ABSTRACT

Problematic Alcohol Use in College Students and

Its Association with Cardiovascular Reactivity and Adaptation

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Blunted cardiovascular responses to stress have been associated with alcohol use disorders, but the nature of the relationship remains largely unknown. Literature examining the relationship between cardiovascular reactivity habituation and alcohol use disorders has also been inconclusive. Recent research has noted the inadequacy of singular stress exposures and highlights the need to measure cardiovascular reactivity across multiple stress exposures as to obtain a more comprehensive cardiovascular profile. The present study investigated problematic alcohol consumption's effects on cardiovascular stress reactivity, as well as cardiovascular reactivity over time. Two hundred and twenty healthy, young adults (mean (SD) age = 19.77 (1.59); 60.5% female; 64.1% Caucasian; 17.7% Hispanic) who all reported consuming alcohol on a regular basis, completed a single laboratory visit, which included two identical stress protocols. Blood pressure (BP) and heart rate (HR) were measured during the baseline period and stress tasks, and problematic alcohol use was measured with the College Alcohol Problems Scale–revised (CAPS-r). There was a negative correlation between heart rate and the social subscale of the CAPS-r over the first exposure, while no significant relationship was indicated between any of the cardiovascular variables and the CAPS-r subscales over both exposures. These results emphasize the necessity of future research incorporating multiple stress exposures within their protocols.

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Problematic Alcohol Use in College Students and its Association with Cardiovascular Reactivity and Adaptation to Repeated Stressors

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Contents

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To भैया. Thank you for being the oldest child of immigrant parents. You walked so I could run, and your support engenders most of my confidence.

CHAPTER ONE

Introduction

Substance use disorders (SUDs) are a major public health concern in the United States, which cost the public an estimated $442 billion every year in health care, loss of productivity to employees, and legal and social ramifications for patients (Sacks et al., 2015; National Drug Intelligence Center, 2011; U.S. Surgeon General, 2016; U.S. Department of Health and Human Services, 2016; Center for Behavioral Health Statistics, 2017). Alcohol misuse is one of the most common types of SUDs, with roughly 14.4 million people diagnosed in the United States and with lifetime prevalence rates as high as 29.1% in adults 18 and older (Grant et al., 2015; Substance Abuse and Mental Health Services Administration [SAMHSA], 2018). These statistics compel researchers to investigate risk factors for alcohol use disorders (AUDs), as it could aid in handling this public health burden. While many different factors impact the development, maintenance, treatment, and relapse of AUDs, one of the most common risk factors is stress (Brady et al., 2006; Brady & Sinha, 2005; Sinha, 2008; Sinha, 2001; Sinha,2003). Stress interacts with and exacerbates the effects of other risk factors like family history, mood dysregulation, and mild cognitive deficits, and contributes to problematic drinking (Sinha, 2008; Lovallo, 2019).

However, the relationship between stress and AUDs is not completely clear (Keyes et al., 2012). Since consumption of alcohol peaks for many people during late adolescence and early adulthood, studying alcohol misuse during these periods can be crucial for understanding the development of AUDs (SAMHSA, 2018).

SUDS and Cardiovascular Reactivity

Research suggests diminished cardiac and cortisol reactivity are biomarkers for developing a SUD (Brenner & Beauchaine, 2011; Evans et al., 2012; al'Absi, 2013; Ginty et al., 2014; al'Absi et al., 2005; Nakajima et al., 2013; Lovallo, 2011; Lovallo, 2013; Lovallo et al., 2000; Lovallo et al., 2019; Panknin et al., 2012). However, the data are not necessarily conclusive. Some laboratory studies have found exaggerated cardiovascular reactivity (CVR) in smokers compared to non-smokers (Sheffield et al., 1997; Girdler et al., 1997), while others have found gendered differences in reactivity in smokers (Childs and de Wit, 2009). Research regarding alcohol and CVR is similarly paradoxical. While acute exposures to alcohol have been shown to increase heart rate (Rush et al., 1989; Conrad et al., 1997; Stewart et al., 1992), alcohol has also been associated with attenuated responses to stress, particularly blood pressure responses (Higgins et al., 1993; Rush at al., 1989; Hoaken et al., 2003). This variation necessitates future research, as determining the directionality between SUDs and CVR could aid in the development of therapies and could also engender new areas of research for other mental illnesses.

SUDs and Habituation

Examining the interactions between alcohol use and CVR to repeated stress may be critical to understanding the stress-alcohol use relationship, as repeated alcohol use increases the chances of future cardiovascular pathology (Shield et al., 2014; Piano, 2017). However, to date, no studies have examined this. A review investigating CVR habituation proposed a singular exposure to stress may not be an adequate experimental paradigm, as CVR is dynamic and subject to change over repeated exposures to stress (Hugheset al.,, 2018). For instance, an initial

heightened CVR could be part of an adaptive short-term cardiovascular response, which could eventually diminish as to not place any undue strain on the cardiovascular system. However, in dysfunctional systems, exaggerated CVR could be maladaptive and could be extended across multiple stress exposures. Research has documented that CVR changes in response to multiple acute psychological stressors (al'Absi et al., 1997; Kelsey et al., 1999).

Research examining the relationship between SUDs and cardiovascular habituation have been largely limited to nicotine and cocaine consumption (Hughes & Higgins, 2010; Sinha, 2001; Back et al., 2008; Braun et al.,1997). One study matched smokers with non-smokers and examined differences in reactivity patterns to multiple exposures of the same stressor, with results indicating that smokers had a higher diastolic blood pressure (DBP) than non-smokers and female non-smokers demonstrate DBP response sensitization (Hughes & Higgins, 2010). Smokers of either sex did not have any change in blood pressure reactivity when exposed to the first stressor, but the number of cigarettes smoked per day was inversely associated with HR reactivity to the second stressor. The stability of blood pressure reactivity and the attenuated HR responses suggest that more research is required to determine why the differences exist in cardiac reactivity habituation and to compare to the processes which exist for other substances, especially alcohol.

