ALCOHOL USE AND CARDIOVASCULAR HEALTH

IN COLLEGE STUDENTS

by

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>iv</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>vi</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>vii</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>viii</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>x</td>
</tr>
<tr>
<td>CHAPTER</td>
<td></td>
</tr>
<tr>
<td>I.  INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>II. BACKGROUND INFORMATION</td>
<td>8</td>
</tr>
<tr>
<td>III. HYPOTHESES AND RATIONALE</td>
<td>34</td>
</tr>
<tr>
<td>IV. METHOD</td>
<td>38</td>
</tr>
<tr>
<td>V.  RESULTS</td>
<td>47</td>
</tr>
<tr>
<td>VI. DISCUSSION</td>
<td>57</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>66</td>
</tr>
</tbody>
</table>
## LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Approximate Timeline of Experimental Session in Minutes</td>
<td>45</td>
</tr>
<tr>
<td>2. Demographic Variables</td>
<td>47</td>
</tr>
<tr>
<td>3. Descriptives for Alcohol History Variables by Drinking Group</td>
<td>49</td>
</tr>
<tr>
<td>4. Descriptives for DMQ Scales by Drinking Group</td>
<td>49</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mean Scores on SSAI at Each Point of Administration</td>
<td>50</td>
</tr>
<tr>
<td>2. Comparison of SVB Scores Pre- and Post- Stress by Drinking Group</td>
<td>53</td>
</tr>
<tr>
<td>3. Significant Correlation between Alcohol SVB Change and ‘Most Drinks’</td>
<td>55</td>
</tr>
<tr>
<td>4. No Correlation between Neutral SVB Change and ‘Most Drinks’</td>
<td>56</td>
</tr>
</tbody>
</table>
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB</td>
<td>Attentional Bias</td>
</tr>
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<td>ANS</td>
<td>Autonomic Nervous System</td>
</tr>
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<td>BD</td>
<td>Binge Drinking (group)</td>
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<tr>
<td>DMNX</td>
<td>Dorsal Motor Nucleus (of the Vagus)</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
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<td>FH</td>
<td>Family History of Alcoholism</td>
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<tr>
<td>HF</td>
<td>High Frequency</td>
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<tr>
<td>HPA</td>
<td>Hypothalamus-Pituitary Adrenal (axis)</td>
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<td>HRV</td>
<td>Heart Rate Variability</td>
</tr>
<tr>
<td>IAPS</td>
<td>International Affective Picture System</td>
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<tr>
<td>LF</td>
<td>Low Frequency</td>
</tr>
<tr>
<td>NA</td>
<td>Nucleus Ambiguus</td>
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<td>NB</td>
<td>Non-Binge drinking (group)</td>
</tr>
<tr>
<td>NIAAA</td>
<td>National Institute on Alcohol Abuse and Alcoholism</td>
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<tr>
<td>PASAT</td>
<td>Paced Auditory Serial Addition Test</td>
</tr>
<tr>
<td>QFI</td>
<td>Quantity Frequency Index</td>
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<tr>
<td>RMSSD</td>
<td>Root Mean Square Successive Difference</td>
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<tr>
<td>RSA</td>
<td>Respiratory Sinus Arrhythmia</td>
</tr>
<tr>
<td>SDNN</td>
<td>Standard Deviation of Normal to Normal (beats)</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
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</tr>
<tr>
<td>SVB</td>
<td>Sympathetic Vagal Balance</td>
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<td>VLF</td>
<td>Very Low Frequency</td>
</tr>
</tbody>
</table>
ABSTRACT

Previous studies suggest that distinct cardiovascular profiles in response to stress and alcohol cues may index risk for alcohol dependence. However, the majority of such studies have focused on older, alcohol-dependent adults, often with co-morbid health conditions. For otherwise healthy young social drinkers, the connections between alcohol use and cardiovascular cue-reactivity, as measured by heart rate variability (HRV), are not as well understood. In the current study, 23 binge drinkers (BD) and 13 non-binge drinking controls (NB) participated in a testing session in which HRV was assessed at rest and in response to visual cues (alcohol versus control images) before and after a timed math stressor. BD and NB groups were hypothesized to exhibit differential sympathetic-vagal balance (SVB) at rest, in response to alcohol cues, and in response to alcohol cues following a stressor. Exploratory analyses of alcohol-related variables and change in SVB to alcohol cues were also conducted. It was hypothesized that the BD group would have a significantly higher SVB, signifying increased sympathetic activity, at rest compared to the NB group. It was also expected that the BD group would have a significantly higher SVB in response to alcohol cues (pre-stress), indicative of increased craving for alcohol, compared to both control picture cues (within group) and compared to the NB group’s response to alcohol cues (between groups). Furthermore, an interaction was predicted, such that during the stress- primed cue-reactivity task, the NB group would have an increase in SVB score, with no differences between picture conditions, while the BD group would have a decrease in SVB score to alcohol cues post-stress, but not to
other picture types. Results indicated no significant group differences at rest or during the pre-stress cue-reactivity task. There was a statistically significant interaction post-stress, such that the NB group had a significant increase in SVB post-stress. The BD group did not show this pattern, but rather, exhibited a blunted response to stress. Further, the BD group did not show the hypothesized selective reduction in SVB to alcohol cues post-stress. Exploration of alcohol-related variables revealed that change in SVB to alcohol cues (calculated as post-stress SVB alcohol cue scores minus pre-stress SVB alcohol cue scores) was negatively correlated with the most drinks ever consumed, as well as the social and conformity scales of the Drinking Motives Questionnaire. This suggests that increases in parasympathetic activity to alcohol cues post-stress were related to higher drinking levels and greater endorsement of social and conformity motives, giving further evidence that heavy alcohol use may blunt the stress response in young adults. Overall, the results indicate that the NB group experienced a normal stress response, while the BD group appears to have a blunted stress response. These results are intriguing and warrant further research in a larger and more diverse sample of young adults who engage in binge drinking.
I. INTRODUCTION

In many cultures, including the United States, people tend to drink alcohol to celebrate, to socialize, or to relax. However, the practice of consuming alcohol to cope with life’s stresses can, in some cases, lead to a vicious cycle of stress mismanagement, alcohol consumption, and negative outcomes. In a 2012 national survey, 56.3% of people aged 18 and older reported drinking alcohol in the last month, and among those individuals, approximately 7.2% (about 17 million people) also had a diagnosable alcohol use disorder [National Institute on Alcohol Abuse and Alcoholism (NIAAA), 2014a].

Though drinking is not necessarily a problem, drinking too much, even infrequently, may result in a myriad of unintended consequences. For example, heavy drinking episodes can cause cardio-toxic effects, such as abnormal heart rhythms and though these abnormalities tend to subside after a few days (Wazkiewicz, Szulc, & Zwierz, 2013), the long-term effects of heavy drinking episodes in a non-dependent population are not well characterized.

Indeed, the vast majority of studies on the health consequences of alcohol use have focused on older (male) adults, typically with pre-existing alcohol dependence and/or comorbid health problems. Notably, one well-established finding is that alcohol consumption can impact cardiovascular health (Romanowicz, Schmidt, Bostwick, Mrazek, & Karpyak, 2011; Walker et al., 2013). The relationship between alcohol consumption and cardiovascular health is likened to a J- or U-shaped curve in older adults, whereby moderate drinking (1 drink a day for women and two drinks a day for men; NIAAA, 2014b) appears to be cardio protective, compared to individuals who abstain, or chronic, heavy drinkers (Person, 1996; Karpyak, Romanowicz, Schmidt,
Lewis, & Bostwick, 2014). Chronic, heavy drinkers have an increased risk of developing an array of cardiovascular problems including cardiomyopathy, cardiac arrhythmias, hypertension, and even heart failure (Walker et al., 2013). Though the cardiovascular consequences of chronic heavy drinking have been thoroughly investigated, the impact of periodic heavy drinking on cardiovascular health in a non-dependent population has received little attention in the research literature.

Heavy episodic drinking or ‘binge drinking’ is viewed by many as an acceptable, and even expected, component of the college experience. The NIAAA (2014b) defines binge drinking as a “pattern of drinking that brings blood alcohol concentration (BAC) to 0.08 [grams percent or above]…which typically occurs after 4 drinks for women and 5 drinks for men in about two hours.” In 2014(a), the NIAAA reported that 24.6% of college students aged 18-22 had engaged in binge drinking within the past month. Though little research (see Pletcher et al., 2005) has been done assessing the impact of binge drinking on long-term cardiovascular health in young, and otherwise healthy, adults it is possible to study this relationship through the measurement of heart rate variability.

Heart rate variability (HRV), or the changes in fluctuations of the length of interbeat intervals, is used to measure individual differences in the cardiac response (Karpyak et al., 2014). Though there are disputes concerning the meaning of some HRV indices (which will be discussed in depth later), HRV is regarded as an objective physiological measure of psychological phenomena (e.g. stress) by most researchers (see Acharya, Joseph, Kannathal, Lim, & Suri, 2006; Bernston et al., 1997; Karpyak et al., 2014; Thayer & Lane, 2000). For example, increased HRV has been associated with good
heart health, while decreased HRV has been associated with poor heart health, as well as both psychological and physiological stress-related disorders (Karpyak et al., 2014; Thayer & Lane, 2000). Some researchers have proposed that HRV measures may even be used to index the predisposition to alcohol dependence (Garland, Franken, & Howard, 2012a; Garland, Franken, Sheetz, & Howard, 2012b). This proposition is based on the work of Garland and colleagues (2012a, 2012b), who found that among alcohol dependent adults in recovery, there may be distinct cardiovascular profiles (changes in HRV indices) to stress and alcohol cues (e.g. pictures of alcohol) that predict relapse (Garland et al., 2012a).

Though these experiments will be described in full detail later in this thesis, a brief synopsis now will clarify the importance of these findings in informing the thesis project. In Garland’s studies, the direction of HRV change differed based on type of attentional bias (AB), approach or avoidance, to alcohol pictures (Garland et al., 2012b). Attentional bias is the tendency for salient cues in the immediate environment to preferentially draw and hold one’s attention (Field & Cox, 2008). Thus, an approach alcohol AB indicated that an individual reacted significantly quicker to alcohol cues compared to neutral cues, whereas an avoidance alcohol AB indicated that an individual exhibited no significant differences in reaction times to alcohol cues versus neutral cues (Garland et al., 2012b). The researchers found that approach AB was associated with a significant increase in a HRV measure of parasympathetic activity (indicating less physiological arousal) after being exposed to stress and alcohol cues. In contrast, an avoidance AB was associated with a decrease in parasympathetic activity (indicating more physiological arousal) after being exposed to stress and alcohol cues. These results
suggest that the approach AB group had a blunted stress response, whereas the avoidance AB group had a normal stress response. Furthermore, a related study found that an increase in parasympathetic activity (i.e. reduced physiological arousal) during a similar stress-primed alcohol cue reactivity task significantly predicted onset and timing of relapse in a six month follow up (Garland et al., 2012a). Together, these studies indicate that an approach alcohol AB and a blunted cardiovascular response to stress and alcohol cues may significantly, and independently, predict relapse in an alcohol dependent population, thus it begs the question: can HRV reactivity to stress and alcohol be used in a non-dependent population as a phenotype of risk for alcohol and/or cardiovascular problems?

Though differential attentional strategies were found to result in differential HRV changes to stress and alcohol cues in recovering alcohol-dependent adults (see Garland et al., 2012b), the relationship between alcohol consumption, attentional bias, stress, and HRV in non-dependent adults who drink has yet to be assessed in a similar manner. Understanding how consumption patterns, and other variables (such as drinking motives and family history of alcoholism), influence resting HRV and HRV reactivity to stress and alcohol cues in young, non-dependent adults is necessary to determine whether or not HRV reactivity may be used to index a predisposition for later alcohol and/or cardiovascular problems. Therefore, the goal of this thesis is to assess how alcohol consumption patterns in young, non-dependent adults may impact HRV at rest and HRV in reaction to stress and alcohol cues.

