FRONTOLIMBIC CIRCUITS, DOPAMINE AND ATTENTIONAL BIAS TO ALCOHOL CUES

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ABSTRACT

Monica Lynn Faulkner: Frontolimbic Circuits, Dopamine, and Attentional Bias to Alcohol Cues.
(Under direction of Charlotte Boettiger)

The excess allocation of attention toward addiction-related stimuli has been widely reported across a wide variety of addictions, including alcohol use disorders (AUDs). This phenomenon is defined as addiction attentional bias (AB) and is thought to reflect Pavlovian conditioning processes associated with the repeated pairing of sensory stimuli with the rewarding properties of reinforcing substances. AB to alcohol related stimuli has been reported in alcohol addicted and heavy social drinking populations. The presence of addiction AB is of clinical importance as it has been reported to correlate with drug craving, addiction severity, and treatment outcomes. A more recent study found that another form of AB, generalized reward (non-drug related), AB was also heightened in addicted individuals. In a population of substance abuse users (SUDs) generalized AB reflected an increase allocation of attention to a monetary reward.

This phenomenon of generalized reward AB is true for healthy young adults with no SUD history. The presence of heightened addiction and generalized AB in addicted and healthy populations may suggest individual differences in susceptibility to reward conditioning. Preclinical models of addiction have reported marked individual differences in the responses to reward conditioned stimuli and that a tendency toward greater sensitivity to reward conditioning is a risk factor for addiction. However, these individual differences have not been greatly explored in humans, and not been investigated in at-risk social drinking populations. Moreover, very few studies to date have investigated the neural mechanisms of addiction and generalized reward AB.

Thus the overall goal of this dissertation was to characterize alcohol and generalized reward attentional bias in a social drinking sample and the neural mechanisms that contributes to the expression of these behavioral phenomena. Specifically, we investigated two distinct forms of alcohol AB in heavy, binge and moderate social drinkers and assessed the role of current and past binge drinking behavior on alcohol AB. To probe the underlying mechanisms of alcohol AB, we assessed sensitivity to reward conditioning, a process that may potentially underlie AB and investigated the role of adolescent binge alcohol exposure on sensitivity to reward conditioning.

To further explore the neural mechanisms of AB, we probed the role of dopamine (DA) in alcohol AB and reward conditioning. Using a phenylalanine/ tyrosine (P/T) depleted amino acid (AA) beverage to pharmacologically manipulate DA levels, we assessed changes in AB and functional connectivity of the frontolimbic network, a key network for reward conditioning in heavy, binge and moderate social drinking males. Our investigations of AB revealed a significant difference in alcohol AB on one of our tasks, but with moderate drinkers showing greater AB than our hypothesized heavy, binge drinkers. Current and adolescent binge drinking measures negatively correlated with alcohol AB on this task as well. We also found that alcohol AB was inversely related to the magnitude of AB toward a reward-conditioned cue in a reward conditioning task. Furthermore, in a subset of female participants, we detected a significant relationship between frequency of adolescence binge drinking and reward conditioning. Specifically, a greater frequency of binge drinking before age 18 predicted significantly greater expression of reward conditioning, independent of current binge alcohol use. Finally, our investigations of the role of DA and the frontolimbic network revealed that frequency of binge drinking prior to age 18 negatively correlated with changes in alcohol AB after dopamine depletion. Current and past binge drinking significantly predicted changes in alcohol AB but only in heavy drinkers. Furthermore, current binge drinking was directly related to alcohol AB while adolescent binge drinking was inversely related. Our neuroimaging analysis revealed a significant relationship between the change in functional connectivity and alcohol AB. Specifically, increased AB was positively correlated with increased functional connectivity of the VTA and executive region of the Striatum and the VTA and DLPFC. Taken

together, these studies contribute to our understanding of alcohol related attentional bias, generalized reward conditioning and the role of dopamine and frontolimbic neurocircuitry in these behavioral phenomenon and emphasis the importance of investigating individual differences to AB and reward conditioning in humans.