The current study sought to investigate how problematic alcohol use affected cardiovascular reactivity to the first exposure of an acute psychological stressor and how this use changed over both exposures, if at all. Based on previous research with single stress exposures and with smoking (Hughes & Higgins, 2010; al'Absi, 2013), it was hypothesized that problematic alcohol use in response to psychological stress would be associated with lower HR but higher DBP reactivity. The latter prediction is due to the fact that elevated DBP poses a risk

of cardiovascular morbidity independent to that posed by SBP and that people with some SUDs (especially smokers) demonstrate higher DBP reactivity, particularly in women (Hughes & Higgins, 2010; Prospective Studies Collaboration, 2002; Girdler et al., 1997; Back et al., 2008). It was also hypothesized that problematic alcohol use would be associated with lower blood pressure and heart rate reactivity habituation.

CHAPTER TWO

Literature Review

Stress

Stress is a seemingly ubiquitous phenomenon, ever-present through all our lives (Heminway & Sapolsky, 2008). Due to its universality, stress has been a difficult concept to define for research. The current operational definition for studying stress has defined it as a competition between available resources and outside demands; an individual is stressed when their environmental demands exceed an individual's adaptive capacity (Cohen et al., 2016). Stressful experiences can be emotionally or physiologically challenging (Sinha, 2001; Sinha, 2008) and can trigger psychological, behavioral, and biological responses which aim to alleviate said stress. Emotional stressors include the loss of a loved one or interpersonal conflict, while physiological stressors could be food deprivation or insomnia (Sinha, 2001; Cohen et al.,1995). By categorizing stress as an interaction between stressors and responses, stress research allows for separate considerations of the triggers, cognitive appraisal, and behavioral and physiological adaptations of stress.

Measurements of Stress and Cardiovascular Reactivity

Though stressful events can be either acute or chronic in duration, most experiments study acute stressors. For clarity's sake, this review will establish as stressors which last less than one week (Dimsdale, 2008). When studying acute stressors, research approaches the investigation in two different ways; they either take advantage of chance exposure – as in the case of the 1994 Northridge earthquake (Leor et al., 1996) –or they model stress in the

laboratory. Stressors created in the laboratory offer a more controlled environment that can determine directionality of the phenomena witness in naturalistic studies. However, there are limited options for stressors that are reliable and valid. Stressors are divided up into three main categories: physical, psychological, or pharmacological (Thomas et al., 2012). Physical stressors are usually stimuli that are easily operationalized, such as exercise (e.g., bicycling tasks, isometric handgrip exercises), pain measures, or extreme temperatures (e.g., a cold pressor task, which is a test in which a participant's hand is submerged in ice-cold water). Pharmacological stressors induce the release of corticotropin-releasing factor (CRF) and vasopressin, which eventually induces the release of cortisol (Zanstra and Johnston, 2011). For psychological stressors, researchers often conduct mental arithmetic and performance tasks. Mental arithmetic tasks include the paced auditory serial addition task (PASAT), which requires participants to add the last two numbers read out in a series, and a subtraction task, which requires participants to subtract an odd number from an arbitrarily large number (e.g., "Count backwards from 1,022 in intervals of 13."). The advantage of these tasks is their objectivity – math tasks have easily identifiable answers, which makes it easy to determine how well the participant did. The PASAT is also a reliable method for perturbing the cardiovascular systems and has good test-retest reliability (Ginty et al., 2013; Ring et al., 2002; Gronwall, 1977). Our laboratory employed the PASAT to streamline the protocol and to provide an objective measure of improvement across two exposures to the stressor. Participants were told that they were being videotaped, and research assistants played an unpleasant noise at pre-determined intervals, which added a layer of social evaluation and induced more stress (Veldhuijzen Van Zanten et al., 2004). Cardiovascular reactivity (CVR) to this stressor was calculated as the observed difference in some measure of

cardiovascular function (e.g., heart rate or blood pressure) between periods of rest and periods of exposures to stressors (Zanstra & Johnston, 2012; Anastasiades & Johnston, 1991).

The Reactivity Hypothesis

While the measurement of CVR is described directly above, CVR can be defined as the difference in these measures of cardiovascular function (e.g., blood pressure, heart rate) between periods of rest and periods of stress (Turner, 1994). Understanding and measuring physiological responses to stress is clinically important, as CVR may influence cardiovascular disease (Treiber et al., 2003). Indeed, several decades of research has found a relationship between exaggerated CVR and detrimental cardiovascular health outcomes, including hypertension (Hines & Brown, 1932; 1936; Menkes et al., 1989; Carroll et al., 2001; Everson et al., 1996; Light et al., 1999; Matthews et al., 1993), atherosclerosis (Treiber et al., 2003; Gianaros et al., 2002; Roemmich et al., 2011), and cardiovascular mortality (Carroll et al., 2003; Carroll et al., 2012; Matthews et al., 2006; Chida & Steptoe, 2010).

Researchers have questioned how CVR could serve as an intermediate link to eventual health outcomes and how variation in responses could mitigate risk for cardiovascular disease. One question considered how responses to psychological stressors differed from responses to physical ones. After all, both these stressors seemed to lead to similar reactivity changes and physical arousal. How was it that one type of reactivity was harmful, while the other protective? Looking at the mechanisms of the reactivity, Obrist and colleagues suggested that CVR during exercise might be metabolically appropriate, or the body reacted as not to overwhelm its physiological systems, a feat not possible during exposures to psychological stressors (Obrist, 1981; Blix et al., 1974; Stromme et al., 1978; Carroll et al., 2009). In other words, the increase in

metabolic activity during the stress exposure was disconnected from the increase in strain on the physiological system. This disconnect is referred to as metabolic uncoupling.