Though the relationship between alcohol consumption, attentional bias, stress, and HRV reactivity have yet to be assessed holistically, several of these variables have been
assessed separately. Studies indicate that for non-dependent adults, the more often one drinks alcohol, the faster one reacts to alcohol cues (as measured by reaction times in a dot probe task), indicating an increased alcohol attentional bias among heavy social drinkers compared to light social drinkers (Field, Mogg, Zetteler, & Bradley, 2004; Townshend & Duka, 2001). Studies have also indicated that subjective craving is correlated to both increased attentional bias to alcohol cues as well as increased consumption in a non-dependent population, suggesting that these variables co-occur (Field et al., 2004; Field, Munafo, & Franken, 2009). Furthermore, stress has been shown to increase subjective alcohol craving in social drinkers and, for social drinkers who score higher on a drinking to cope with stress measure, stress significantly increases attentional bias to alcohol cues (Field & Powell, 2007). Though no studies have examined the effects of heavy drinking on HRV in a non-dependent population, one study found that moderate drinking (versus abstention) resulted in a significantly higher resting HRV for males (but not for females) (Quintana, Guastella, McGregor, Hickie, & Kemp, 2013b). The authors noted that females also had significantly higher resting HRV than males, which may be why there were no statistically significant differences between female moderate drinkers and female abstainers (Quintana et al., 2013b). Nevertheless, this study is consistent with findings that moderate drinking may be cardio-protective (compared to abstention) and provides evidence that drinking may impact cardiovascular health, even in young adults without alcohol-dependence. Overall, these studies show alcohol consumption, attentional bias, craving, stress, and resting HRV may be interrelated. However, specific connections between these variables require further study. Eventually, this research may provide information about how consumption patterns and cardiovascular reactivity to
stress and alcohol cues in young adults may impact later alcohol use and cardiovascular health longitudinally.

Though there seems to be a significant relationship between craving, stress, alcohol consumption, and HRV (at rest and in cue-reactivity tasks), it is complicated by differences in HRV based on age, gender, and other factors (see Quintana, Guastella, McGregor, Hickie, & Kemp, 2013b; Karpyak et al., 2014). Specifically, younger adults have increased resting HRV compared to older adults and females typically have increased resting HRV compared to males (Quintana et al., 2013b). Furthermore, evidence suggests that drinking motives may influence HRV reactivity to alcohol cues (Kuntsche, Knibbe, Gmel, & Engels, 2005). Drinking motives may also play a role in the degree of attentional bias, such that enhancement motives are associated with both frequent alcohol use and greater alcohol attentional bias in a non-dependent population (Colder & O’Conner, 2002).

The question of whether or not HRV reactivity to stress and alcohol cues in young adulthood may be used to index a predisposition to alcohol and/or cardiovascular problems later in life is complicated and it is influenced by many factors. Several gaps in the literature must be filled to address this question. For instance, identifying how heavy episodic drinking may impact cardiovascular health is of particular importance. The purpose of this thesis is to provide clarification on how alcohol consumption patterns in young adults (binge drinkers versus non-binge drinkers in particular) may influence resting HRV and HRV reactivity to alcohol cues and stress.

In the next section of this thesis, the neurophysiological relationships between the autonomic nervous system, the cardiovascular system, and the vagus nerve that connects
these systems will be reviewed. This review is essential so that the reader will understand how alcohol consumption and psychological factors influence the cardiovascular response. This review will be followed by a comprehensive overview of heart rate variability measurements and their meaning in terms of alcohol consumption and psychological factors. Finally, the complex relationships between alcohol consumption, attentional bias, cue-reactivity, and stress will be examined, first separately, then within the context of HRV. This background information will clarify why particular variables and procedures were used in the thesis experiment and help in interpreting the meaning of the results.
II. BACKGROUND INFORMATION

Autonomic Nervous System

The human nervous system consists of two main divisions, the central nervous system, comprised of the brain and spinal cord, and the peripheral nervous system, consisting of all nerves and ganglia outside of the central nervous system (Watson & Breedlove, 2012). The peripheral nervous system is responsible for relaying information from organs and extremities to the brain via sensory nerves and transmitting information from the brain to the body via motor nerves (Watson & Breedlove, 2012). The autonomic nervous system (ANS), a subdivision of the peripheral nervous system, consists of nerves that send signals from the brain to the internal organs, enabling their autonomic function (Watson & Breedlove, 2012). The ANS controls the actions of the glands, regulates the involuntary muscles of the respiratory, circulatory (e.g. cardiovascular), digestive, and urogenital systems, and has a reciprocal effect on internal secretions, including hormone regulation (Watson & Breedlove, 2012). The ANS has two main branches, the sympathetic nervous system and the parasympathetic nervous system.

The sympathetic and parasympathetic systems are typically described in dichotomous terms whereby they act in opposition to each other, thus, ensuring the body responds appropriately to different situations (Watson & Breedlove, 2012). The phrase ‘fight or flight’ characterizes the function of the sympathetic nervous system, which acts to maximize bodily resources when one is presented with stressful or arousing stimuli (Matic, 2014). When physiologically aroused, blood vessels constrict in less critical organs to make more blood available in muscles for exertion, the heart rate increases, and lung airways relax and open to prepare the body to act (Matic, 2014). In contrast, the
parasympathetic nervous system puts the body in ‘rest and digest’ mode to conserve energy (Matic, 2014). The heart rate decreases, airways constrict, saliva and secretion of digestive enzymes increase, and there is some degree of voluntary control over parasympathetic impulses like urination and defecation (Matic, 2014). When functioning properly, the shifting balancing between these signals allows for homeostatic control of internal organs.

However, in situations of prolonged psychological stress, these systems can become dysfunctional (Taylor, 2011). The sympathetic nervous system evolved to help organisms fight or flee from danger, but in modern society, the sympathetic nervous system is often activated by psychological stress, which can continue indefinitely, leading to a cascade of maladaptive physiological effects (Taylor, 2011). The chronic activation of the sympathetic nervous system (and simultaneous reduction of parasympathetic activity) can cause increased heart rate and variations in normal heart rhythms, affecting heart rate variability (HRV; Taylor, 2011). Specifically, stress-related disorders (e.g. anxiety, addiction, and coronary heart disease) are associated with decreased HRV, which is a marker of poor heart health (Karpyak et al., 2014). Thus, neurobehavioral processes, like stress, can be objectively studied by examining the mechanistic interplay of sympathetic and parasympathetic influences on the cardiovascular response. The next two sections of this thesis will provide a description of cardiovascular system activity and an examination of how psychological states influence cardiovascular activity via the vagal nerve. These details are necessary for understanding later descriptions of how HRV measures are calculated and what they mean in terms of sympathetic and parasympathetic activity.
Cardiovascular System

The heart is the ‘pump’ of the cardiovascular system, providing a consistent flow of oxygenated blood to the rest of the body (Berntson, Quigley, & Lozano, 2007). There are three types of cardiac muscles that serve as the electrical conducting system of the heart: atrial, ventricular, and specialized conducting fibers (Berntson et al., 2007). The pumping mechanism of the heart is due to an electrical conduction through the atrial and ventricular chambers that contain muscle cells that permit a rapid spread of depolarization across the heart (Berntson et al., 2007). This extremely fast spread of depolarization from one cardiac muscle cell to the other is crucial to the pumping action of the heart where the atrial and ventricular portions must function as a single pumping unit (Berntson et al., 2007). Depolarization of the sinoatrial and atrioventricular nodes provides the electrical drive that causes contraction of the heart (Berntson et al., 2007). The sinoatrial node is the ‘pacemaker’ of the heart because the speed of depolarization in this node is typically quicker than the atrioventricular node, and thus, generally controls the rate of the heartbeat (Berntson et al., 2007).

The cardiac cycle is what occurs from one beat to the next beat (Berntson et al., 2007). The cycle comprises of two main epochs: diastole (when the heart is full of blood prior to the pumping action) and systole (the heart pump) (Berntson et al., 2007). This cycle can be seen on an electrocardiogram (ECG) recording, which typically has five deflections arbitrarily named (in the order that they occur) P, Q, R, S, and T (Berntson et al., 2007). The cycle starts with depolarization of the sinoatrial node, which corresponds to the P wave one would see in an ECG recording (Berntson et al., 2007). The P wave is shortly followed by atrial contraction (depolarization of the right and left ventricle)
during which the QRS complex occurs (considered together because they occur in rapid succession and reflect a single event) (Berntson et al., 2007). The QRS complex reflects ventricular contraction and demarcates the onset of systole (Berntson et al., 2007). During this ventricular contraction, ventricular pressure is high enough to close the atrioventricular valves (Berntson et al., 2007). Late in the ventricular contraction phase, the ventricles repolarize; this is the T wave seen on ECG (Berntson et al., 2007). After contraction, as pressure changes, the atrioventricular valves open and blood rapidly fills the ventricles (diastole) (Berntson et al., 2007).

The rate of the heartbeat is controlled by both the sympathetic and parasympathetic branches of the ANS, which are heavily interconnected throughout the body (Berntson et al., 2007). The preganglionic fibers of the sympathetic system lie along the spinal vertebrae and a few more remote ganglia (Berntson et al., 2007). The parasympathetic system has a direct connection with the brainstem, specifically the dorsal motor nucleus in the dorsomedial medulla and the nucleus ambiguous in the ventrolateral reticular formation (Berntson et al., 2007). The dorsal motor nucleus (DMNX) and the nucleus ambiguous (NA) are the primary motor fibers of the vagus cranial nerve (Porges, 1995). In the heart, these nuclei terminate on the sinoatrial node (Porges, 1995). Since the sinoatrial node is the ‘pacemaker’ of the heart, psychological phenomena like stress, reflected by the activity of the parasympathetically-mediated vagus nerve, can be readily examined through one’s variability in heart rate (or HRV), which will be described in detail later in this review.
Role of Vagus Nerve

The vagus nerve has a regulatory role in the internal physiological changes related to emotion (Porges, 1995). Neurophysiological regulation of heart rate is primarily via this pathway (the right vagus to the sinoatrial node; Porges, 1995). One dominant theory linking psychological states to physiological changes is Polyvagal theory, which details how changes in emotion will produce changes in vagal tone, i.e. the degree of activity of the parasympathetic nervous system (Porges, 1995). A related theoretical model, the neurovisceral integration model, describes how disorders of affect (e.g. anxiety as well as addiction) are due to dysregulation in emotional and attentional processing and how the severity of this dysregulation is reflected in heart rate variability (Thayer & Lane, 2000). Specifically, because successful affective and attentional processing is characterized by an ability to be flexible and adapt to environmental demands, this model proposes that HRV is an index of the flexibility of related physiological processes (Thayer & Lane, 2009). For example, reduced HRV is associated with poor flexibility while increased HRV is associated with the ability to appropriately respond to environmental demands (Thayer & Lane, 2009). Together, these models provide the theoretical framework for clarifying how HRV may provide information relevant to neural and behavioral inhibition, and social functioning (Quintana, McGregor, Guastella, Malhi, & Kemp, 2013c). For instance, other studies have shown that reduced HRV is linked to dysfunctional vagal activity, which has been associated with impaired social functioning (Ingjaldsson et al., 2003). These theories may also be relevant to physiological differences that have been noted among alcohol dependent individuals. Chronic heavy alcohol use has been associated with problems in shifting attention appropriately,
impaired frontal lobe functioning (important for inhibition and self-control), and reduced HRV (Ingjaldsson, Laberg, & Thayer, 2003).

The complex role of the vagus nerve is explained by three important details. First, several neural pathways originating in many different areas of the brain converge on the vagus (Porges, 1995). Second, there are three branches of the vagus, that evolved in a hierarchical fashion (hence, poly-vagal) and each branch supports different adaptive behavioral strategies (Porges, 1995; Porges, 2007). Third, vagal fibers are both efferent and afferent, resulting in a feedback mechanism between visceral organs (e.g. the heart) and the brainstem (Porges, 1995; Porges, 2007). Further, the term neuroception was coined to describe the unconscious neural processing of the environment for threats and it is through neuroception that autonomic states are regulated (Porges, 2009). The areas of the brain responsible for neuroception include the limbic system (the neural structures involved in emotion and arousal) and parts of the temporal lobe associated with detecting movement and intention, which in turn project to the vagal nuclei to regulate autonomic reactivity (Porges, 2006). Neuroception regulates autonomic states by enabling mammals to engage in social behaviors when the environment is deemed safe by promoting vagal (parasympathetic) dominance (Porges, 2009). Studies have found that individuals with decreased resting HRV (characteristic of those with alcohol dependence, as well as other psychological disorders like anxiety and depression) are less able to engage in accurate neuroception, meaning that they feel threatened when in fact they are not (Karpyak et al., 2014; Thayer & Lane, 2000). How neuroception regulates autonomic activity is explained by the interactions between the two primary medullary nuclei of the vagus.
nerve, the nucleus ambiguus and the dorsal motor nucleus, in relation to the sympathetic-adrenal system.