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LIST OF ABBREVIATIONS

AUD	Alcohol Use Disorder
AUDIT	Alcohol Use and Disorders Inventory Test
AB	Attentional Bias
ACC	Accuracy
ANOVA	Analysis of variance
AnCC	Anterior Cingulate Cortex
AA	Amino Acid
AUQ	Alcohol Use Questionnaire
BDS	Binge Drinking Score
BIS-II	Barrett Impulsivity Scale
BOLD	Blood Oxygenation Level Dependent
CAUPQ	Carolina Alcohol Use Patterns Questionnaire
CR	Conditioned Responses
DASS	Depression Anxiety Stress Scales
DMQ-R	Coopers Drinking Motivations Scale-Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-IV
DLPFC	Dorsolateral Prefrontal Cortex
DUSI-I	Drug Use Screening Inventory-Domain I
FIC	Fronto-Insular Cortex
fMRI	functional magnetic resonance
FTQ	Family Tree Questionnaire
HD	Heavy Binge Drinkers
IFG	Inferior frontal gyrus
IFGop	Inferior Frontal Gyrus, pars opercularis
IES	Inverse efficiency scores

ISI	Interstimulus Interval
ITI	Inter-trial-Interval
LCD	Liquid-Crystal Display
ms	Milliseconds
mOFC	Medial Orbitofrontal Cortex
MD	Moderate Social Drinkers
NIAAA	National Institute on Alcohol Abuse and Alcoholism
OFC	Orbitofrontal Cortex
NaC	Nucleus Accumbens
PET	Positron emission tomography
PCC	Posterior Cingulate Gyrus
SOA	Stimulus Onset Asynchrony
SUDs	Substance Use Disorders
P/T	Phenylalanine/ Tyrosine
RF	Radio Frequency
ROI	Regions of Interest
rs-fcMRI	Resting State Functional Connectivity
RT	Reaction Time
RSVP	Rapid Serial Visual Presentation
VTA	Ventral tegmental area
TMS	Transcranial Magnetic Stimulation

CHAPTER 1:

General Introduction

Public Health and Alcohol

Alcohol is one of the most widely used drugs in the world. While alcohol is used in many aspects of society and culture, such as social gatherings and religious ceremonies, it is also one of the most commonly abused substances globally. Alcohol abuse and misuse in the United States has increased between the years of 2002 and 2013 by 11 percent (Grant et al. 2017). Approximately 6.2% of individuals over the age of 18 in the US have an alcohol use disorder (AUD), and 24.2% of heavy alcohol drinkers report active drinking, with heavy drinking episodes occurring within the last 30 days (NIAAA, 2017). AUDs are defined as a persistent and often chronic need or desire to drink alcohol despite increasingly negative consequences (American Psychiatric Association, 2013). AUDs and hazardous drinking pose a particular threat to individuals and public health as they are the third leading lifestyle cause of death in the US (Mokdad et al. 2004; 2005).

Several life threatening diseases and conditions have been linked to AUDs and hazardous drinking. Incidences of several chronic and terminal diseases increase with rates of alcohol consumption and AUDs. Risk and incidence of liver disease, heart disease, breast cancer and arthritis all increases with the diagnosis of an AUD (Bruha et al. 2012; McDonald et al. 2013; Udo et al. 2015). Moreover, in 2010 the US spent approximately 249 billion dollars on AUDs and hazardous drinking, as a result of loss of productivity, healthcare costs, criminal prosecution, and treatment (Sacks et al. 2015). Embedded within the overall problem of hazardous alcohol use is a specific pattern of high quantity, rapid alcohol consumption defined as binge drinking. The National Institute of Alcohol and Alcoholism define binge drinking as five of more drinks in a two hour period for males and four or more drinks in a two hour

period for women. Ninety percent of all heavy drinkers in the US report having engaged in binge drinking in the last 30 days, and while most heavy drinkers engage in binge drinking, binge drinkers often do not meet criteria for or self-identify as having an AUD or drinking problem (Esser et al. 2014). However, binge drinking is of particular concern because three quarters of the 249 billion dollar costs of alcohol abuse, is attributed to binge drinking (Sacks et al. 2015). This suggests that the major public health concern regarding alcohol use centers on the phenomena of binge drinking.