This metabolic uncoupling forms the basis of the reactivity hypothesis, which initially posited that exaggeratedly large cardiovascular reactions to psychological stress increases the risk for cardiovascular pathology (Krantz & Manuck, 1984; Treiber et al., 2003; Lovallo & Gerin, 2003). This hypothesis engendered the implicit understanding that the smaller the responses to psychological stressors, the less of a risk for cardiovascular disease since the body was not creating an undue burden on the physiological system. The less a participant responded, the more protected they were from future cardiovascular disease.

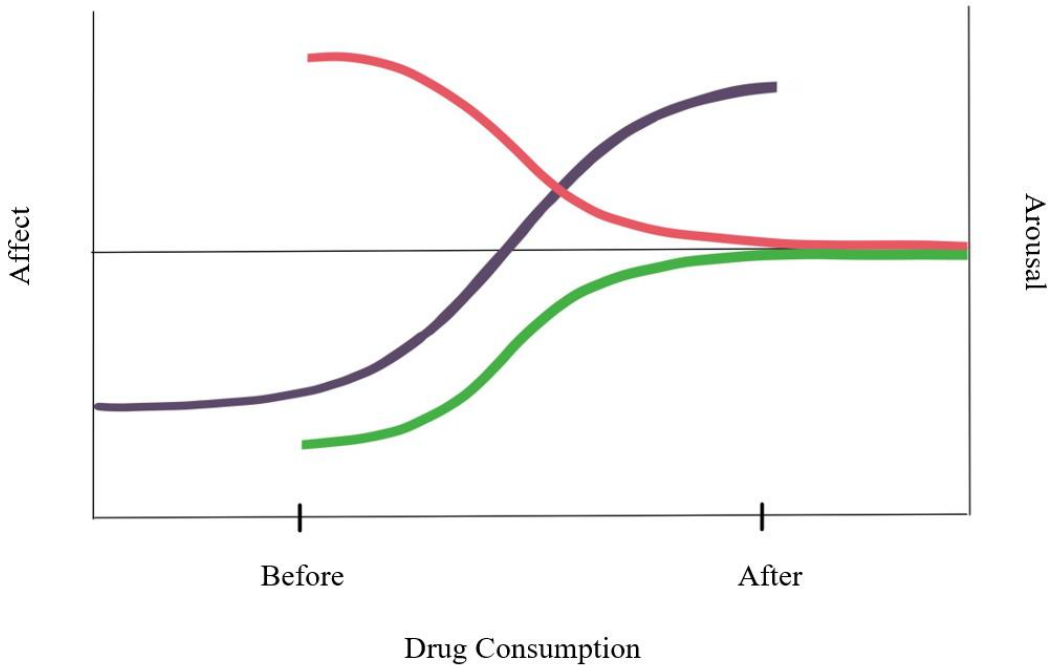
Blunted Reactivity

Though the linear relationship between cardiovascular responses and cardiovascular disease risk (Carroll et al., 2001; Schnall et al., 1998; Lovallo, 2005; Chida & Hamer, 2008; Light et al., 1999; Brydon & Steptoe, 2005; Mathews et al., 2004) gained a robust amount of support over the years, the relationship was too simplistic. The reactivity hypothesis was called into question when individuals with seemingly blunted ("healthy") responses to stress also experienced adverse health outcomes such as depressive symptoms (Carroll et al., 2007; de Rooji et al., 2010; Phillips et al., 2011), obesity and disordered eating (Carroll et al., 2008; Phillips et al., 2012; Ginty et al., 2012a), and SUDs (al'Absi et al., 2005; Lovallo et al., 2000). Since blunted reactivity could be considered a biomarker for these adverse conditions, the possibility for a linear relationship between cardiovascular reactivity and deleterious health outcomes was no longer considered valid. This realization created a proposal for a normative midrange for CVR – this normative midrange varied somewhat from individual to individual, but within this range was the healthy response to stress (Turner, 2020; Lovallo, 2011).

Stress and SUDS

There are a few models which connect the role of stressful life events to the development of SUDs (Sinha, 2001). The first is the stress-coping model of addiction, which postulates that using psychoactive substances both reduces negative affect and increases positive affect, reinforcing drug consumption as a coping strategy (Wills & Shiffman, 1985). The second, the relapse prevention model, suggests that at-risk individuals (e.g., parental substance use) with poor coping strategies have a higher chance of problematically using drugs. The self-medication hypothesis proposes that individuals use substances to reduce hyper-arousal (Khantzian, 1985). The final model posits that individuals who engage in problematic substance use may be inherently hypo-aroused and may use drugs to achieve a state of normalized arousal; this is the stimulus-seeking hypothesis (Evans et al., 2012). All the models imply that substance use and stress positively reinforce each other. The current study focuses on the stimulus-seeking hypothesis. Most college-aged students do not have a SUD. However, those that do develop SUDs begin engaging in problematic alcohol use at around this time of their lives (SAMHSA, 2018). Thus, this study suggests that individuals who engage in problematic substance use may exhibit symptoms of hypo-arousal when exposed to stressors. A visualization of each model is presented in Figure 1.

Figure 1. Models of Addiction



Note. The purple line represents the stress-coping hypothesis, the red the self-medication hypothesis, and the green the stimulus-seeking hypothesis. The relapse prevention model is not present in this figure.

