discrete cue
ATT intake	Group	153	12.42	0.01	BH > MD
	Condition	2414	17.51	<0.0001	Stress and alcohol > neutral
	Group	164	8.69	0.004	BH intake > MD intake
Craving prediction of ATT intake	Condition	2 410	3.53	0.03	Craving in stress and alcohol --> ↑ intake relative to neutral
	Craving × Group × Condition	2411	4.09	0.02	BH craving in stress and neutral conditions --> ↑ intake relative to MD
	Cortisol	1432	13.25	0.0003	↓ in cortisol ↑ intake
Cortisol prediction of ATT intake	Group	186	10.99	0.001	BH > MD
	Cortisol × Condition	2409	5.57	0.004	↓ in cortisol stress, alcohol > neutral --> ↑ intake
	Cortisol × Group × Condition	2409	12.05	<0.0001	BH ↓ cortisol stress --> ↑ intake, MD ↓ cortisol alcohol --> ↑ intake
	Intake	1133	8.13	0.005	↑Intake ↑ craving
	Timepoint	4622	5.15	0.0004	↑ Time ↓ craving
Phase II: post-ATT craving	Intake × Timepoint	4622	3.95	0.004	↑Intake ↑ craving @ +15, not +30, +45, +60
	Intake × Timepoint × Group	4622	4.12	0.003	BH ↑Intake↑ craving, MD ↑ intake ↓ craving
	Intake	1132	6.77	0.01	↑Intake ↑ cortisol
Phase II: post-ATT cortisol	Timepoint	4612	5.58	0.0002	↑ Time ↓ cortisol
	Intake × Timepoint	4612	5.76	0.0001	↑Intake ↑ cortisol @ +30, not +15, +45, +60

Abbreviations: df = degrees of freedom, F = F-value, P = p-value.