Researchers and clinicians alike have spent considerable time researching ways to better understand and ultimately treat AUDs and hazardous drinking behavior, such as binge drinking. However, despite over forty years of research much progress remains to be made in the successful treatment of AUDs. The prevalence rate of AUDs in the United States in 2015 was approximately 6.2% with only 3 FDA approved medications for the treatment of AUDs (Winslow et al. 2016). In contrast, disorders such as schizophrenia which has a much lower prevalence rate (1.1%), and currently has 15 new medications in the clinical trial phase for treating this significantly less prevalent disorder (Regier et al. 1993). This discrepancy in treatment options and high rates of prevalence and significant health consequences represents an important gap in our understanding and ultimately our ability to treat AUDs. From the neural mechanisms to behavior after treatment, there has been significant research on AUDs and the resulting changes to ones neurobiology and behavior but far less research has been focused on binge drinking behavior. Taking into account that most heavy alcohol drinkers frequently engage in binge drinking (Esser et al. 2014), binge drinking is associated with many of the same increases in health problems as AUDs (World Health Organization, 2014), and that this pattern of drinking behavior is highly prevalent in populations particularly vulnerable to the effects of excessive drinking (SAMSHA, 2017) better understanding the neurobiological and cognitive consequences of binge drinking is one way to reduce our gap in knowledge of AUDs and treatments.

There has been much research on the cognitive changes that accompany AUDs, however it remains unclear to what extent these same changes occur in social binge drinking populations (Fadardi and Cox 2006; Jones et al. 2006; Sharma et al. 2001; Tiffany 1990). To decrease the gap of knowledge in this area

of hazardous drinking behavior we can investigate cognitive behaviors and processes that appear altered as a result of binge drinking and AUDs. One widely reported cognitive change involves visual attention and reactivity to reward related stimuli (Fadardi et al. 2016; Field and Cox 2008). Investigating these changes should involve a thorough examination of cognitive behavioral changes by utilizing laboratory based visual attention paradigms in heavy binge drinkers and a lower drinking comparison group.

Furthermore, functional neuroimaging can be used to identify neural regions and circuitry involved in these cognitive behavioral changes and pharmacological manipulations can be used to identify the role of key catecholamine function in changes not only behavioral but also neural changes. This dissertation aims to address this gap in the literature by utilizing all of these methods to further our understanding of the specific changes that occur in visual attention processes as a result of social binge drinking. In the subsequent sections I will briefly summarize aspects of visual attention that are particularly relevant to the studies described in Chapters 2, 3, and 4. Next, I will introduce the cognitive phenomenon of attentional bias and summarize the literature regarding attentional bias and addiction related cues. Following the summary of attentional bias, I will briefly summarize the literature on reward-driven attentional bias in addicted and healthy populations. Finally, I will summarize the aims of this dissertation and briefly identify specific hypothesis and methods that will be discussed more thoroughly in the following chapters.

Visual Attention

Visual attention is an important cognitive process as it informs our perception of our environment and aides in driving behavioral choices. The act of selectively applying your mind to stimuli is a crucial daily function. Visual attention is required to evaluate stimuli for value and importance and aids in determining the appropriate behavioral response. Theories of visual attention suggest that we align our attention with that of environmental stimuli in various steps.

This process is complex due to the nature of our environment, which is often characterized by cluttered and crowded scenes of stimuli with varying levels of importance and value. To further complicate the processing of visual stimuli our attention system has a limited capacity making it that much more important for our visual attention to have the ability to quickly identify and process the most

important stimuli in our environment. Several factors play a role in what stimuli or objects in a scene are processed and 'seen'. Physical properties of stimuli such as color, shape, orientation are processed at the earliest stages of visual attention and are combined to drive attentional resources to selectively attend to relevant spatial locations (Itti and Koch 2000; Koch and Ullman 1985; Xu and Chun 2009). The integration of physical properties and value with these selected spatial locations is thought to enable the creation of topographical representations of early processed physical features and location, these representations are defined as saliency maps (Koch and Ullman 1985). Saliency maps combines information about stimulus features, location, and value leading to selective attention and has been shown to predict visual fixation in humans (Duncan and Humphreys 1989; Li 2002; Treisman 1982; Treisman and Gelade 1980).