The dorsal motor nucleus of the vagus (DMNX) is, evolutionarily, the oldest pathway (Porges, 1995). It is unmyelinated, thought to be a function of immobilization behaviors, and plays an important role in the magnitude of neurogenic bradycardia (slowing of the heart) (Porges, 1995). The sympathetic-adrenal system originates in the spinal cord and is responsible for mobilization behaviors (Porges, 2007). The nucleus ambiguus (NA) efferent fibers to the sinoatrial node are the most recent evolutionary pathway and it is via this pathway that neuroception processes control autonomic reactivity to psychological and environmental demands (Porges, 1995; Porges, 2009). The NA pathway is myelinated and largely responsible for respiratory sinus arrhythmia (RSA) (Porges, 1995). RSA is a measure of the naturally occurring variation in HRV that corresponds to the frequency of breathing and is utilized as a measure of vagal activity (Porges, 2007). Furthermore, the NA pathway is linked to the cranial nerves that control facial expression and vocalization (part of the social engagement system in mammals) and, overall, it is thought to play a role in attention, motion, emotion, and communication (Porges, 1995; Porges, 2006). When an organism deems an environment to be safe, as determined via neuroception processes, the myelinated NA pathway actively inhibits the sympathetic-adrenal system’s influence on the heart and dampens hypothalamic-pituitary adrenal (HPA) activity (active in the stress response) (Porges, 2007). Therefore, it is thought that the decreased resting HRV seen in chronic heavy alcohol users may be due to the NA pathway not being able to successfully inhibit the sympathetic-adrenal system’s impact on the heart because of dysfunctional neuroception processes (Thayer,
Hall, Soller, & Fisher, 2006). Or, put another way, chronic heavy drinking may interfere with proper functioning of the vagal nerve.

According to Polyvagal theory, shifts in emotion parallel shifts in respiratory sinus arrhythmia (RSA), such that during a state of negative affect or arousal there will be a withdrawal of vagal tone and decrease in RSA, whereas during a state of positive affect the nucleus ambiguus (NA) efferent fibers would send a signal to increase RSA (Porges, 1995). This occurs because the myelinated NA pathway serves to acts as a vagal brake (see Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996), such that the rapid response to environmental demands (mobilization or restoration) occurs by inhibition or disinhibition of vagal tone on the sinoatrial node of the heart (Porges, 2007). Thus, vagal brake activity can be measured by RSA amplitude which, in the analysis of HRV, is reflected in the power of the high frequency (HF) band (Seyedtabaii, 2009). Findings that heavy drinkers exhibit a decreased HF HRV power at rest compared to moderate drinkers (Karpyak et al., 2014) gives further credence to the idea that the vagal brake is impaired in these individuals, resulting in an inability to appropriately respond to environmental demands, as evidenced by problems in shifting attention (Stormark, Laberg, Nordby, & Hughdahl, 2000).

Because vagal fibers are both efferent and afferent, resulting in both feedback and feedforward loops between the heart and the brain, dysfunction in neural areas involved in affect and/or attention, or dysfunction in autonomic activity, may cause greater impairment to the inhibitory function of the vagal nerve (Porges, 2007; Thayer & Lane, 2000). It is still unclear whether dysfunction in affect and/or attention is the cause of impairment to the vagal nerve, causing autonomic dysfunction, or whether the reverse is
true. Regardless, due to the feedback and feedforward mechanism of the vagal nerve, dysregulation of one of these systems (affect, attention, or autonomic functioning) seems to increase dysregulation in the others (Porges, 2007). There is some evidence that treatments, like biofeedback, which seek to improve autonomic regulation, may improve affective and attentional regulation (Thayer & Lane, 2009). Additionally, as will be described later in this paper (see ‘Literature on HRV, Attention, Craving and Relapse’ section), increased attentional regulation in an alcohol-dependent population is associated with increased autonomic regulation and a significantly reduced likelihood of relapse (Garland et al., 2012a). Presumably, better regulation of affect, attention, or autonomic functioning helps to improve regulation in all of these functions due restoration of the previously impaired inhibitory functioning of the vagal nerve (Porges, 2007).

Overall, Polyvagal theory and the neurovisceral integration model successfully provide the framework for understanding how alcohol dependence is characterized by impaired inhibitory functioning of the vagal nerve. Furthermore, understanding these models, and the role of the vagal nerve, helps to clarify how HRV measures can be used to identify the degree of vagal functioning, and ultimately, how HRV measures may (potentially) be used as a phenotype of risk for later alcohol and/or cardiovascular problems.

**Heart Rate Variability (HRV)**

*Sympathetic and Parasympathetic Influences*

Heart rate variability (HRV) is valuable tool to non-invasively examine the effects of sympathetic and parasympathetic activity on cardiac physiology (Karpyak et al., 2013). HRV analysis measures the variation in RR intervals by utilizing time and
frequency domain metrics (Seyedtabaii, 2009). Multiple studies have confirmed that HRV is a more sensitive biomarker of external and internal demands than heart rate and is reliably associated with severity of stress-related physiological and psychological disorders (Karvay et al., 2013; Thayer & Lane, 2000). Heart rate variability reflects competing neurotransmitter influences (e.g. acetylcholine versus epinephrine and norepinephrine) on the heart as determined by vagal tone.

In healthy individuals, when vagal tone is high (i.e. during a state of calm), parasympathetic mediators work by releasing acetylcholine on sinoatrial and atrioventricular nodes, which slows down conduction at the atrioventricular node, causing decreased heart rate and increased HRV (Karim, Hasan, & Ali, 2011). When aroused or stressed, epinephrine and norepinephrine from sympathetic nerve fibers act on the sinoatrial and atrioventricular nodes of the heart to speed up cardiac contraction, causing vagal withdrawal and decreased HRV (Karim et al., 2011). Research indicates that the heart is typically under tonic inhibitory control by parasympathetic influences, but, when sympathetic activity is high, vagal activity (in the medulla) is inhibited by higher centers in the hypothalamus (Higgins, Vatner, & Braunwald, 1973). This means that when psychologically or physiologically stressed, the inhibitory functioning of the vagal nerve is inhibited, allowing for the sympathetic-adrenal system to exert its influence, resulting in faster heart rate and decreased HRV (Porges, 2007).

Chronic, heavy alcohol use has been associated with alterations in how the sympathetic and parasympathetic systems act on the heart (Karpyak et al., 2014). Studies have shown that acute alcohol consumption causes over-activation of the sympathetic nervous system and chronic, heavy drinkers have significantly reduced resting HRV.
compared to age-matched controls, indicating that heavy drinkers have greater than normal sympathetic activation at rest (when not consuming alcohol; Karpyak et al., 2014). Additionally, studies have found that among alcohol-dependent individuals going through alcohol withdrawal, symptom severity is positively correlated with the amount of released norepinephrine (involved in the sympathetic-adrenal stress response) and corticotropin-releasing factor (involved in the HPA-axis stress response) (Hawley et al., 1994; Linnoila, Mefford, Nutt, & Adinoff, 1987). Though resting HRV does increase in alcohol-dependent individuals after a prolonged period of abstention, HRV is still reduced compared to age matched non-dependent controls, giving evidence that chronic alcohol abuse may cause permanent damage to cardiovascular health by altering the inhibitory functioning of the vagal nerve, allowing for persistent over-activation of the sympathetic nervous system (Karpyak et al., 2014).

HRV Measures

Heart rate variability is measured using time and frequency domain metrics that tease apart spectral bands and use the power of these bands to calculate sympathetic-vagal balance (SVB), which was the measure of HRV used in this thesis project. Because frequency domain analysis incorporate time domain metrics to extract ECG data necessary for calculating SVB, a brief overview of time domain metrics is needed. Time domain metrics are based on normal RR intervals [i.e. the duration between two consecutive peaks (R-waves) seen on an ECG output; Berntson et al., 2007]. From the original RR intervals, the standard deviation of NN intervals (SDNN) and the root mean square successive difference of intervals (RMSSD) can be calculated (Acharya et al., 2006). SDNN is thought to be a mixed measure of P and S activity and correlates to the
low-frequency (LF) range of the HRV spectrum in some studies (Colombo, Arora, DePace, & Vinik, 2014; Otzenberger et al., 1998). RMSSD measures short term variation and is usually applied as a measure of high frequency (HF) heart period variability and RSA in healthy individuals (Wang & Huang, 2012). Though the validity of RMSSD as a substitute measure of HF is debated (Wang & Huang, 2012), many researchers use RMSSD as an estimate of parasympathetically-mediated HRV (Garland et al., 2012b).

Though the SDNN and RMSSD measures may be useful in assessing cardiac system activity (particularly in terms of identifying temporal variations), extraction of frequency bands with frequency domain analysis appears to more efficiently identify the amount of the sympathetic and parasympathetic activity on the heart over smaller time segments (e.g. 5 minutes versus 24 hours; Acharya et al., 2006; Wang & Huang, 2012).

Frequency domain analysis reflects the differential contributions of ANS activity by converting time function into different frequencies, such as the low frequency and high frequency bands, that are generally thought to reflect sympathetic and parasympathetic activity, respectively (Acharya et al., 2006). Frequency domain analysis utilizes fast Fourier transformation for power spectral density to extract frequency bands based on the differential receptor termination rates of sympathetic versus parasympathetic neurotransmitter activity (Acharya et al., 2006; Berntson et al., 1997). When the parasympathetic system is active the vagal nerve releases acetylcholine, acetylcholine then binds to muscarinic receptors on the heart and cause changes in the ionic current (Berntson et al., 1997). This process occurs more quickly when compared to the sympathetic system, which acts through adrenergic receptors with a second messenger activation that leads to a slower change in ionic current (Berntson et al., 1997). For this
reason, parasympathetic activity is thought to be reflected in the power of the high
frequency (HF) band [between 0.15-0.4 Hz (up to 1 Hz)] in HRV analyses (Berntson et
al., 1997). The relatively slower sympathetic activation of the heart is reflected in the
power of the low frequency (LF) band (between 0.06-0.10 Hz) in HRV analyses
(Berntson et al., 1997; Karemaker, 1999; Porges, 2007). Notably, the dependent variable
for this thesis project, sympathetic-vagal balance (SVB), is calculated from the LF/HF
ratio (Berntson et al., 1997). Because SVB is the ratio of the power of the LF band
relative to the power of the HF band, SVB scores greater than 1 indicate that heart rate is
being controlled by sympathetic neurotransmitters, whereas SVB scores less than 1
indicate that the heart rate is being controlled by parasympathetic (vagal)
neurotransmitters.

Some researchers argue that the use of the LF/HF ratio may not accurately reflect
sympathetic-vagal balance (SVB), due to findings that the LF band is also influenced (to
a lesser degree than the HF band) by vagal activity (Reyes del Paso et al., 2013).
However, other researchers have argued that any distortions or misinterpretations due to
the use of the LF band alone may be avoided by using the LF/HF ratio or normalized
units (when assessing sympathetic or vagal activity alone; Pagani et al., 1997; Reyes del
Paso et al., 2013). Nevertheless, it may be more accurate to describe the LF/HF ratio (and
SVB) in terms of vagal efferent activity (Porges, 2007). In fact, though the power in both
the LF and HF bands may simultaneously increase or decrease (because vagal activity
may influence both), researchers typically describe increases in HRV as being
synonymous with increases in parasympathetic activity (e.g. RMSSD, HF HRV, RSA;
Garland et al., 2012a, 2012b), giving further credence to the idea that SVB should be
discussed in terms of vagal activation. Yet, because vagal withdrawal is a result of increased sympathetic activation, changes in SVB accurately reflect the competing actions of the sympa-thetic and parasympathetic systems on the heart (Berntson et al., 1997). Thus, the aim of this thesis project is to examine HRV in terms of the differential contributes of the sympathetic and parasympathetic systems in different drinking groups under various conditions, thus, SVB is that the most appropriate dependent variable for this study.

**HRV in Alcohol-Dependent and Non-Dependent Adults**

In this section, HRV differences in alcohol-dependent and non-dependent adults will be reviewed and discussed in terms of alcohol consumption patterns, age, gender, and family history of alcoholism. As mentioned previously, increased resting HRV (lower LF and higher HF) is associated with good heart health (e.g. fitness and aerobic exercise) and decreased HRV (higher LF and lower HF) is associated with poor heart health (e.g. aging, vulnerability to stress, and a variety of medical and psychiatric disorders; Romanowicz et al., 2011; Karpyak et al., 2014). In general, the relationship between HRV and alcohol use follows a J-shaped curve in older adults, such that consistent, low-dose ‘moderate’ use is associated with increased HRV compared to abstainers and heavier drinkers (Karpyak et al., 2014). Alcohol-dependent adults have reduced HRV compared to age-matched non-dependent controls (Karpyak et al., 2014). Women typical have increased HRV compared to men, after controlling for drinking habits (DePetrillo, White, Liu, Hommer, Goldman, 1999; Quintaina et al., 2013b), and younger people display increased HRV compared to older people (Agelink et al., 2001). Additionally, family history of alcoholism seems to result in a blunted stress response, as
evidenced by greater reductions in cardiovascular reactivity to stress following alcohol consumption (Sinha, Robinson, & O’Malley, 1998). Elaboration on these findings will help to clarify the eventual results of this thesis project.