Indeed, stress can be a contributing factor in the initiation, development, and even maintenance of SUDs and all those stages can lead to harmful health outcomes (Brady et al., 2006; Brady and Sinha, 2005; Goeders, 2003; Meaney et al., 2002; Sinha, 2008; Laucht et al., 2009; Schwabe et al.,, 2011). Exposure to chronic stress early in life (Carliner et al, 2017; Banducci et al., 2014; Brenhouse et al., 2013; Enoch, 2011; Lovallo, 2013), and the presence of comorbid mental health disorders, such as anxiety and depression (Grant et al., 2004; Burns & Teeson, 2002), all are associated with higher rates of SUDs. Alcohol-dependent individuals can increase alcohol intake in response to stressful situations compared to non-alcoholics (Miller et al., 1974). Prolonged stress exposures enhance the use of nicotine, psychostimulants, and alcohol (Sinha, 2008; Sinha, 2005; Turner &Lloyd, 2003; Lloyd & Turner, 2008). Abstinence from chronic alcohol is related to altered sympathetic and parasympathetic responses (Ingjaldsson, et

al.,2003; Adinoff, 2005; Rechlin, 1996; Sinha et al., 2008). These all demonstrate the significance of the relationship between stress and drug use.

Blunted Reactivity and SUDs

Stress reactivity can potentiate the development of SUDs (Sinha, 2008), but the mechanism underlying this relationship is unclear. Cardiac reactivity and cortisol levels seem to provide evidence for the stimulus-seeking hypothesis and demonstrate hypo-arousal before SUDs develop. In a study conducted with adolescents between the ages of 14 and 20 years old, participants who consumed more than 2 drinks had a lower resting heart rate throughout an entire stress protocol (Evans et al., 2012). Reduced cardiac pre-ejection period reactivity has been associated with increased likelihood of future alcohol use for children (Brenner & Beauchaine, 2011) and children of substance using parents demonstrate hypo-responsiveness of cortisol in response to stress (Mick et al., 2013). Smokers, too, exhibit significantly lower cortisol and heart rate reactions to stress compared to non-smokers (al'Absi, 2003; Ginty et al., 2014). Heart rate variability (HRV), the fluctuations in beat-to-beat intervals in heart rate, is also affected by drugs. In healthy individuals, an increase in HRV is typically seen as a marker of attention, while a decrease in HRV is engendered by physical or intense emotional stressors, since stressors require activation of metabolic resources (Thayer et al., 2012). Individuals with low resting HRV exhibit delayed recovery from psychological stressors of cardiovascular responses compared to those with higher levels of resting HRV, suggesting that individuals with higher resting levels of HRV appear more able to produce context appropriate responses (Weber et al., 2010). A recent review states that acute alcohol reduced resting HRV in healthy subjects, demonstrating an increase in arousal (Ralevski et al, 2019). This finding was also demonstrated in another earlier review looking at resting HRV in chronic drinkers with and without alcohol dependence – people

who regularly consumed low doses of alcohol (1-2 drinks) had higher resting HRV, while people who drank more than 1-2 drinks daily had lower resting HRV (Karpyak et al., 2014). Blood pressure also seems to be blunted in those with a chance of developing a SUD. In a study with high risk drinkers, stress-induced changes in DBP were greater in the absence of alcohol than in the presence of alcohol (Nakajima et al, 2013).

Chronic alcohol misuse alters the HPA axis responses and causes autonomic dysregulation, even during prolonged abstinence periods, which maintains the presence of a SUD for an individual (Lovallo, 2011). When comparing alcohol dependent drinkers with social drinkers, alcohol dependent drinkers had increased systolic blood pressure responses and blunted cortisol responses when exposed to a stressor and alcohol cue (Sinha et al., 2009). Drinkers who relapsed had lower responses than those who did not (Junghanns et al, 2003; Adinoff et al., 2005). Smokers who had attenuated HPA stress responses during the first 24 hours of relapse also had an increased risk of relapse during the next four weeks (al'Absi, 2005). Alcohol patients had significantly higher resting HR compared to social drinkers (Sinha et al., 2009). In fact, increased baseline HR and decreased HR variability has been reported during acute alcohol withdrawal and during alcohol abstinence periods up to four weeks (Ingjaldsson et al, 2003; Bar et al., 2006; Thayer et al., 2006).

There is also considerable evidence that heavy alcohol consumption and misuse dysregulates physiological function, even after alcohol use stops (Piano, 2017; O'Keefe et al., 2007; Lucas et al., 2005; Malyutina et al., 2002; Juonala et al., 2009; Mukamal et al., 2010). Chronic alcohol misuse (e.g., binge drinking, which ia drinking more than 5 standard drinks in a single sitting) is linked with increases in blood pressure and hypertension (Potter et al., 1986; Rosito et al., 1999, Braisoulis et al., 2012), strokes (Ronksley et al., 2011), and heart failure

(Larsson et al., 2015). Thus, discerning the relationship between cardiovascular reactivity and alcohol use is not only crucial for alcohol use disorders, but also for potential cardiovascular disease risk.

Measuring SUDs

Commonly used substance use disorder screening questionnaires include the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), the Alcohol Use Disorders Identification Test (AUDIT), and the DSM-V. Both ASSIST and AUDIT were created by the World Health Organization as brief assessments of alcohol misuse (Babor et al., 2001; Hides et al., 2009). The AUDIT is scored on a scale of 0-40, where scores of >20 would be considered dependent on alcohol and >30 would be severely dependent. The English version of the AUDIT has been proven reliable for identifying alcohol dependence (Saunders et al., 1993; Stockwell et al., 1983). The Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS-V) is an interview designed for trained lay interviewers (Grant et al., 2001), which assesses disorders according to the DSM-V. It is a reliable measure of alcohol use disorders (Hasin et al., 2015).