Another component of visual attention is the capacity of the system, or limited capacity of this system. Capacity limits prevents our attention system from being overloaded with information, as result only the most salient environmental stimuli is gated through to higher processing for decision making and behavior (Marois and Ivanoff 2005; Posner et al. 1980; Todd and Marois 2004). This theory suggests that the attention system has a limited capacity or resource availability to process all relevant or salient stimuli resulting in attentional filtering and depletion of environmental stimuli (Awh et al. 2006; Dux and Marois 2009). Taken together, we see that the visual attention has evolved to orient and focus our attentional resources on salient information in the environment in order to make behavioral choices. Attention works closely with memory processes to help us decide which actions to initiate in the presence of learned stimuli. This process becomes particularly important in the study of addiction. One of the hallmarks of addiction is the development of addiction related cues or stimuli to become salient, ultimately driving drug use behavior. The role of attention in addiction is one of great neurobiological and clinically relevance.

Attentional Bias and Alcohol

The visual attention system and it related cognitive behaviors have been found to be vulnerable to hazardous alcohol drinking. While focusing attention on environmental stimuli of importance is normal,

in addiction we see an excess allocation of attention to environmental stimuli that are associated with alcohol and hazardous drinking behavior (Fadardi and Cox 2006; Field and Cox 2008; Ryan 2002; Sharma et al. 2001; Townshend and Duka 2001; Weinstein and Cox 2006). Attentional bias (AB) is defined as the excess allocation of attention to drug related stimuli or cues and has been reported in a wide variety of addictions, including opiates (Marissen et al. 2006), nicotine (Chanon et al. 2010; Waters et al. 2003), cocaine (Hester et al. 2006), and alcohol (Cox et al. 2002; Ryan 2002). Physiological and behavioral reactions to drug related cues correlate with subsequent drug use, craving, treatment adherence, and relapse (Carter and Tiffany 1999; Marissen et al. 2006; Monti et al. 2000; Robbins et al. 1999). These findings of reactivity to drug related cues suggest that they can become salient and meaningful in the context of addiction. As previously highlighted in our visual attention section, salient stimuli are prioritized by our attention systems giving rise to more attentional resources being allocated for the processing of these salient drug related cues. The theory of saliency maps posits that attention would be directed to spatial locations of drug related cues. Shifting of attention to these areas represents selective attention capture and delays in shifting attention away from locations of drug related cues would represent deficits in disengagement (Gladwin et al. 2013). The role of visual attention, and subsequent vulnerability towards the development of AB, coupled with the clinical relevance and widespread presence of AB in addiction, has given rise to significant laboratory research aimed at better understanding the underlying cognitive and neural mechanisms of this phenomenon. The AB field has provided researchers and clinicians with an assortment of tools and methods to probe AB in alcohol use disorders (AUDs) and hazardous drinking. The next section will highlight the key findings of the alcohol AB field and remaining gaps in our knowledge of alcohol related AB.

AB has been assessed using a variety of cognitive paradigm in the laboratory setting. AB tasks generally fall into two categories, direct and indirect measures of AB. Indirect measures are most commonly used, and AB is surmised if the participant's performance on a primary task (e.g. color-naming, or identifying the orientation of a target) is impaired when alcohol-related stimuli are present. Primary task designs often include the presentation of alcohol and non-alcohol related cues and dependent

measures are reaction time (RT) or accuracy (ACC) differences on alcohol vs non-alcohol-related trials. Frequently used indirect measure paradigms of AB include the addiction Stroop task, where participants are required to name the color of an alcohol–related or neutral word. It is believed that slower color naming of alcohol related words reflect slower processing of the cognitive material due to the meaningfulness of the word (Cox et al. 2006). AB is quantified by calculating the differences in ACC when the word is alcohol related vs non-alcohol related. Using this task, alcohol users have been found to have increased AB to alcohol-related stimuli compared to controls (Fadardi and Cox 2008; Field et al. 2007; Sharma et al. 2001; Stetter et al. 1995). Calculating AB as a function of change in reaction time or accuracy can occur in a positive or negative direction, however generally an increase in response time and decrease in accuracy are accepted as indicators of AB (Field and Cox 2008; Field et al. 2009b; Robbins and Ehrman 2004). Alternative calculation methods of AB that account for both response time and accuracy are also often used due to the speed accuracy trade off phenomenon, most frequently used in spatial cueing tasks, such as the dot probe task.