Studies have consistently found that alcohol dependent adults (15+ years of alcohol abuse) have significantly faster heart rates and significantly reduced HRV compared to age-matched non-dependent adults who drink (Rechlin, Orbes, Weis, & Kaschka, 1996). Importantly, these findings are particularly prominent for power in the HF band (Rechlin, Orbes, Weis, & Kaschka, 1996). This is significant, as other studies have found that power in the HF band can be used to predict craving (Quintana, Guastella, McGregor, Hickie, & Kemp, 2013a) and relapse (Garland et al., 2012a) in alcohol-dependent adults. In general, as alcohol consumption increases beyond the recommended ‘moderate’ use (1 drink for women and 2 drinks for men per day; NIAAA, 2014b), HRV indices of vagal modulation decrease (e.g. decreased HF, RMSSD, and LF/HF ratio; Minami et al., 2002; Thayer et al., 2006). This finding supports the notion that HRV measures are reflecting dysfunctional attentional and emotional regulation due to an impaired inhibitory mechanism by the vagal nerve (Ingjalddsson, Laberg, & Thayer, 2003). Indeed, favorable treatment outcomes in alcohol-dependent adults are associated with increased resting HRV, nevertheless, even after prolonged periods of abstinence resting HRV in dependent adults is reduced in comparison to non-dependent adults (Karpyak et al., 2014). However, the association between favorable treatment outcomes and increased resting HRV supports the idea that restoration of vagal nerve inhibition (as indicated by increased HF HRV and overall increased HRV at rest) is associated with increased attentional regulation (ability to shift attention away from alcohol related cues).
and increased emotional regulation (ability to suppress unwanted thoughts and increased positive affect scores; Garland et al., 2012b; Ingjaldsson et al., 2003). Overall, these studies show that severity of alcohol dependence is linked to HRV measures, as evidenced by differences in HRV based on consumption patterns.

However, the relationship between consumption patterns and resting HRV becomes more complex when gender is considered. In one study with older adults (both alcohol-dependent and non-dependent), an interaction between gender and resting HRV was found, such that there was a main effect for alcohol use (dependent participants had a reduced HRV compared to controls) and a main effect for gender (dependent males had significantly reduced HRV compared to male controls, but dependent females did not significantly differ from female controls; DePetrillo et al., 1999). A study examining the effects of increased average daily alcohol dose (up to 84 grams) found that women, compared to men, had increased resting HRV (Kupari, Virolainen, Koskinen, & Tikkanen, 1993). Yet, when only non-dependent males were examined, moderate consumption was definitively associated with increased HRV and significantly greater RMSSD compared to abstenation (Flanagan et al., 2002) and heavier alcohol use (Minami et al., 2002; Thayer, Hall, Sollers, & Fisher, 2006). These studies provide some evidence that females have higher resting HRV than males and that moderate drinking is indeed cardio-protective compared to abstenation and heavy drinking. Age has also been identified as an important variable in HRV, such that younger people have increased resting HRV compared to older people (Agelink et al., 2001), however, there is a gap in the literature regarding how consumption patterns influence HRV in young adults.
The only published study to assess alcohol consumption and resting HRV in young adults \((M_{\text{age}} = 20)\) supports the notion that moderate, habitual drinking (defined in that study as 1 standard drink 5 days a week) is associated with increased HRV when compared to abstainers (defined in this that as 2 or fewer drinks in the past month) (Quintana et al., 2013b). However, while a main effect was found for alcohol intake (moderate drinkers had significantly higher HF HRV than abstainers), this was revealed to be driven by male moderate drinkers having a significantly higher HF HRV than male abstainers (Quintana et al., 2013b). There was also a statistically significant main effect for gender, such that females had higher HF HRV than males overall but there was no significant difference in HF HRV between female drinking groups (Quintana et al., 2013b). The authors of that study concluded that moderate alcohol intake in young adults may only be cardio-protective for males due to their overall lower HRV (Quintana et al., 2013b). Notably, the non-significant relationship between moderate consumption and increased HRV in young women may be explained by a potential ceiling effect since young people and women have increased HRV compared to older people and men, respectively (Agelink et al., 2001; Quintana et al., 2013b). Unfortunately, Quintana and colleagues (2013b) did not assess the effects of binge drinking, despite its prevalence in young adults (NIAAA, 2014a). In fact, despite documentation of “binging-induced cardiotoxicity,” with effects such as acute abnormal cardiac rhythm (Wazkiewicz et al., 2013, pp. 1261), the literature remains sparse with respect to studies that specifically examined the effects of binge drinking on HRV in non-dependent drinkers after the initial effects of binging-induced cardiotoxicity dissipate. Overall, HRV studies suggest that the cardio-protective effects of moderate drinking are most pronounced in males (regardless
of age) and, to a lesser extent, middle-aged women (up to age 55; Agelink et al., 2001; Karpyak et al., 2014; Quintana et al., 2013b).

Family history of alcoholism may also be an important variable when interpreting HRV measures for a two reasons. One, family history of alcoholism (FH+) is a well-known risk factor for the development of alcoholism (Dawson, Harford, & Grant, 1992; Sinha, Robinson, & O’Malley, 1998). Two, studies have shown that, when compared to those without a family history of alcoholism (FH-), both males (Conrod, Peterson, Pihl, & Mankowski, 1997) and females (Sinha et al., 1998) exhibit a blunted stress response, particularly following acute alcohol consumption. One explanation for this involves the tension reduction hypothesis (Conger, 1956), later elaborated on as the stress dampening response hypothesis (Sinha et al., 1998). This hypothesis states that under stressful conditions, alcohol may reduce the intensity of anxiety-based responses, an assumption supported by numerous studies showing that alcohol reduces the magnitude of physiological response to stressful stimuli (Levenson, Sher, Grossman, Newman, & Newlin, 1980). The drive to reduce anxiety with alcohol may result in a bidirectional relationship between stress and alcohol, such that, alcohol consumption reduces stress and stressful situations motivate alcohol consumption (Sher, Bartholow, & Peuser, 2009). Over time, the stress-response-dampening effect of alcohol causes alterations (via the vagal feedback loop) in neural processes involved in affect and attention, which impact vagal tone and the cardiovascular response to stress (Sorocco, Lovallo, Vincent, & Collins, 2006). Some studies suggest that these alterations may be genetically inherited, such that family history positive (FH+) individuals are predisposed to have a blunted stress response, particularly following alcohol consumption (Sorocco et al., 2006).
Findings that FH+ individuals who experience this stress dampening response are more likely to drink with increased frequency and quantity when stressed, support the notion that alcohol may be differentially reinforcing for FH+ individuals (Sher, 1987; Sinha et al., 1998). Put plainly, FH+ individuals may exhibit a reduced stress responses (regardless of their current alcohol consumption patterns) compared to FH- individuals (Sorocco et al., 2006), meaning that they may experience less sympathetic activation in response to stress. Now that these variables (amount of alcohol consumption, gender, age, and family history of alcoholism) that may influence HRV have been reviewed, an examination of the theoretical models and empirical findings on the psychological phenomena that influence alcohol consumption, and therefore HRV, will follow.

**Cue-reactivity, Attentional Bias, and Stress**

Regular alcohol use and dependence is associated with ‘cue-reactivity’ for alcohol-related stimuli (Field & Cox, 2008). In relation to alcohol use and dependence, cue-reactivity may describe both subjective craving and changes in objective physiological measures, like HRV, in response to stress and alcohol cues (Field & Cox, 2008). Regular alcohol use and dependence is also associated with increased attentional bias towards alcohol cues meaning that individuals who have a strong positive association with alcohol (perhaps due to drinking in response to stress) exhibit enhanced cognitive processing of alcohol-related cues (Field & Cox, 2008). This section of the thesis will explore the theoretical models that may explain the inter-relationships between physiological cue-reactivity, attentional bias, stress, and alcohol consumption.

Overall, theories on the relationship between attentional bias and autonomic reactivity have focused on the motivational properties of salient drug cues. The incentive-
sensitization theory, for example, suggests that repeated administration of an addictive substance produces a dopaminergic response that becomes increasingly larger with each succeeding administration (Robinson & Berridge, 1993). This effect may be even more pronounced when stress precipitates drinking (Garland et al., 2012b). Due to classical conditioning, the salience of alcohol-related cues is increased over time, altering the ways in which those cues are perceived, enhancing craving, and increasing alcohol consumption (Field & Cox, 2008). In other words, alcohol cues acquire incentive-motivational properties over time, such that alcohol cues gain greater attentional processing, prompt craving, and seeking alcohol becomes an increasingly important goal (Field & Cox, 2008). Thus, the cycle of problem drinking may develop.

The theoretical discussion of Field and Cox (2008) were informed by the work of Franken (2003), who proposed that once alcohol acquires incentive-motivational properties, subjective craving and attentional bias become mutually excitatory, that is, one increases the other and vice versa (Field & Cox, 2008). Franken (2003) suggested that dopamine release in response to a conditioned drug stimulus (e.g. alcohol) occurs in areas of the brain associated with both reward (causing craving) and attention (resulting in motor preparation and a hyper-attentive state toward the drug cue). The result is that when alcohol cues become the focus of attention, craving increases, which in turn, increases the “attention grabbing” properties of alcohol cues, and so on, until alcohol is consumed (Field & Cox, 2008, pp. 3). Studies have found that not only does alcohol attentional bias co-occur with subjective cue-reactivity (i.e. craving; Field et al., 2009) it also co-occurs with objective cue-reactivity (i.e. HRV reactivity; Garland et al., 2012b). Though further studies are needed to determine the extent of these relationships, these
results indicate that once a drug cue acquires incentive-motivational properties, attentional bias and cue-reactivity (both subjective craving and objective HRV) do indeed influence each other.

In addition to attentional bias (AB) occurring in conjunction with reactivity toward alcohol related cues, studies have consistently shown that stress also increases appetitive responses by intensifying attentional and autonomic factors (Garland et al., 2012b). This may explain why, under conditions of stress and negative affect, some alcohol-dependent individuals may be motivated to consume alcohol even after extended periods of abstinence (Garland, Boettiger, & Howard, 2011). Though typically, subjective cue-reactivity (craving) and objective cue-reactivity (changes in HRV) co-occur, such that cue-elicited increases in HRV are associated with more craving for addictive substances (Garland et al., 2012b), stress may alter this relationship. For example, a study utilizing a drug cue exposure task (without additional stressors) in a group of methamphetamine users found that low levels of craving were associated with increases in sympathetic activity (supporting the traditional theory of cue-reactivity), but high levels of craving (possibly indicative of greater psychological stress) were associated with an increase in parasympathetic activity in this drug dependent sample (Culbertson et al., 2010). These findings are consistent with results from a study by Garland and colleagues, which examined alcohol attentional bias in alcohol dependent participants. In that study, alcohol dependent participants exhibited an increase in parasympathetic activity to alcohol cues following stress (Garland et al., 2012b). Thus, though alcohol AB typically co-occurs with cue-reactivity (i.e. greater AB = greater
craving = increased sympathetic activity), stress may alter HRV cue-reactivity, such that AB and craving become associated with greater parasympathetic activity instead.

Based on the previously reviewed studies, two possibilities exist for the thesis project. First, because the participants in this thesis project were not alcohol-dependent, it was possible that prior to being stressed, participants who reported heavier alcohol use might exhibit a sympathetically-mediated HRV profile in response to alcohol, which would be similar to the low craving drug users in the study by Culbertson and colleagues (2010). However, after stress, it was possible that stress coupled with the presentation of appetitive stimuli (alcohol images) might results in differential autonomic reactivity (differences in SVB) based on participants’ degree of alcohol attentional bias and intensity of craving. The next section of this thesis elaborates on the studies that have informed these predictions.