For college students, a few questionnaires have been developed to test alcohol use disorders. The Student Alcohol Questionnaire (SAQ), initially developed during 1974, is still highly reliable (Engs, 1994). Our study used the College Alcohol Problems Scale (CAPS). The CAPS determines which students are classified as problematic drinkers. The CAPS was initially developed in 1997, using 20 different items to assess alcohol-related problems among undergraduates who had violated their university's alcohol policies (O'Hare, 1997). The CAPS was retested in 2001 by examining the data of 382 introductory psychology students and was found to fit the data poorly; several items had high modification indices (Maddock et al., 2001).

Thus, the CAPS was revised (CAPS-r) and retested with the data of 276 students. The CAPS-r was found to fit well across all measures of model fit and the scale was externally valid (Maddock et al., 2001). This was reconfirmed in 2009 in a study of 3403 first-year students (Talbott et al., 2009). Some limitations of the CAPS-r could lie in the fact that studies conducted on its validity had an overrepresentation of females and white people. However, since our study did have a majority white population and a majority female population, the CAPS-r is a structurally valid and reliable measure.

Habituation and the Current Study

Prolonged stress leads to greater instability of situations and larger stress responses, as homeostasis – the ideal state of the body – is unattainable (Sinha, 2008; Lazarus, 1999; McEwen, 2007; Lovallo, 2011; Meaney et al., 2002). Sometimes, falling out of homeostasis is an adaptive mechanism. In the case of a threatening stimulus, the body must confront the danger and be prepared; arousal is therefore important (Hughes et al., 2018). When stimulating this danger or stress event in the laboratory, however, it is important to recognize the frequency of such events – stressful situations are usually rare and thus do not occur often. Therefore, investigating how the body changes and responds to multiple stress exposures is salient, as it determines whether the body continues to engage in metabolically draining behaviors, or if it adapts to the repeated exposures. The former possibility, where the body keeps or even increases the magnitude of its response, is known as sensitization. If the body does the opposite and decreases the magnitude of its response, it is known as habituation (Eisenstein et al., 2011). While cardiac variables seem to habituate over multiple exposures to stressors, vascular variables seem to sensitize (Carroll et al., 1990).

Studying how habituation and sensitization are affected in the context of alcohol is incredibly salient, as dysregulated stress reactivity could inform the directionality of the relationship between alcohol consumption and stress reactivity. As aforementioned in the "Stress and SUDs" section, there are different models examining stress and the development of SUDs – investigating how cardiovascular reactivity changes over multiple exposures to stressors could provide evidence for a particular model. Does a maladaptive response to multiple exposures of a stressor correlate with problematic alcohol use? Examining habituation and sensitization prior to the development of an AUD could illuminate this relationship. Additionally, studying how CVR changes over multiple exposures in the context of alcohol could help explain the growing body of evidence of J-shaped risk curves. Most studies examining the health effects of alcohol report J-shaped curves, where light to moderate drinkers have less risk than those who do not consume alcohol, and heavy drinkers are at the highest risk for adverse health outcomes (O'Keefe et al., 2007; Lucas et al., 2005). Perhaps examining how the body reacts to multiple stressors could provide another explanation for this phenomenon. One study investigating habituation was conducted in the context of tobacco use – researchers anthropometrically matched 28 smokers and non-smokers and then challenged the participants with a visuo-spatial target-tracking task. The study suggested that smokers had higher DBP than non-smokers and that female non-smokers demonstrated DBP response sensitization (not habituation) to stress (Hughes & Higgins, 2018). Other studies have examined the role of gender in habituation-sensitization (Hughes, 2007; Schmaus et al., 2008), but as to our knowledge, no such study has been conducted for alcohol.

CHAPTER THREE

Materials and Methods

Participants

Data collection for a study examining cardiovascular stress reactivity habituation took place over approximately one year from January 2019 to February 2020 and included 453 healthy volunteers (Mean age (SD) = 19.5 (1.3) years; 60.5% female; 64.1% Caucasian; 17.7% Hispanic). Participants were recruited from Baylor University's introductory to neuroscience and psychology courses and participants were granted 2 SONA research credit hours. The inclusion criteria for participation included no history of epileptic seizures; no immune (e.g., rheumatoid arthritis), cardiovascular (e.g., hypertension), metabolic, and/or kidney disease; no prescribed medication in the last four weeks (excluding birth control and non-steroid asthma treatments); and no previous participation in another stress study conducted in the same laboratory. Out of the eligible participants, 236 were excluded based on abstinence from alcohol in the past year. Preliminary analyses removed two statistical outliers for units of alcohol consumed per week. Thus, a total of 220 participants (Age Range = 18-33; Mean age (SD) = 19.77 (1.59); 60.5% female; 63.7% White; 17.9% Hispanic) remained in the current study's analyses. Consent was obtained from all participants and the protocol was approved by the university's Institutional Review Board.

College Alcohol Problems Scale-revised

The College Alcohol Problems Scale-revised (CAPS-r) was used to assess level of problematic drinking (O'Hare, 1997; Maddock et al., 2001; Talbott et al., 2009). The scale

breaks down problematic drinking into two realms: social and personal problems. An example of a personal problem is “feeling sad, blue, or depressed” as a result of drinking, while a social problem example is “engaging in unplanned sexual activity.” There are a total of 8 items on the scale, with a Likert scale provided as responses ranging from 1 to 6 (1 = “never”, 6 = “10 or more times”). The CAPS-r has been found to be a valid measure of problematic alcohol consumption (Maddock et al., 2001). The questionnaire was administered after completion of the stress procedure and for the current sample, revealed acceptable overall internal consistency (Cronbach’s $\alpha = .77$). The internal consistency for the social subscale was adequate ($\alpha = .69$), while for the personal subscale was good ($\alpha = .82$).