The dot probe task is another commonly used indirect measure of AB to alcohol cues. In this task, two stimuli, neutral- and alcohol-related, (pictures or words) are presented simultaneously, side by side, followed by the presentation of a probe or target that signals the participant to respond often by pressing a key or button. Participants are instructed to identify the location of the target by pressing the key that corresponds to its spatial location (Field and Cox 2008; Field et al. 2009b; Robbins and Ehrman 2004). When the target appears in the same spatial location that the alcohol image appeared, the response time will be faster according to the visual attention theories. This increase in response time is due to the location having already being attended to because the previous presence of salient stimuli, the alcohol related cue (Field and Cox 2008; Field et al. 2004; Field et al. 2009b; Manchery et al. 2017; Posner et al. 1980; Townshend and Duka 2001). Heavy social drinkers exhibit greater AB to alcohol cues using this paradigm (Manchery et al. 2017; Townshend and Duka 2001). One of the key manipulations in this task is the timing of stimulus presentation or stimulus onset asynchrony (SOA). Studies have varied the SOA from 17ms-2000ms and have found that SOAs up to 300 ms (short SOA) produce facilitation of

processing at the cued location resulting in increased RTs, while longer SOAs do not (Posner and Cohen 1984b). Facilitation of processing is thought to reflect quick, automatic capture of attention or selective attention capture. This form of attentional capture has been well characterized such that basic perceptual research studies have repeatedly shown that the SOA reflects initial orienting of attention (Theeuwes and Chen 2005). While this task isn't as commonly used in alcohol research as it is in other addictions, using this task in both alcohol and samples with SUDs have revealed increased AB captured by the dot probe task using the short SOA and the underlying neural mechanisms of this phenomenon (Bradley et al. 2004; Field and Cox 2008; Hester and Luijten 2014; Luijten et al. 2011; Noel et al. 2006). Studies of alcohol AB varying the SOA from 300ms-2000ms (long SOA) have found different results. For example, (Townshend and Duka 2001), found a significant AB in heavy social drinkers using a 1000ms SOA, while Field et al (2004), found similar results using a 500 and 2000ms SOA. The longer SOA are thought to reflect maintained attention in part because the timing allows for the decaying of the initial orienting of attention seen at shorter SOAs and multiple shifts of attention between addiction and neutral stimuli reflecting a more voluntary attentional process. The longer SOA may also reflect delayed disengagement from addiction related material, complicating what is thought to reflect maintained attention with inhibition of return (Duncan et al. 1994; Field and Cox 2008; Theeuwes and Chen 2005). In addition to these more traditional paradigms of AB, other well validated cognitive paradigms have been modified for use in addicted populations providing insight into other forms and aspects of AB. One of these paradigms is the modified attentional blink task discussed below.

The attentional blink task is named after a cognitive phenomenon that refers to a temporal attention process in which, during a rapid serial visual presentation, embedded targets are not identifiable depending on when they appear in the stream (Chun and Potter 1995; Raymond et al. 1992; Shapiro et al. 1994). More specifically, when a second target appears in close temporal proximity to a detected first target, individuals are more likely to fail to detect the second target. The attentional blink paradigm is frequently used in cognitive neuroscience focusing on basic visual attention processes and emotional valence and less frequently disorders directly related to maladaptive attention processes, such as ADHD

(Armstrong and Munoz 2003; Keil and Ihssen 2004; Mason et al. 2005; Most et al. 2005; Raymond et al. 1992; Shapiro et al. 1994; Smith et al. 2006).