**Literature on HRV, Attention, Craving and Relapse**

A study conducted by Garland, Franken, Sheetz, and Howard (2012) examined alcohol attentional biases in association with stress-primed alcohol cue-reactivity (measured by HRV indices) in alcohol dependent patients. Participants ($N = 58$) all met the criteria for lifetime alcohol dependence but had completed at least 18 months of treatment and sobriety at the time of the study (Garland et al., 2012b). A spatial cueing task, in which participants had to identify a target probe, was used to measure alcohol attentional bias. Alcohol attentional bias was evidenced by shorter reaction times when alcohol cues are replaced with neutral cues (Field et al., 2009). Participants completed assessments of stress and craving before and after an affect-modulated cue-reactivity protocol intended to induce stress prior to alcohol cue exposure (Garland et al., 2012b).
Though all participants experienced a significant increase in subjective stress and subjective craving after the task, significant changes in HRV cue-reactivity were not evident until the researchers categorized participants based on attentional differences (Garland et al., 2012b). Specifically, ‘approach’ attentional bias (AB) was associated with longer reaction times when attention was incorrectly cued to a non-target location by an alcohol stimulus and shorter reaction times when attention was cued to a target location by an alcohol stimulus (Garland et al., 2012b). Participants who did not have an attentional bias for alcohol cues were classified as the ‘avoidance’ AB group. Once the AB variable was dichotomized, follow up analyses revealed that the alcohol AB, craving, and baseline RMSSD were significant predictors of RMSDD during cue-exposure, such that significant increases in RMSSD (a measure of parasympathetic activity) was associated with greater alcohol AB and craving (Garland et al., 2012b). Furthermore, alcohol AB and baseline HF HRV were significant predictors of HF HRV during alcohol cue-exposure (Garland et al., 2012b). Thus, higher levels of alcohol attentional bias (approach group) was linked to a significant increase in parasympathetically-mediated HRV measures (RMSSD and HF HRV) during the stress-primed alcohol cue-reactivity task, while the avoidance AB group had a non-significant reduction in HRV during the stress-primed alcohol cue-reactivity task, indicating a sympathetic response (Garland et al., 2012b). These results indicate that those in the approach AB group may have greater dysfunction in neural areas involved in affect and attention, resulting in vagal dysfunction and a blunted stress response compared to the avoidance AB group.

These results are similar to the study conducted by Culbertson and colleagues (2010), which found that high craving was associated with parasympathetically-mediated
response (increased HRV) during a drug-cue condition in methamphetamine users. The parasympathetically-mediated HRV responses seen in the ‘approach’ AB group (Garland et al., 2012b) and the ‘high craving’ group (Culbertson et al., 2010) may indicate the presence of perturbed visceral homeostasis that requires an intense vagal activation in response to appetitive stimuli (Garland et al., 2012b). Put plainly, when stressed and exposed to alcohol cues, internal homeostatic forces prepare the body for acute alcohol consumption by releasing greater amounts of acetylcholine on the heart to counteract the anticipated increase in sympathetic activation caused acute alcohol consumption (Romanowicz et al., 2001). Similarly, it is also possible that these individuals have a blunted stress response due to prolonged drug/alcohol use, as explained by the stress dampening response hypothesis (Sinha et al., 1998). This means that due to the expectation that the drug will reduce stress, exposure to the drug cue actually prompts a parasympathetically-mediated increase in HRV, reflecting a blunted stress response (Conger, 1956). Another possible explanation is that these participants were calmed by the alcohol/drug cues after being stressed (Garland et al., 2012b), an explanation which assumes their stress response is normal (that is, without perturbed visceral homeostasis).

In contrast, the sympathetic response seen in the ‘avoidance’ AB group of Garland and colleagues (2012b) and the ‘low craving’ group of Culbertson and colleagues (2010) may have been due to the anxiety associated with increased craving (for both groups) coupled with the cognitive strain of actively avoiding alcohol cues (particular to the avoidance AB group; Garland et al., 2012b). Also, individuals in the avoidance AB group may be exhibiting greater regulatory attentional and affective functioning, as indicated by being able to shift attention away from the alcohol cues and less craving than the approach AB
group, resulting in improved autonomic functioning, as indicated by their ‘normal’ stress response (i.e. increased sympathetic activity after the stressor; Garland et al., 2012b)

Another study conducted by Garland and colleagues found that alcohol AB and stress-primed alcohol cue-reactivity (measured by HRV) significantly, and independently, predicted the occurrence and timing of relapse by 6-month follow up (2012a). Participants ($N = 47$) were recruited from a 2 year treatment facility and had been in treatment and sober for at least 18 months at the time of the study. Of those 47, nine (19.1%) relapsed in the 6-month period follow-up. Statistical analysis indicate that participants who relapsed had significantly greater HF HRV reactivity to both alcohol cues and to stress cues than participants who did not relapse by the 6-month follow-up (Garland et al., 2012a). While there were no statistically significant differences in alcohol AB between the two groups, examination of descriptive variables indicated that participants who relapsed had a higher mean alcohol AB ($M = 11.40$) than participants who did not relapse ($M = 1.06$). Larger increases in alcohol cue HF HRV reactivity and higher alcohol AB scores were significantly associated with onset and timing of relapse (Garland et al., 2012a). Specifically, participants with greater HF HRV cue-reactivity (compared to baseline) and greater alcohol AB were more likely to relapse and relapse sooner, than those with lower HF HRV reactivity and lower alcohol AB (Garland et al., 2012a). These findings support the idea that gains in regulating attention and a return to a ‘normal’ cardiovascular stress response (i.e. increases in sympathetic activity after being stressed) are associated with greater emotional regulation and a reduced likelihood of relapse.
These studies reveal that while the ‘big picture’ of holistic inter-relationships between alcohol attentional bias, craving, and HRV reactivity to stress and alcohol cues needs further exploration to be fully understood, clear associations do exist between these individual components. Since HRV indices in response to stress and alcohol cues may be useful in predicting relapse among alcohol-dependent adults, it is possible that HRV measures may also be useful in identifying young adults who may later develop alcohol and/or cardiovascular problems. However, before that can be determined, the inter-relationships between alcohol consumption patterns, stress, resting HRV, and HRV cue-reactivity in young, healthy, non-dependent adults need further clarification. This thesis represents a first step toward identifying how these factors may influence one another within a single experiment.
III. HYPOTHESES AND RATIONALE

This study had three aims and one exploratory analysis. The first aim of the current study was to examine baseline resting HRV in healthy young drinkers with different self-reported drinking patterns: one group that reported heavy episodic or “binge” drinking at least once in their life (BD group) and another group of light drinkers and abstainers (NB group). Based on previous studies (Karpyak et al., 2014), it was hypothesized that heavy episodic or “binge” drinkers would have increased sympathetic activity at rest resulting in a faster resting heart rate and decreased resting HRV compared to non-binge drinkers, who were hypothesized to have a high vagal tone at rest resulting in a comparatively higher HRV. Specifically, since SVB scores greater than 1 indicate greater sympathetic activity relative to vagal activity, it was hypothesized that the BD group would have a significantly higher SVB score than the NB group at rest.

The second aim was to compare the BD and NB groups on their HRV responses to visual cues, including alcoholic beverage images, non-alcoholic beverage images, and negative, positive, and neutral images taken from the International Affective Picture System (IAPS), in a (pre-stress) cue-reactivity task. As previously mentioned, evidence suggests that non-dependent heavy, social drinkers exhibit an increased attentional bias for alcohol cues (Field et al., 2004; Townshend & Duke, 2001) as well as increased craving for alcohol when exposed to alcohol cues (Field et al., 2009), which, according to the traditional theory of cue reactivity, will result in greater sympathetic activity (Culbertson et al. 2010). Thus, it was hypothesized that the BD group would have significantly increased sympathetic activation to alcohol cues, due to the belief that this group would have both increased attentional bias to alcohol cues and increased craving.
for alcohol. Compared to heavy, social drinkers, light social drinkers and abstainers do not appear to have an attentional bias for alcohol cues (Townshend & Duka, 2001), thus, the NB group was not expected to experience alcohol AB, craving for alcohol, nor increases in sympathetic activity to alcohol cues.

Specifically, hypothesis 2a stated that the BD group would have significantly larger SVB scores to alcohol cues relative to other cue types (within-group). Hypothesis 2b stated that the BD group would also have significantly larger SVB scores than the NB group to the alcohol cues. Therefore, an interaction of drinking group x image type was hypothesized, such that it was expected that SVB scores to alcohol images would be positively correlated with the participant’s alcohol consumption and the extent of their attentional bias to alcohol cues and craving.

The third aim was to compare the effects of acute mental stress on resting HRV and HRV reactivity to visual cues (alcoholic beverage images, non-alcoholic beverage images, and images from the IAPS) in the two groups. Based on the work of Garland and colleagues (2012a, 2012b) it was expected that the NB group would have a stress response similar to the ‘avoidance’ AB group, such that they would have a normal stress response, as indicated by an increase in sympathetic activity after administration of the stressor. Because this group was not expected to have an increased attentional bias toward alcohol cues, it was expected that the increase in SVB post-stress within this group would not differ between the alcohol cues and the other conditions. In contrast, the BD group was expected to be similar to the ‘approach’ AB group in the studies conducted by Garland and colleagues (2012a, 2012b), such that they would experience a blunted stress response to alcohol cues, as indicated by an increase in parasympathetic
activity after administration of the stressor. Though young, it is thought that greater amounts of alcohol consumption may have already altered vagal nerve functioning such that when prompted by stress and exposed to alcohol cues, their bodies prepare for alcohol consumption. Because acute alcohol consumption increases sympathetic activity on the heart (Romanowicz et al., 2011), it is thought that internal homeostatic forces will prompt the vagal nerve to release greater amounts of acetylcholine to counteract the anticipated effects of acute alcohol consumption.

Specifically, hypothesis 3 stated there would be an interaction of drinking group (BD vs. NB) and image type on pre-/post- stress changes in HRV at rest and in response to visual cues. Since psychological stress should activate the sympathetic nervous system (Taylor, 2011), it was expected that during the post-stress resting baseline condition, all participants would have sympathetically-mediated HRV, as reflected in SVB scores greater than one. However, because it was expected that the BD group would have a sympathetically-mediated SVB score during the pre-stress baseline condition, the difference in SVB scores pre-stress baseline to post-stress baseline were not expected to increase significantly for this group. The NB group was expected to have a significant increase in SVB during all post-stress conditions with no differences between picture types, while the BD group was expected to have a significantly reduced SVB score to alcohol cues, but not at rest or to other picture types.

Lastly, because there evidence that variables such as gender (Quintana et al., 2013b), family history of alcoholism (Sinha et al., 1998), and drinking motives (Colder & O’Conner, 2002) may differentially impact cardiovascular reactivity to stress and alcohol an exploratory analysis utilizing survey data and cardiovascular cue-reactivity data was
conducted. No particular hypotheses were made in regard to these exploratory analysis. Nevertheless, evidence that cardiovascular reactivity to alcohol cues may be correlated with consumption behaviors and relapse in alcohol-dependent individuals (Garland et al., 2012a) led to speculation that the change in SVB to alcohol cues from pre and post stress may be correlated to one or more of the alcohol related variables. If a relationship between stress-primed alcohol-cue SVB scores is found to be correlated with alcohol-related behaviors, it may signify a need to further explore that relationship. Thus, a variable was created to assess if any relationship between cardiovascular reactivity and self-report variables existed. This variable was calculated by subtracting pre-stress alcohol condition SVB scores from the post-stress alcohol condition SVB scores. If the variable was positive, it indicated that participant had an increase in SVB to alcohol cues post-stress (less vagal activity, more sympathetic activity) compared to the pre-stress alcohol condition, which would indicate a normal stress response. If the variable was negative, it indicated that the participant had a decrease in SVB to alcohol cues post-stress (more vagal activity, less sympathetic activity) compared to the pre-stress alcohol condition, which would indicate a blunted stress response. This variable was then correlated to alcohol use variables and drinking motives scales. Additionally, a control variable, the change in SVB to neutral affect pictures, was created to ensure that any significant correlations found for the change in alcohol SVB were actually assessing relationships between reactivity to alcohol cues and alcohol related variables and not a result of changes in state anxiety.
IV. METHOD

Participants

A total of 36 participants (30 females; $M_{age} = 20.2$) completed the study. Sample characteristics are included in Table 2 in the Results section. Some participants were recruited through the Human Participants Pool in the Department of Psychology at Texas State University and received course credit for their participation. Other participants were recruited via flyers, in-class announcements and word-of-mouth. Participants recruited through this method received $10/hour for their participation. Recruitment procedures and project methods were approved by the Texas State University Institutional Review Board.

Exclusionary criteria included any serious medical conditions (e.g. diabetes, any cardiovascular disease or irregularities- including heart murmurs or high blood pressure), current co-morbid psychiatric disorders and/or a history of clinical treatment for alcoholism or other substance dependence. In addition, participants were excluded for habitual use of tobacco or tobacco products or marijuana (defined as using more than 2 days per week), and prescription of stimulants (e.g. Ritalin) or depressants (e.g. Valium). Participants were required to be between the ages of 18-26 and to abstain from alcohol, tobacco, marijuana and cold medicines 24 hours prior to participation.