Procedure Prior to the PASAT

Participants completed one laboratory visit, with the protocol lasting approximately 2 hours. Participants attended the laboratory session between the hours of 7 A.M and 9 P.M. Prior to arrival, participants were required to abstain from drinking alcohol for 12 hours, engaging in exercise for 12 hours, and eating and drinking (except water) for 2 hours. Participants were also excluded if they had any current illness or infection.

After participants provided consent, they completed questionnaires assessing baseline affect and anxiety levels. Anthropomorphic measures (e.g., waist, hip, height) were then obtained, which were used to calculate BMI. Participants then had a blood pressure cuff attached to their non-dominant arm. Heart rate (HR), systolic and diastolic blood pressure (SBP and DBP) were measured using a standard brachial artery cuff and a semi-automated sphygmomanometer. Electrocardiogram (EEG) electrodes were placed on the upper body and were used to trace heart rate activity (MindWare Mobile Impedance Cardiograph, Model 50-2303-00).

Once seated in an upright chair with all the equipment, participants entered a ten-minute adaptation period and a ten-minute baseline period. The adaptation period allowed the participants to adjust to the equipment and environment, and research assistants often used this period to answer any questions about the equipment. Next, the baseline period was conducted. The participant was instructed to remain still, have their feet flat on the floor, and to abstain from talking for the duration of the baseline period to ensure more accurate blood pressure measures. Blood pressure (BP) and heart rate (HR) were collected five times (every 120 seconds). Following this baseline period, participants received instructions for an acute psychological stress task known as the Paced Auditory Serial Addition Task (PASAT). Participants were also given a practice version and were allowed the opportunity to ask any questions to the research assistants after receiving instructions.

Participation in the PASAT

During the four-minute version of the PASAT, participants were verbally presented with a series of numbers between one and nine and were asked to add each consecutive number to the number they had just heard (Gronwall,1977). Participants were required to give their responses verbally to the researcher. Although participants were told the numbers were given at fixed intervals apart, the interval between numbers was 2.4s for the first minute of the task and increased by .4s each minute until completion. The PASAT has been shown to elicit a significant cardiovascular response (Mathia et al., 2004; Ring et al., 2002) and demonstrates good test-retest reliability (Ginty et al.,2013). The task also involved elements of social evaluation (Ginty et al.,, 2012a), as participants were informed that they were being videotaped for future assessment of body language by experts. No such videotaping occurred. Participants were also required to look at themselves in a mirror placed .5 m away for the duration of the PASAT and were scored in

real time by a researcher standing about .25 m, who hit a buzzer at standardized intervals. HR and BP were recorded every minute during the duration of the stress task. Once participants had finished, they underwent a 10-minute recovery period before completing the entirety of the stress protocol for a second time.

Calculations of Cardiovascular Stress Reactivity

Baseline cardiovascular activity was operationalized as the average of the five readings for HR, SBP, and DBP during each resting baseline period, and stress cardiovascular activity was the average of the four readings of the same measures taken across the duration of each of the PASATs. Baseline, stress, and CVR values were calculated separately for each stress session. Cardiovascular reactivity was calculated by finding the difference between the respective baseline average and stress average (Stress 1 – Baseline 1 and Stress 2 – Baseline 2).

Covariates

Demographic information such as age, race/ethnicity, sex, and BMI were collected after retrieval of consent and after the stress protocol. Subsequent data analyses controlled for these covariates and the respective initial cardiovascular baseline levels; these variables were selected based on the control processes of previous studies and their relationship with cardiovascular stress reactivity (Ginty et al.,, 2020; Nakajima & al'Absi, 2014; Hughes & Higgins, 2010).

Statistical Analyses

Statistical analyses were performed by using SPPS version 25 (IBM Corp, USA). The study used a two-way repeated-measure analyses of variance (ANOVA) design. Repeated-measure ANOVAs were performed to see if the acute psychological stress tasks indeed perturbed the cardiovascular system (baseline 1, stress 1, baseline 2, stress 2) for each cardiovascular

variable (SBP, DBP, HR) separately. Mauchly (*W*) tests were used to assess sphericity assumptions and Greenhouse-Geisser correction values were reported where these assumptions were violated (Greenhouse & Geisser, 1959). A significant effect indicates that the PASAT significantly perturbed the cardiovascular system. Cardiovascular reactivity was calculated by subtracting the baseline average from the stress average (stress 1 – baseline 1 and stress 2 – baseline 2) for all variables. Pearson's bivariate correlations were run to examine the relationship between reactivity 1 (stress 1 – baseline 1) and reactivity 2 (stress 2 – baseline 2) and the subscale scores of the College Alcohol Problems Scale-r (CAPS-r).

To investigate habituation of reactivity across both stress exposures, a series of separate repeated-measure ANOVAs were performed using the reactivity scores from the 3 variables (SBP, DBP, and HR) – three ANOVAs for two levels for the reactivity 1 and 2. Then, a series of analyses of covariance (ANCOVAs) were performed to examine the associations between each subscale of the CAPS-r with habituation of reactivity (Johnson et al., 2012; Tyra et al., 2020). Reactivity values for each stress exposure were entered as a two-level within-subjects factor, and the CAPS-r scores were entered as covariates. Identical repeated-measures ANCOVAs were then performed which controlled for BMI, sex, race, and ethnicity (Gallagher et al., 2018; Hughes et al., 2011). Statistical significance was defined by a p value of < 0.05.

CHAPTER FOUR

Results

Demographic Information and Elicitation of Stress

Demographic information of the participants is listed in Table 1. Mean phase values for systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) are displayed in Table 2. Repeated-measures ANOVAs examined the mean phase values for SBP, DBP, and HR. These analyses revealed the stress tasks did elicit a significant stress response during the first stress task, as indicated by a significant main effect of phase with a Greenhouse-Geisser correction for SBP, $F(1.95, 419.92) = 517.23$, $p < .001$, partial $\eta^2 = .71$; DBP, $F(1.98,427.47) = 526.52$, $p < .001$, partial $\eta^2 = .71$; and HR, $F(1.68,360.45) = 188.82$; $p < .001$, partial $\eta^2 = .47$. As indicated in Table 2, the cubic function (i.e.increase-decrease-increase) did explain each curve the best (p's <.001).