There are several versions of the attentional blink task; the two most commonly used are the single and dual task versions of the task. In the single task blink paradigm, participants are required to view a stream of rapidly appearing images and identify the orientation or rotation of a target image with in the stream at the end of each trial. Embedded in the stream are critical distractor images that can be addiction or neutral either in close (2 lags) or distant (8 lags) temporal proximity to the single target. Accuracy of target identification when the critical distractor is in close proximity to the target is the measure of interest in this task. The dual task version of the attentional blink paradigm requires participants to identify 2 targets compared to 1 in the single task. Participants are required to view a rapid stream of images and to identify two targets that appear on images either 2-6 images apart. Targets are generally numerals, letters, or features of the image and there are two pieces of information that must be identified and encoded again with accuracy at target identification being the measure of interest. Theories of the attention blink effect state that it reflects extended attentional hold and the capacity limitations of our attention system (Choi et al. 2012; Chun and Potter 1995; Dell'acqua et al. 2009; Dux and Marois 2009; Kelly and Dux 2011; Marois and Ivanoff 2005; Raymond et al. 1992; Shapiro et al. 1997). Specifically, theories suggests that the attention system has a limited capacity or resource availability to process all relevant or salient stimuli resulting in attentional filtering and depletion of environmental stimuli (Dux and Marois 2009). More recently, addiction research has incorporated modified versions of the attentional blink paradigm in SUDs. AB was been reported in nicotine and opiate users utilizing attentional blink tasks (Chanon et al. 2010; Liu et al. 2008; Munafo et al. 2005). These studies employed a dual task version of the attentional blink paradigm where participants were required to identify 2 targets participants are required to view a rapid stream of images and to identify two targets that appear on images either 2-6 images apart. Using this dual version of the blink paradigm resulted in mixed findings; Munafo et al. (2005) found no significant differences in AB between smokers and nonsmokers, Chanon et al (2010) found increases in AB in active smokers towards cigarette related stimuli compared to nonsmokers, while Waters et al. (2007) found

decreases in AB in smokers to smoking related stimuli compared to nonsmokers. Moreover, Liu et al. (2008) found addiction related stimuli reduced the attentional blink in recovering opiate addicts, and suggested that addiction-associated information was selected by the brain for attentive and perceptual processing. Increases in the attentional blink task are conceptualized as extended attentional hold, while decreases are thought to reflect hyper-vigilance of attention or priority processing of addiction related stimuli due to their salient properties (Keil and Ihssen 2004; Raymond and O'Brien 2009; Waters et al. 2007) These findings support the promise of using attentional blink paradigms in other drug and alcohol abusing populations.

Indirect measures of attentional bias, while widely used, do intrinsically pose some interpretation challenges. The interpretation of AB using indirect measures is confounded by the primary task demands and other cognitive properties. Overall task goals of responding quickly or accurately to a target can result in competition between two meaningful stimuli, the task-irrelevant drug-related stimuli and the stimuli relevant to the task goal. Furthermore, cognitive processes such as memory have repeatedly been shown to play in AB, such as working memory capacity and duration of memories (longer held memories) being positively correlated with magnitude of AB and extended attentional hold (Anderson et al. 2013; Chanon and Hopfinger 2008; Cowan 2001; Parks and Hopfinger 2008; Weinstein and Cox 2006). Although all of these measures of AB have their shortcomings, taken together their findings support the validity of AB to salient stimuli in healthy and clinical populations. There are a number of ways, as indicated by these cognitive tasks, to validly assess AB in clinical populations in the laboratory setting. Our ability to successful capture AB in the laboratory coupled with its significant clinical relevance in AUDs and SUDs emphasizes the importance in furthering our understanding of its underlying neural mechanisms.