As previously mentioned, participants were divided into two groups based on self-reported drinking habits as assessed by questionnaire. The groups were classified as (1) participants who have reported binge drinking at least once in their lifetime, i.e. Binge Drinkers (BD) and (2) moderate social drinkers with no history of binge drinking and non-drinkers, i.e. Non-Bingers (NB).
Instruments & Measures

Questionnaire

Upon arrival to the laboratory, participants completed an online questionnaire powered by SurveyMonkey on a computer provided by the Psychology Department. Questions addressed demographics, alcohol consumption history [e.g. most drinks ever consumed in one drinking episode and alcohol consumption patterns in the last 6 months broken down by alcohol type (liquor, wine, and beer)], family history of drug and alcohol use, drinking motives, and perceived stress.

Alcohol use in the previous six month period was assessed using the quantity/frequency index (QFI; Cahalan et al., 1969), which has been shown to have test-retest reliability in addition to content, criterion, and construct validity (Sobell & Sobell, 1995). The QFI was calculated for wine, beer, and liquor separately, then added together for a total QFI score. Each QFI score was calculated by asking participants to estimate how often they drank each type of alcohol in the last 6 months. Each possible forced choice answer (i.e. every day, 5-6 days/week, 3-4 days/week, 1-2 days/week, 3 times per month or less, or none at all) was assigned a jessor weight and each type of alcohol was assigned code based on the alcohol content. Participants were then asked to estimate how many drinks they consumed during a typical drinking episode, which was then multiplied by the jessor weight and alcohol code. For example, if a participant reported drinking a six pack (72 ounces) of Budlight (beer code = .04) 3-4 days a week (jessor weight = .50), then the Beer QFI would be calculated by multiplying 72 x .04 x .50. Wine and liquor scores were calculated similarly (with different alcohol ‘codes’) and each score was added to calculate Total QFI.
Binge drinking patterns [defined by the NIAAA (2014b) as 4 or more alcoholic drinks for women and 5 or more alcoholic drinks for men in approximately 2 hours] over the last six months were evaluated using methods developed by Cranford, McCabe and Boyd (2006). This method involved defining binge drinking, then asking participants to self-report if they had engaged in binge drinking in the last 6 months, and if so, how often (open answer). However, since this study categorized participants based on whether they had engaged in binge drinking at least once in their life, two variables, (1) ‘most drinks ever consumed in one episode’ and the follow-up (2) ‘how many hours that episode lasted’ were examined to make sure participants were correctly grouped based on the NIAAA (2014b) definition of binge drinking. For example, even if a female participant did not report binge drinking in the last six months, but reported consuming 10 drinks during one episode that lasted 4 hours, she was placed in the BD group.

Family history of alcoholism was measured quantitatively using the pedigree method of Mann and colleagues (1985). Family history of alcoholism was a dichotomous variable such that if a participants reported they had at least one first degree relative (i.e. parents or siblings = 1) or at least two second degree relatives (i.e. aunts, uncles, grandparents = 0.5) with a history of alcoholism, that participant was classified as having a positive family history or alcoholism (FH+). If the family history of alcoholism score was less than one (i.e. if there was no family history or if only one grandparent was reported to have had an alcohol dependence) then the participant was classified as having a negative family history of alcoholism (FH-). Several studies have used similar criteria for categorizing FH+ versus FH- individuals (see Conrod et al. 1997, Sinha et al., 1998).
The Drinking Motives Questionnaire (DMQ) assessed the degree to which social, coping, enhancement, and conformity motives encouraged drinking behaviors (Cooper, 1994). Studies indicate that the DMQ is a reliable and valid instrument across cultures to assess drinking motives (Kuntsche, Stewart, & Cooper, 2008). Participants were asked to rate on a 5 point scale how likely they were to drink based on each of the statements, with a score of 5 indicating that they would always drink for that reason. None of the items were reversed so each scale was calculated by adding together the scores from each statement that related to that scale. The different DMQ scales have even been linked to alcohol consumption patterns. Specifically, social motives are associated to moderate drinking, enhancement movies are associated with heavy drinking, and coping motives are associated with alcohol related problems (Kuntsche et al., 2005).

The Perceived Stress Scale (PSS), a well validated and reliable instrument, was used to assess stress within the last month (Cohen, Kamarck, & Mermelstein, 1983). This scale asked participants to rate how often (in the last month) each statement described how they felt on a 5-point scale (with 5 being very often). Some items (i.e. the ‘positive items’) had to be reversed so that higher scores indicated greater perceived stress. Measurement of stress perception prior to the experimental conditions was necessary to assess whether or not there were statistically significant differences in stress between the drinking groups. This was important to assess because studies indicate that higher perceived stress is inversely related to the HF component of HRV at rest in healthy individuals, indicating that stress may reduce vagal tone (Dishman et al., 2000).

The Spielberger State-Trait Anxiety Inventory – State Version (SSAI) was used to assess state anxiety at three time points (Spielberger, 1983). Questions on the state-
Anxiety scale measured the participants’ level of anxiety “right now at this moment” and higher scores indicated greater levels of anxiety. The first SSAI was completed immediately following the 5-minute baseline HRV data collection, prior to the cue-reactivity task and acute math stressor (PASAT). The second SSAI was completed immediately following the math acute stressor (PASAT). The third SSAI was completed after the second picture viewing. This instrument served as a manipulation check to ensure that the PASAT was sufficient as an acute stressor.

*Acute Stressor (PASAT)*

A computerized version of the Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977) was used to induce acute psychological stress. In this task, numbers were sequentially presented through speakers in an otherwise quiet environment. Participants verbally reported the sum of the last two numbers they heard. For example, if the first two numbers were 2 and 7, the participant would say 9; if the next number was 5, the participant would say 12. Four blocks of numbers were presented, and the inter-number interval was decreased with each successive block (3, 2, 1.5 and 1 seconds, respectively). The PASAT has been shown to increase anxiety (Ceballos, Guiliano, Wicha, & Graham, 2012) and heart rate, as well as, induce changes in skin conductance reflecting a stress response (Lejuez, Kahler, & Brown, 2003).

*Cue-Reactivity Task*

Participants completed an alcohol cue-reactivity task. The cue-reactivity task was based on the work of Garland and colleagues (2012b) and involved passive viewing of five conditions of 30 pictures each. Each picture was presented at a rate of one every 10 seconds for a total of 5 minutes. Pictures included alcoholic beverages, control pictures
(non-alcoholic beverage pictures), and IAPS images with negative, positive, and neutral valences. Though encouraged to remain motionless during the task, participants were allowed to move or speak as needed during rest breaks in between conditions. HRV was measured during the task, which was administered once before the PASAT (stressor) and again after the stressor. All five conditions were presented both before and after the acute stressor and counterbalanced within and between participants.

**HRV Measurements**

Heart rate variability was measured at rest (before and after stressor) and during the each picture condition (before and after stressor). A Biopac MP150 data acquisition system (Biopac Systems, Goleta, CA) was used to collect HRV data. Ag/Ag Cl electrodes (8mm) were placed on the participants’ right arm, left arm, and left leg. Participants were seated in a comfortable chair and continued breathing normally, as they were not given any instructions to modify their breath. To obtain a baseline resting HRV and post-stress resting HRV, participants were asked to “not think about anything in particular” and remain as motionless as possible for a period of 5 minutes. For the picture cue-reactivity portion (pre- and post-stress) participants were asked to pay attention to the photographs and remain motionless and silent. HRV was not measured during the PASAT.

HRV data were analyzed using AcqKnowledge software (Version 4.3.1, BioPac Systems, Goleta, CA) for detection of R-R intervals from the raw ECG data at a sampling rate of 200 samples/second and frequency band extraction. Prior to HRV analysis, data were bandpass filtered with a high pass of 1Hz and a low pass of 35Hz with 8,000 coefficients. Next, artifact removal and data analysis were conducted in accordance with
AcqKnowledge software manual guidelines (specifically, *Application Note 233*, n.d.). Artifact removal was conducted to remove ‘noise’ associated with movements, yawns, sneezes, etc. using a ‘normal’ QRS complex for that participant and experimental session as a template for correlation in the AcqKnowledge software artifact reduction routine. Finally, HRV analysis was performed to obtain a SVB score. In order to extract HRV frequency bands needed to calculate SVB, the software computed power spectral density using Welch’s method. In this method, time-sampled waveforms are frequency-transformed by portioning data in smaller segments, transforming each segment, then averaging the results over all segments to create a composite frequency-space waveform. To determine sympathetic-vagal balance, the ratio of the power of the low frequency band (.04 to .15 Hz) to power of the high frequency band (.15 to .40 Hz) was calculated. Thus, SVB values higher than 1 reflect greater sympathetic activity, relative to vagal activity, while SVB values lower than 1 indicate a higher vagal tone.

**Experimental Procedure**

Each experimental session lasted approximately two hours. See Table 1 for an approximate timeline of the experimental session. Upon arrival to the laboratory, the experimenter reviewed the exclusion criteria and provided participants with an overview of procedures and expectations. Participants read and signed a consent form. Next, participants were assigned a participant number to be used for identification on the surveys and to help ensure confidentiality. Participants completed the questionnaire (see above section for details). Then, ECG electrodes were applied.

HRV measures were obtained at rest (5 minutes), during each condition of the cue-reactivity task (i.e. the five picture conditions before and after the stressor), and again
after the administration of the stressor (5 minutes). Participants also took a state anxiety survey after the baseline HRV measure, immediately following the PASAT, and after the second presentation of pictures. After the second picture viewing and third state anxiety survey, participants were thanked and debriefed.

Table 1

**Approximate Timeline of Experimental Session in Minutes**

<table>
<thead>
<tr>
<th>Time Frame</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:00 - 0:30</td>
<td>Consent, Overview, and Survey</td>
</tr>
<tr>
<td>0:30 - 0:40</td>
<td>Baseline HRV and SSAI$_1$</td>
</tr>
<tr>
<td>0:40 - 1:05</td>
<td>Pre-Stress Cue-Reactivity Task</td>
</tr>
<tr>
<td>1:05 - 1:20</td>
<td>PASAT (Stressor) and SSAI$_2$</td>
</tr>
<tr>
<td>1:20 – 2:00</td>
<td>Post-Stress Cue-Reactivity Task</td>
</tr>
</tbody>
</table>

**Data Analyses**

Categorical variables (gender, family history of alcoholism, and ethnicity variables) were analyzed using Chi-Square. Continuous variables (age, typical number of drinks consumed, most number of drinks consumed, DMQ scales, perceived stress score, and state anxiety scores) were analyzed via independent samples t-tests comparing NB and BD groups. A manipulation check of the PASAT was assessed using a Repeated Measures ANOVA with time of SSAI assessment as the within-subjects factor; post-hoc pairwise comparisons were used to identify the location of significant differences in anxiety throughout the assessment session. Hypothesis 1 was addressed with an independent samples t-test, with resting baseline SVB as the dependent variable and the drinking groups as the independent variable. Hypothesis 2 was tested with an omnibus repeated measures ANOVA, with drinking group (BD versus NB) as the between-subjects variable, the five picture cue types as the within-subjects variable, and SVB score as the dependent variable. Hypothesis 3 was also tested with an omnibus repeated
measures ANOVA, such that drinking groups were the between subject variable and both time (two levels: pre-stress and post-stress) and condition (six levels: resting SVB and SVB for each picture type) were the within-subject variables. The exploratory analysis was completed using a series of bivariate correlations between variables of interests, such as the created variable ‘change in SVB to alcohol cues’ and participant reported variables like the ‘most drinks ever consumed’ and the scales of the DMQ.
V. RESULTS

Background Characteristics

The final sample consisted of 36 participants (30 females) with a mean age of 20.2 (range = 18 to 24 years). Approximately 42% of participants identified as having Hispanic heritage. Thirteen of the 36 participants were classified as non-bingers (NB) due to never having met the criteria for binge drinking, while the remaining 23 participants were classified as binge drinkers (BD). An independent samples t-test confirmed that the groups did not differ on age \[ t(34) = -0.86, p = .40 \]. Statistical analysis (two-sided Fisher’s exact test) indicated that the drinking groups did not significantly differ on gender \( (p = .40, \text{Fisher’s exact test}) \). A Chi-square analysis found no statistically significant differences in the drinking groups on ethnicity (Hispanic versus Non-Hispanic) \[ \chi^2 (1) = 1.2, p = .30 \] or race (Caucasian versus Non-Caucasian) \[ \chi^2 (1) = 3.30, p = .07 \]. Groups did not differ significantly on family history of alcoholism (FH+ versus FH-) \[ \chi^2 (1) = 1.70, p = .20 \]. For a breakdown these variables by drinking group consult table 2. The mean and standard deviation is reported for the age variable, while the other variables are reported as percentages.