Table 1. Demographic statistics

Variable	Mean/N	SD/%
Age (years)	19.5	1.3
Gender (% female)	220	60.5%
Race		
Caucasian	141	64.1
Asian	38	17.3
Black or African American	22	10.0
Mixed Race/Other	19	8.6
Ethnicity		
Hispanic	39	17.7
Non-Hispanic	181	82.3
CAPS-r Scores		
Personal	7.06	3.95
Social	5.63	2.70

Table 2. Mean and standard deviations (SD) for cardiovascular measures at each phase

Phase										
	Baseline 1		Stress 1				Stress 2		Cubic Function	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*p*	Partial η^2
SBP (mm Hg)	117.60	11.60	134.37	14.57	117.81	11.51	129.42	13.67	<.001	.781
DBP (mm Hg)	68.38	7.19	81.52	9.21	69.87	7.56	79.41	9.40	<.001	.773
HR (bpm)	74.39	11.61	85.83	14.84	74.26	11.10	80.81	13.07	<.001	.551

Note. SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; mm Hg = millimeters of mercury; bpm = beats per minute.

Cardiovascular Reactivity to Stress Across Each Exposure

Pearson's bivariate correlations examined the relationship between each of the cardiovascular reactivity variables and the subscale scores of the CAPS-r. Results indicated statistically significant positive correlations between all cardiovascular reactivity variables (*p*'s < .01). The correlations also indicated a significant negative correlation between the CAPS-r social subscale and heart rate reactivity during the first exposure to stress (stress 1 – baseline 1). No statistically significant relationship was found between the scores on the CAPS-r and cardiovascular variables during the second exposure. These correlations are listed in Table 3.

Table 3: Correlations between cardiovascular reactivity values and CAPS-r scales

Measure	1	2	3	4	5	6	7	8
1. Δ SBP1	-							
2. Δ DBP1	.624**	-						
3. Δ HR1	.536**	.332**	-					
4. Δ SBP2	.656**	.502**	.426**	-				
5. Δ DBP2	.576**	.679**	.310**	.679**	-			
6. Δ HR2	.406**	.303**	.752**	.416**	.365**	-		
7. CAPS-r Personal	-.106	-.083	-.085	-.079	-.060	-.045	-	
8. CAPS-r Social	.004	.025	-.140*	-.002	.067	-.114	.276**	-

**Correlation is significant at the .01 level (2-tailed).

*Correlation is significant at the .05 level (2-tailed).

Cardiovascular Habituation Across Stress Exposures

Table 4 demonstrates cardiovascular habituation on average across the sample from the first stress exposure to the second, as the mean SBP, DBP, and HR reactivity decreased significantly between the first and second stress exposure.

Table 4. Mean cardiovascular reactivity

	Stress Exposure 1				Stress Exposure 2				F	*p*	Partial η^2
	Mean	SD	Min	Max	Mean	SD	Min	Max			
ΔSBP	16.72	8.80	-1.15	47.30	11.58	8.06	-8.50	37.55	117.81	<.001	.35
ΔDBP	13.13	6.30	-4.30	32.35	9.46	6.76	-12.05	33.55	106.88	<.001	.33
ΔHR	11.41	10.55	-13.20	51.30	6.58	8.20	-14.50	37.55	107.93	<.001	.33

Note. Δ = difference between stress and baseline (i.e. reactivity). SBP = systolic blood pressure.
DBP = diastolic blood pressure; HR = heart rate.

CAPS-r Scores and Habituation of Cardiovascular Stress Reactivity

Habituation was calculated by acquiring the differences between the first and second stress exposure's reactivity values. When conducting repeated-measure ANCOVAs to examine the separate associations of the personal and social CAPS-r subscales with habituation of reactivity, reactivity values were entered as a two-level within-subjects factor and the subscale in question was entered as a covariate. Thus, each cardiovascular reactivity variable had 2 ANCOVAs performed, with each subscale being entered as a covariate. There were 6 ANCOVAs in total. Scores of the CAPS-r personal and social subscales were not significantly related to any of the cardiovascular variables measured (p's > .05).

CHAPTER FIVE

Discussion

Summary

The present study examined the relationship between problematic alcohol use and cardiovascular reactivity to repeated acute psychological stress. Operationalizing problematic alcohol use as higher scores on the College Alcohol Problems Scale-revised (CAPS-r), it was hypothesized that higher problematic alcohol use scores would be correlated with lower heart rate reactivity, but higher diastolic blood pressure during the first stress exposure and lower cardiovascular habituation across both stress exposures. Indeed, there was a negative correlation between heart rate and the CAPS-r social subscale during the first stress exposure. However, no significant effects were found between scores on the CAPS-r subscales and any of the cardiovascular variables measured.