AB to addiction-related stimuli characterizes addiction and studies of AB to addiction cues have revealed its clinical relevance across multiple substances of abuse (Field and Cox 2008; Weinstein and Cox 2006). Research studies of either individuals with AUDs or heavy binge drinkers have both found AB toward alcohol-related stimuli (Roberts and Fillmore 2015; Ryan 2002; Schoenmakers et al. 2007; Sharma et al. 2001; Townshend and Duka 2001). For example, investigations of AB to alcohol cues in

heavy social drinkers compared to occasional social drinkers found that heavy social drinkers showed significantly more AB to alcohol related images (Bruce and Jones 2004) or words (Field et al. 2004; Townshend and Duka 2001) than did occasional drinkers. Moreover, heavy social drinkers have been found to exhibit more maintained attention on alcohol related pictures (Field et al. 2004), and this form of AB was correlated with their subjective alcohol craving (Field et al. 2005b). AB to alcohol related cues has not only been report amongst heavy drinking adults, but also among heavy drinking adolescents (Field et al. 2007; Melaugh McAteer et al. 2015). Taken together, this evidence suggests the importance of further investigating AB in alcohol drinking populations as it is present in a broad spectrum of drinkers, from those with AUDs to subclinical heavy social alcohol drinkers. However, far less research has been conducted on AB in subclinical or social drinking populations, such as heavy, binge drinkers. Characterizing AB in heavy, binge drinkers is of significant importance as these individuals make up a large portion of the heavy drinking population (Esser et al. 2014) and preclinical and clinical research suggests that this pattern of heavy drinking has specific hazardous consequences (Boutros et al. 2014; Courtney and Polich 2009; Crews and Boettiger 2009; Crews et al. 2016; Vetreno and Crews 2015; Viner and Taylor 2007).

Development of AB

AB is thought to be the result of Pavlovian conditioning (Berridge 2004; Berridge and Robinson 1998; Field and Cox 2008; Uslaner et al. 2006). The repeated pairing of alcohol related stimuli with the rewarding effects of alcohol consumption, results in the alcohol related stimuli becoming conditioned cues. In addition, pairing neutral stimuli with the rewarding properties of substances of abuse results in the formation of Pavlovian conditioning such that a formerly neutral stimulus acquires 'incentive salience' (Robinson and Berridge 1993). The formerly neutral stimulus now elicits 'wanting' and can act as a cue to motivate and initiate drug associated behavior and automatic or habitual drug related behavior. Alcohol conditioned cues are theorized to develop incentive salience, hedonic and motivating properties, associated with consuming alcohol. This process is often referred to as the Incentive Sensitization model.

The Incentive sensitization model has been widely investigated and characterized in animals of addiction and substance use and is readily seen across many substances of abuse. More recently distinct individual differences in the extent to which incentive sensitization is established have been found in rodent studies (Flagel et al. 2008; Robinson and Berridge 2003). Animal models utilizing food and cocaine have been used to explore variation in the extent individual differences predict response to reward cues and acquire incentive sensitization. Two distinct behavioral profiles have arisen from these investigations and are identified as sign-tracking and goal-tracking (Flagel et al. 2009; Srey et al. 2015; Tomie and Sharma 2013). Sign-tracking animals will acknowledge the presence of the reward cue, approach, and investigate it, while goal-tracking animals will approach the location of reward delivery (Meyer et al. 2012; Robinson et al. 2014; Saunders et al. 2014; Saunders and Robinson 2013). This difference in approach and response to the reward related cue and actual reward is indicative of incentive salience with sign-tracking animals showing clear orienting towards the cue and goal-trackers the actual reward. Sign- and goal-tracking animals have also been shown to differ in acquisition of drug self-administration and reinstatement paradigms (Robinson et al. 2014). Investigations into the neural bases of this phenomenon confirm the involvement of the Ventral Tegmental Area (VTA), Nucleus Accumbens (NaC) but it remains unclear what precise role dopamine plays in these two forms of conditioned approach, and if that role differs in sign- and goal-tracking behaviors (Flagel et al. 2009; Flagel et al. 2011; Uslaner et al. 2006). Better understanding the underlying neural mechanisms associated with individual differences in reward conditioning and response to reward will allow better characterization of addiction phenotypes and potentially develop more effective and individualized treatments for addiction.