Table 2

Demographic Variables

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NB group ( (n = 13) )</th>
<th>BD group ( (n = 23) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>19.9 (1.5)</td>
<td>20.4 (1.8)</td>
</tr>
<tr>
<td>% Males</td>
<td>7.7</td>
<td>21.7</td>
</tr>
<tr>
<td>% Hispanic</td>
<td>53.8</td>
<td>34.8</td>
</tr>
<tr>
<td>% Caucasian</td>
<td>38.5</td>
<td>69.6</td>
</tr>
<tr>
<td>% FH+</td>
<td>38.5</td>
<td>60.9</td>
</tr>
</tbody>
</table>
A series of independent samples t-tests comparing the two drinking groups on variables related to participant’s alcohol history indicated that the groups did not significantly differ on age of first alcoholic drink \( [t(33) = 1.60, p = .12] \), age of first drunken episode \( [t(27) = -0.60, p = .96] \), nor the age at which they started drinking regularly \( [t(27) = 0.60, p = .53] \). As might be expected, statistical analysis revealed that the groups did significantly differ on the variables ‘typical number of drinks per drinking episode’ \( [t(34) = -4.20, p < .001] \), ‘most drinks ever consumed in one drinking episode’ \( [t(31) = -5.90, p < .01] \), and ‘total QFI score’ \( [t(30) = -2.90, p < .01] \). In addition to these variables, the DMQ scales were analyzed to determine if the drinking groups significantly differed on any of the subscales. The groups were significantly different on the DMQ social scale score \( [t(34) = -3.90, p < .001] \), the DMQ enhance subscale score \( [t(34) = -3.50, p < .001] \), and the DMQ total score \( [t(34) = -3.10, p < .001] \). An examination of the means revealed that the BD group had significantly higher scores on these scales compared to the NB group. This result is consistent with other research findings that the DMQ social scale and the DMQ enhancement scale are positive correlated to increased alcohol consumption (Kuntsche et al., 2005). For a breakdown of alcohol history variables by group, see table 3. For a breakdown of scores on the DMQ, see table 4.
Table 3

Descriptives for Alcohol History Variables by Drinking Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NB group (n = 13)</th>
<th>BD group (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td>Age of First Drink</td>
<td>16.1 (3.8)</td>
<td>14.2 (3.1)</td>
</tr>
<tr>
<td>Age of First Drunken Episode</td>
<td>17.0 (2.6)</td>
<td>17.0 (1.7)</td>
</tr>
<tr>
<td>Age of Regular Consumption</td>
<td>16.5 (6.9)</td>
<td>17.9 (4.4)</td>
</tr>
<tr>
<td>Typical # of Drinks/Episode*</td>
<td>1.5 (1.6)</td>
<td>4.3 (2.1)</td>
</tr>
<tr>
<td>Most Drinks Ever (in Episode)*</td>
<td>2.3 (2.3)</td>
<td>10.1 (5.0)</td>
</tr>
<tr>
<td>Total QFI*</td>
<td>0.09 (0.16)</td>
<td>0.41 (0.10)</td>
</tr>
</tbody>
</table>

* p < .01, two-tailed.

Table 4

Descriptives for DMQ Scales by Drinking Group

<table>
<thead>
<tr>
<th>Scale</th>
<th>NB group (n = 13)</th>
<th>BD group (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M (SD)</td>
<td>M (SD)</td>
<td></td>
</tr>
<tr>
<td>DMQ Scales</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social Motives *</td>
<td>11.5 (6.8)</td>
<td>19.0 (4.8)</td>
</tr>
<tr>
<td>Coping Motives</td>
<td>8.9 (5.1)</td>
<td>9.8 (5.7)</td>
</tr>
<tr>
<td>Enhancement Motives *</td>
<td>8.8 (4.6)</td>
<td>15.3 (5.8)</td>
</tr>
<tr>
<td>Conforming Motives</td>
<td>7.7 (4.8)</td>
<td>9.1 (4.9)</td>
</tr>
<tr>
<td>DMQ Total Score</td>
<td>36.8 (17.6)</td>
<td>53.2 (13.4)</td>
</tr>
</tbody>
</table>

* p < .01, two-tailed.

Analysis (an independent samples t-test) of the perceived stress scores indicated that the groups were not significantly different on this scale \[t(34) = .50, p = .60\].

Additionally, a repeated measures with pairwise comparison analysis confirmed that the groups score on the SSAI at each time point was not significantly different \[F(2,68) = 2.80, p = .07\]. These results indicate that differences in HRV cannot be attributed to differences in perceived psychological stress or state anxiety between the groups.
Manipulation Check

A repeated measures analysis confirmed that the PASAT was effective as an acute psychological stressor \([F(2,70) = 65.70, p < .001]\). Results indicated that from the first SSAI (SSAI1; immediately following the baseline resting period) to the second SSAI (SSAI2; immediately following the PASAT) subjective anxiety significantly increased \((p < .001)\). The mean of SSAI score was 29.1 \((SD = 7.7)\) at Time 1 and 47.9 \((SD = 12.0)\) at Time 2. From SSAI2 to the third SSAI (SSAI3; immediately following the second picture cue task) there was a significant decrease in subjective anxiety \((p < .001)\). The mean score at SSAI3 was 32.3 \((SD = 8.4)\). Notably, there was not a statistically significant difference between SSAI1 and SSAI3 scores \((p = .10)\). These results indicate anxiety nearly doubled as a result of the math stressor and subsequently declined during post-stress picture viewing task. See figure 1 for the mean SSAI scores at each time point (groups combined).

Figure 1. Mean Scores on SSAI at Each Point of Administration

Note: Error bars indicate Standard Deviation. \(*p < .001, two-tailed.\)
HRV Data

Hypothesis 1 stated that the BD group would have a significantly higher resting SVB at baseline compared to the NB group. An independent samples t-test indicated that there was not a statistically significant difference in baseline SVB scores between the two groups \( t(34) = -1.30, p = .21 \). Examination of the mean baseline SVB scores revealed that the NB group had a vagal dominant response at baseline (SVB = 0.76), while the BD group had a sympathetic dominant response at baseline (SVB = 1.34).

Hypothesis 2a stated that the BD group would have a significantly higher SVB score for alcohol cues compared to other picture types, while hypothesis 2b proposed that the BD group would have a significantly higher SVB score than the NB group to alcohol cues. To test hypothesis 2a, a condition was set so that only the BD group was analyzed then an omnibus repeated measures ANOVA with the averaged SVB scores for each picture type (five levels) as the within-subjects variables was conducted. The analysis indicated no significant differences by picture type \( F(4,19) = .71, p = .60 \). A descriptive analysis of the BD group’s SVB score for each picture condition was also conducted and revealed the following means and standard deviations: alcoholic beverage cues \( M = 1.4, SD = 1.0 \), non-alcoholic beverage cues \( M = 1.2, SD = 1.2 \), neutral affect cues \( M = 1.3, SD = 1.0 \), negative affect cues \( M = 1.1, SD = 1.1 \), and positive affect cues \( M = 1.3, SD = 0.9 \). Hypothesis 2b was tested with an omnibus repeated measures ANOVA with picture cue type (five levels) as the within-subjects variables and drinking groups as the between subjects variable. This analysis revealed that there was not a statistically significant interaction for picture type x drinking group \( F(4,31) = 1.50, p = .21 \).

However, examination of the means revealed that the NB group had a vagal dominant
response to alcohol cues ($M = 0.86$) but a sympathetic dominant (SVB score > 1) response to all other picture types.

Hypothesis 3 predicted that there would be a significant time x condition x drinking group interaction, such that the BD group would have a significantly reduced SVB score to alcohol cues after administration of the PASAT, but a non-significant change for all of the other conditions. Also, it was expected that the NB group would have a non-significant increase in SVB, due to the stressor across, all time 2 conditions (post-stress rest plus all picture cue types). Hypothesis 3 was tested with an omnibus Repeated Measures ANOVA with time (two levels: pre- and post- stress) and condition (six levels: rest and each of the five picture types) as the within-subjects variables and drinking groups as the between subjects variable. Results indicated that there was no main effect for time [$F(1,34) = 3.18, p = .08$] nor condition [$F(5,30) = 1.16, p = .33$]. There was also no significant interaction effect for time x condition x drinking group [$F(5,30) = 1.93, p = .09$] or condition x drinking group [$F(5,30) = 0.45, p = .82$]. However, there was a statistically significant interaction effect for time x drinking group [$F(1,34) = 9.48, p < .01$].

In order to examine what was driving this interaction, a follow-up analyses was conducted by separating the drinking groups and conducting another repeated measures ANOVA with the same within-subjects variables. Results indicated that the NB group had a significant change in SVB pre- to post- stress, indicated by a significant main effect for time [$F(1,12) = 4.80, p < .05$]. Specifically, the NB group had a significant increase in sympathetic activity post-stress, represented by a significant increase in SVB (indicating a normal stress response). The BD group did not have a significant main effect for time
$[F(1,22) = 2.34, p = .14]$. In fact, examination of the mean SVB scores revealed that the BD group had a non-significant reduction in sympathetic activity post stress (indicating a blunted stress response). See figure 2 for a representation of the change in SVB scores from pre- to post- stress compared by drinking groups. The black bars in figure 2 represent the SVB score mean for all the pre-stress conditions and the striped bars represent the SVB score mean for all the post-stress conditions. Standard deviations are represented by the errors bars and noted in parenthesis next to the means.

**Figure 2. Comparison of SVB scores Pre- and Post- Stress by Drinking Group**

Note: Error bars indicate Standard Deviation; *$p < .05$

**Exploratory Analysis**

The exploratory analysis involved a series of bivariate correlations to compare several variables of interest. The main variable of interest was the ‘change in SVB to alcohol cues’ score (calculated as post-stress SVB alcohol cue scores minus pre-stress
SVB alcohol cue scores). Other factors of interest were variables related to alcohol history, such as ‘most drinks ever consumed in one episode’ and ‘total QFI,’ as well as scores from the DMQ. To ensure that any significant correlations found between ‘change in SVB to alcohol cues’ and other variables was specific to HRV reactivity to alcohol cues, another variable ‘change in SVB to neutral cues’ (calculated as post-stress SVB neutral cue scores minus pre-stress SVB neutral cue scores) was created as a control variable.

A bivariate correlation analysis revealed that the ‘change in SVB to alcohol cues’ was significantly correlated to the ‘most drinks ever consumed in one episode’ variable \[r(33) = -.38, p = .03\], the DMQ social scale \[r(34) = -.38, p = .02\], the DMQ conformity scale \[r(34) = -4.32, p = .01\], the DMQ total scale \[r(34) = -.39, p = .02\], and the perceived stress scale \[r(34) = -.35, p = .04\]. Notably, only 35 participants (instead of 36) had a numerical answer for the variable ‘most drinks ever consumed in one episode’. Those data were collected as an open-answer response, and one participant was able to answer “I don't know. I have blacked out before.” This participant was coded as having missing data. None of these variables were significantly correlated to the ‘change in SVB to neutral cues’ variable. Next, the drinking groups were split and the bivariate correlation analysis was repeated with the same variables to determine if the groups were different. For the NB group, the ‘change in SVB to alcohol cues’ variable was still significantly correlated to the ‘most drinks ever consumed in one episode’ variable \[r(11) = -.60, p = .03\] but not to any other variable. For the BD group, the ‘change in SVB to alcohol cues’ variable was still significantly correlated to the DMQ conformity scale \[r(21) = -.47, p = .02\], but not to any other variable. It was notable that Total QFI was
significantly correlated to the DMQ enhance scale \[ r(34) = .47, p < .01 \] since enhancement motives have been correlated to heavy drinking patterns (Kuntsche et al., 2005). Also notable was the finding that none of the variables tested in the exploratory analysis significantly correlated to any of the SVB scores for the individual conditions. To see a graphical representation of the relationship between the variable ‘most drinks ever consumed in one episode’ and change in SVB to alcohol cues see figure 3. To see a graphical representation of the relationship between the variable ‘most drinks ever consumed in one episode’ and change in SVB to neutral cues see figure 4.