The literature surrounding alcohol use disorders and cardiovascular reactivity to acute stressors has some inconsistencies and focuses on those who already been diagnosed (Chen et al., 2020). Some studies reported no significant difference between participants with alcohol dependency and control participants in heart rate (HR) responses to acute stressors (Bernardy et al., 2003; Bibbey et al., 2015; Junghanns et al., 2003; Romero-Martinez et al., 2019). However, in line with the results of the present study, other word has reported attenuated HR responses to be associated with alcohol misuse (Panknin et al., 2002; Demmel et al., 2000; Fox et al., 2009; Sinha et al., 2009). With respect to blood pressure, Bernardy and colleagues (2003) reported higher diastolic blood pressure (DBP) in alcohol-dependent patients, while other studies did not find any significant differences for DBP, systolic blood pressure (SBP) or mean arterial pressure (MAP; Khan et

al., 2019; Panknin et al., 2002). Some explanations for this evident inconsistency could include what kind of task was used to elicit stress among the participants (social vs. nonsocial) and if participants had recently engaged in alcohol use. If divided into categories based upon the type of stress task, studies with nonsocial stress tasks usually demonstrate that patients with alcohol-dependency tend to show a blunted stress response when compared to health controls (Bernardy et al., 1996; Dai et al., 2007; Errico et al., 1993; Demmel et al., 2000; Fox et al., 2009; Sinha et al., 2009). This difference could indicate that social stressors activate different pathways for physiological stress responses. Another reason for the disparity between responses could be more logistical – perhaps studies which applied social stress paradigms had a more difficult time establishing a consistent procedure than those with a nonsocial stress task. Variability could potentially beget differing stress responses. This discrepancy between social and nonsocial tasks and differences in stress reactivity necessitates future research, but in retrospect, does help explain why no significant relationship was demonstrated between blood pressure and the subscales of the CAPS-r, as the PASAT in the current study had several social aspects (e.g., video recording participants for body language analysis, ensuring a research assistant played a loud and aversive noise whenever the participant made an error on the math task). The negative association between DBP and the social subscale of the CAPS-r is interesting, as acute alcohol use tends to increase blood pressure (Tasnim et al., 2020; Potter et al., 1986; Rosito et al., 1999) and other SUDs have an association with increased diastolic blood pressure (Hughes & Higgins, 2018). Further research is needed to examine this particular relationship.

In regard to a younger, student population, some studies examining stress reactivity and problematic alcohol use found no association between alcohol consumption and cardiovascular stress reactivity (Bibbey et al., 2015; Evans et al., 2012; Wemm et al., 2013). This would suggest that blunted stress reactivity as a biomarker for problematic behaviors and health conditions has even more limits (Carroll et al., 2011; Lovallo, 2011). However, the populations in these studies did not necessarily demonstrate true addiction to alcohol (Bibbey et al., 2015), since students tend to consume more alcohol than their non-student counterparts and after graduation, alcohol consumption decreases (Dawson et al.,

2004; Bewick et al., 2008; Klein, 1994). Therefore, problematic alcohol use could just be a temporary phenomenon and would not reflect or engender blunted cardiovascular reactivity.

These previous studies were limited to one exposure to an acute psychological stressor. To the researcher's awareness, the present study was the first to examine the relationship between problematic alcohol use and adaptation of cardiovascular reactivity across multiple stress exposures in a sample before the development of an alcohol use disorder. The results were nonsignificant for habituation, which still supports the importance of examining reactivity across multiple stress exposures (Hughes et al., 2018). Given the inconsistencies of cardiovascular reactivity to one exposure of a stressor when associated with problematic alcohol use, examining the same situation over multiple exposures could elucidate new information. Indeed, the null results of this study add more evidence to the possibility that blunted stress reactivity could be a marker only for established alcohol use disorders and does not affect temporary behaviors such as problematic consumption during college.

Limitations

The research was not without limitations. First, cross-sectional research, such as this study, prevents the determination of causality and the exploration of directionality. There is also the potential for unmeasured variables to confound the results (Christenfeld et al., 2004; Greenland, 1980). Second, the sample was relatively homogenous – the sample was majority White and female and consisted mainly of undergraduates at the same private university (64.1% White and 60.5% female). The rate of drinking was also not comparable to the national averages; while 48.56% of the sample drank, about 69.5% of people 18 and older reported drinking in the past year in 2019 (SAMHSA, 2019). Future research may be strengthened by conducting studies on other kinds of samples (e.g. at-risk youth, adults with parental history of substance disorders) Third, our physiological measurements only consisted of blood pressure and heart rate reactivity. For a more comprehensive profile of reactivity, it may be useful to include other kinds of measurements (e.g., cardiac output, pre-ejection period).

To summarize, only heart rate was associated with the social subscale of the CAPS-r over the first exposure to an acute psychological stressor and neither subscale of the CAPS-r was associated with adaptation of cardiovascular reactivity over two, identical stress exposures. These results were contrary to expectation, as blunted stress reactivity has been associated with adverse health outcomes, including substance use disorders. On re-examination, however, the transient nature of alcohol consumption during college could mean that the sample used in the study did not engage in such problematic alcohol use which could lead to a future diagnosis. The study seems to demonstrate that blunted stress reactivity and habituation is associated with more serious disorders than potentially temporary problematic consumption of alcohol.

Future Directions

Future research should continue to examine the nature of the relationship and underlying mechanisms between problematic alcohol use and cardiovascular reactivity and habituation. Problematic alcohol use often begins in adolescence and can exacerbated by stress into becoming an AUD (Sinha, 2008; SAMHSA, 2019). Examining the other risk factors involved such as the duration of abstinence from alcohol, gender differences, prevalence of other mental health disorders – such as anxiety or depression – and baseline physiological arousal can clarify how physiological responses to stress among people who could develop AUDs change. The results of the current study also suggest that studying problematic alcohol use before development of an AUD may not be enough to understand the progression of the disorder. Instead, conducting a longitudinal study examining physiological responses in those who problematically drink could elucidate how physiology impacts alcohol use and vice versa. Furthermore, it may be helpful to use multiple assessment methods, such as other self-report questionnaires, diagnostic interviews, archival data, and more. Additionally, inducing stress in other manners may be helpful; the PASAT has subjective stress ratings, which by definition, creates different stress responses. Perhaps combining several kinds of stress tasks into one protocol would create a more comprehensive stress response.

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