Figure 3. *Significant Correlation between Alcohol SVB Change and ‘Most Drinks’*

Note: Gray diamonds represent NB participants. White circles represent BD participants.
Figure 4. No Correlation between Neutral SVB Change and ‘Most Drinks’

Note: Gray diamonds represent NB participants. White circles represent BD participants.
V. DISCUSSION

Previous research suggests that HRV may be a useful predictor of the predisposition for alcohol dependence in young adults (Garland et al., 2012a, 2012b). However, before this notion can be tested, several gaps in the literature must be addressed. This thesis represents a first step toward filling some of those gaps. First, though there is evidence that compared to abstention moderate drinking may be cardio-protective for young adult males (but perhaps less so for females; Quintana et al., 2013b), the literature remains sparse with regard to the potential cardiovascular impact of binge drinking in young and otherwise healthy adults. To address this issue, assessment of resting HRV in young adult binge drinkers versus and non-binge drinkers was the first aim of this study. Second, though a relationship between alcohol consumption patterns and HRV reactivity to alcohol cues may exist for young adult social drinkers, to date, this potential relationship has not been a major focus of research. Thus, the second aim of this study was to determine whether or not young adult binge drinkers might exhibit alcohol cue-reactivity as indexed via HRV and whether the binge drinkers’ HRV cue-reactivity might differ compared to aged matched non-binge drinkers. The third aim of the study was to assess potential drinking group differences in HRV cue-reactivity to alcohol images before and after stress. This aim was informed by previous studies which have noted the presence of alcohol attentional bias in heavy social drinkers (but not light social drinkers; Townshend & Duka, 2001), and other work in which attentional bias to alcohol images has been linked post-stress HRV differences for drinkers with an approach orientation toward alcohol cues (Garland et al., 2012a, 2012b). The third aim of this study was designed to examine these issues in an otherwise healthy sample of young adults.
categorized as binge or non-binge drinkers. Lastly, an exploratory analysis was conducted to examine potential correlations between the dependent variables of interest (HRV cue-reactivity before and after stress) and variables such as personal drinking style and alcohol use motives.

For aim 1, though examination of the mean SVB scores indicated that the BD group had sympathetic-dominant resting HRV and the NB group had a vagal-dominant resting HRV, statistical analysis indicated that the group differences were not statistically significant. This may be explained, in part, by the lack of male participants in the study. Research has indicated that there may be a potential ceiling effect for HRV for young females since young adults exhibit increased resting HRV compared to older adults (Agelink et al., 2001) and females exhibit increased resting HRV compared to males (Karpyak et al., 2014; Quintana et al., 2013). Thus, young females may not have statistically significant differences in resting HRV based on consumption patterns. However, another possible reason that the group differences did not reach statistical significance may be the division of drinking groups. The decision to dichotomize the independent variable, instead of dividing participants into more well defined drinking groups (i.e. abstainers, moderate drinkers, and heavy drinkers) was due to an explicit focus on the effects of binge drinking on cardiovascular health in young adults. However, it is worth noting that participants in this study did not fit neatly into well-defined drinking groups. Examination of the raw data revealed that the majority of the college drinkers in this study reported typically consuming alcohol within the range of ‘moderate drinking’ (i.e. 1 drink/day for women and 2 drinks/day for men or ≤ 7 drinks/week for women and ≤ 14 drinks/week for men; NIAAA, 2014b), with occasional bouts of heavier drinking.
drinking, making it difficult to categorize these participants. Furthermore, both the NB group and BD groups included participants who fit NIAAA criteria for moderate drinking. Since moderate drinking may increase resting HRV (Karpyak et al., 2014; Quintana et al., 2013b), including moderate drinkers in both binge and non-binge categories may have increased the similarity of the two groups and diluted potential group differences in heart rate variability. Thus, though no differences were found in resting HRV between drinking groups in this study, more research needs to be conducted assessing the relationship between resting HRV and alcohol consumption patterns in young adults before definitive conclusions can be made. In particular, strategies for future studies might include more stringent grouping criteria (for instance, frequent rather than lifetime occurrence of binge drinking) or might examine alcohol consumption level as a continuous variable, including participants with drinking styles along a continuum from abstainers to heavy drinkers.

For hypothesis 2, statistical analysis indicated that the BD group did not have a significantly higher SVB score to alcohol cues relative to other cue types, nor was the BD group’s SVB score to alcohol cues significantly different from the NB group’s SVB response to the same alcohol images. The expectation that the BD group would have a significant increase in sympathetic activity to alcohol cues was based on previous research (Culbertson et al., 2010). Specifically, studies examining young non-dependent adults have found that heavy social drinkers (compared to light social drinkers) tend to exhibit an alcohol attentional bias (AB) when exposed to alcohol cues (Field et al., 2004; Townshend & Duke, 2001). This alcohol attentional bias has been found to co-occur with increased craving (Field et al., 2009). Because the traditional theory of cue-reactivity
suggests that craving is associated with increases in sympathetic activity (Culbertson et al., 2010; Sinha, 2009), it was expected that the BD group would experience craving when exposed to alcohol cues, which would be reflected in a significant and selective increase in sympathetic activity to alcohol cues. As the NB group was composed of lighter drinkers, this group was not expected to exhibit an alcohol attentional bias or significant increases in alcohol craving when exposed to alcohol cues (Field et al., 2009; Townshend & Duka, 2001). Thus, unlike the BD group, the NB group was not necessarily expected to have a selective increase in sympathetic activity in response to alcohol cues. However, because this study did not assess subjective craving directly, and did not include a behavioral measure of attentional bias, the lack of significant group differences and the failure of HRV responses to differentiate between image types may be due, in part, to similar levels of craving and/or AB in the two drinking groups. Additionally, since few participants in the study reported typical heavy drinking [defined by the NIAAA (2014b) as 5 drinking episodes in the last 30 in which more than 5 drinks were consumed per episode], it is possible that the alcohol cues presented were not salient enough to change craving, attentional bias or HRV in the BD group that was included in this study. Additional studies are needed to address these issues. Future research should include measures of alcohol craving, as well as behavioral indices of attentional bias, in addition to measures of HRV.

Hypothesis 3 predicted a significant time x condition x drinking group interaction, such that the BD group would have a reduced SVB score specific to alcohol cues post stress while the NB group would have an indiscriminate increase in SVB score to all conditions post-stress (compared to pre-stress scores). This hypothesis was partially
supported by the results. Though there was not a significant time x condition x drinking group interaction, there was a significant time x drinking group interaction. This interaction was driven by the significant post-stress increase in SVB across conditions and pictures types for the NB group. This result indicates that the participants in the NB group had a normal stress response as indicated by an overall increase in sympathetic activity following stress. In contrast, the BD group had a non-significant overall reduction in SVB after administration of the stressor. This finding indicates that the BD group had a blunted stress response. Because the groups did not significantly differ on the presence of a positive family history of alcoholism, which has been associated with a predisposition for a blunted stress response (as explained by the stress dampening response hypothesis; Sinha et al., 1998), this finding cannot be attributed to genetic differences.

It is tempting to parallel these findings with the results of the study conducted by Garland and colleagues (2012b). Though the BD group’s reduction in SVB post-stress was not statistically significant, nor specific to alcohol cues, this result indicates that, like participants in the approach AB group from Garland et al. 2012b, participants in the BD group may have experienced slight over-compensation of the vagal brake in response to stress (though not to the same extent as the approach AB group). Specifically, it is possible that, for participants in the BD group, the acute psychological stress induced by the PASAT stressor caused internal homeostatic forces to signal the vagal nerve to release greater amounts of acetylcholine to counteract the anticipated effects of increased sympathetic activation. However, over-compensation of the vagal brake among the approach AB group in Garland et al. 2012b was believed to occur because stress-primed
alcohol cue exposure prompted an internalized expectation that alcohol would be consumed. Because there were no significant differences between picture cues in the thesis project, it is unlikely that the BD group’s blunted stress response was due to anticipation of alcohol consumption. However, it is notable that examination of the SVB means indicated that the BD group had the largest (but non-significant) reduction in SVB post-stress to alcohol cues (from $M = 1.43$ to $M = 1.23$). Though this study did not directly measure alcohol attentional bias, it is reasonable to assume that participants who reported drinking more frequently (that is, the BD group) would be expected to have an alcohol attentional bias. This is because studies have shown that enhancement drinking motives are correlated to both frequent alcohol use and greater alcohol attentional bias in a non-dependent population (Colder & O’Connor, 2002). In fact, the results of the thesis study indicate that total quantity/frequency index of alcohol use was significantly and positively correlated with enhancement motives for drinking alcohol. Thus, it is possible that the differential stress reactions between the groups may be partially due to differences in attentional bias for alcohol cues. However, it is also possible that the blunted stress response seen in the BD group was due to the stress-response-dampening effect of alcohol (Sorocco et al., 2006). The higher consumption patterns in the BD group may have already caused alterations in vagal tone and the cardiovascular response to stress (Sorocco et al., 2006), despite their young age.

Exploratory analysis of the whole sample yielded some interesting findings. Particularly noteworthy was the finding that the variable ‘change in SVB to alcohol cues’ was negatively correlated with the ‘most drinks ever consumed in one episode’ variable. This finding indicates that higher values on the ‘most drinks ever consumed in one
episode’ variable were associated with increases in vagal activity to alcohol cues after administration of the stressor. This may indicate that individuals who drink more are more likely to experience a vagally-mediated response to appetitive stimuli (i.e. alcohol) post-stress, much like the approach AB group in the study conducted by Garland and colleagues (2012b), in which participants had a vagally-mediated response to alcohol cues post-stress. This finding, coupled with the finding that the BD group experienced a blunted stress response, suggests that HRV reactivity to stress and alcohol cues in young adults may have utility as a predictor of the predisposition to alcohol and/or cardiovascular problems later in life (as suggested by Garland and colleagues, 2012a, 2012b). The ‘change in SVB to alcohol cues’ variable was also negatively correlated to the social and conformity drinking motives scales as well as the total DMQ score. One possible explanation may be that the same participants who reported consuming higher values on the ‘most drinks ever consumed in one episode’ variable were also more likely to be motivated to drink for social reasons. The perceived stress scale was also negatively correlated with the ‘change in SVB to alcohol cues’ variable, suggesting that overall levels of stress over the previous month (that is, chronic stress rather than acute laboratory stressors) may be associated with a blunted stress response. The NB and BD groups did not significant differ on the perceived stress scale and this correlation was only true for the group as a whole and it was specific to change in SVB to alcohol cues. The literature suggests that individuals who experience greater levels of overall stress (such as individuals with post-traumatic stress disorder) exhibit a blunted stress response to acute stressors (Thompson et al., 2015), which may partially explain this relationship. Furthermore, because blunted stress reactivity has been associated with both addiction
(Lovallo, Dickensheets, Myers, Thomas, & Nixon, 2000) and negative health outcomes in general (Phillips, Ginty, & Hughes, 2013), additional study on the relationship between higher perceived stress levels and a blunted stress response to alcohol cues may contribute to the ‘big picture’ of holistic inter-relationships between stress, cardiovascular reactivity, and alcohol consumption.

Though the results of this study are intriguing, there were several limitations that remain to be addressed in future research. As mentioned previously, examination of gender differences was not statistically feasible due to the small number of male participants in this study. Due to evidence that gender differences in cardiovascular reactivity exist (Agelink et al., 2001; Quintana et al., 2013b), future studies should aim to have an equal number of male and female participants. The division of drinking groups may have also been problematic. Since moderate drinkers were dispersed between both groups, and moderating drinking is associated with increased HRV, this may have diluted potential group differences in resting HRV. Additionally, there were no overt measures of alcohol attentional bias or subjective craving. Because alcohol AB is thought to play a particularly important role in mediating cue-reactivity, and because craving is suspected to co-occur with AB, future studies examining differences in HRV should also include these measures. The last main limitation was the small sample size ($N = 36$) which resulted in low power and a reduced chance of finding significant differences in the event that they exist.

Other limitations included task-related fatigue. Because each cue-reactivity task required approximately 30 minutes and participants were required to sit still, several participants became drowsy over time. Thus, participants who were fatigued may have
not been paying as much attention to the cues as others who were more alert.

Furthermore, certain factors known to influence HRV such as, time of day (Massin, Maeys, Withofs, Ravet & Gerard, 2000), menstrual cycle (Brar, Singh, & Kumar, 2015), and exercise (Pober, Braun, & Freedson, 2004) were not assessed. Future studies should consider the potential influence of these factors on study results.

Despite these limitations, the thesis study revealed blunted HRV stress responses in the BD group as compared to the NB group, as well as significant correlations between parasympathetically-mediated alcohol cue-reactivity and drinking behaviors and motives. Taken together, these results suggest that HRV reactivity may be a promising method for detecting blunted or parasympathetically-mediated stress and alcohol cue responses in otherwise healthy social drinkers. This is an important result because these factors have previously been discussed as predictors of the predisposition for alcohol use disorders (Garland et al., 2012a, 2012b). Ultimately, this line of research could inform treatment and prevention efforts for problem drinking, particularly among those who may consume alcohol to relieve stress.
REFERENCES