General Reward Conditioning

AB to drug related stimuli is widely researched in addiction research however there are several limitations associated with investigating of AB in addicted populations. While AB has been used to characterize addicted populations, critical analysis of the field of addiction AB reveals that findings of AB have been inconsistent throughout the literature (Christiansen et al. 2015b; Field and Cox 2008; Robbins and Ehrman 2004). Several studies have utilizing similar paradigms in the same addicted populations

have reported different findings of AB. Moreover much of the motivation to investigate AB is due to its assumed clinical relevance which has also been recently called into question (Field et al. 2014). While many studies report that AB has a positive relationship with features of addiction (craving) and addiction severity and even predicts treatment outcome, there also studies that report no relationship between AB and these aspects of addiction (Christiansen et al. 2015b). A few reasons for these inconsistencies have been put forth. The first highlights the low reliability and internal validity of AB tasks used in the field. A meta-analysis using a sample of 7 studies examined the reliability of the frequently used dot probe tasks and showed that they produce unreliable estimate of substance related AB (Ataya et al. 2012a). Instances in which AB was not detected, or only detected in a subset or participants or trial types, are thought to stem from a variety of explanations, including insufficient addiction severity in the tested sample, ineffectiveness of the stimuli used, or simply the lack of internal validity and reliability of the dot probe paradigm. Another reason put forth is that AB is more likely an output of the current motivational state and that the strength of this motivational state is heavily influenced by craving (Field et al. 2009b), mood (Dickter et al. 2014; Garland et al. 2010), and other environmental factors (Christiansen et al. 2015b). Taking into considerations the inconsistencies in finding AB and the possibly that it may be an output of another underlying addiction trait or feature, investigations into the underlying neural mechanisms and processes that may facilitate AB is warranted. Reward conditioning is one such process that appears to be closely related to AB.

AB is thought to reflect basic reward conditioning processes (Anderson 2016), and thus be akin to the conditioned orienting responses observed in preclinical Pavlovian conditioning paradigms, e.g. sign-tracking (Parker and Gaffan 1998; Robinson and Flagel 2009; Uslaner et al. 2008). Sign-trackers is a behavioral phenotype seen in animal models of reward conditioning where animals that are ‘sign-trackers’ more readily approach the cue paired with reward than the reward delivery mechanism(Robinson and Flagel 2009). The preclinical literature suggests marked individual differences in the tendency to establish sign-tracking responses to reward conditioned cues, both general reward and drug-related reward cues (Meyer et al. 2012; Robinson and Flagel 2009; Robinson et al. 2014), and that a tendency toward greater

sensitivity to reward conditioning is a risk factor for addiction in animal models (Flagel et al. 2008; Waselus et al. 2013). Moreover, a review of animal models of cue reactivity has revealed that drug-related cues elicit greater attentional bias even in the presence of high level natural rewards (Kelley and Berridge 2002). Furthermore cue reactivity to generalized or abstract rewards such as food or money has been found to be diminished in addicted individuals and those undergoing treatment (Lubman et al. 2009). Few studies have investigated drug and natural reward reactivity in the same sample. In those studies food- and smoking-cue induced craving were found to be positively correlated in two studies of active smokers (Mahler and de Wit 2010; Styn et al. 2013). These findings from the preclinical literature on reward conditioning, combine with the few studies on reward conditioning in humans suggest that this process may indeed play a role in drug-related AB in humans and investigating reward conditioning in substance using populations may provide significant insight into the underlying mechanism of AB.

Neural Mechanisms of Attentional Bias

The neural bases of AB remain largely unknown, but with the growing use of neuroimaging in addiction AB, researchers have begun to probe the neural correlates of addiction AB in humans. In a functional magnetic resonance (fMRI) study of smokers, AB toward smoking cues positively correlated with activation in response to these cues in the dorsolateral prefrontal cortex (DLPFC), putamen, posterior cingulate gyrus (PCC), and primary motor cortex (Kang et al. 2012). Furthermore, in another study of smoking related AB, using an addiction Stroop task, increases in RT to identify the color in which smoking-related words were displayed was associated with increased activity in the insula, amygdala, hippocampus, parahippocampal gyrus in active smokers (Janes et al. 2010). To our knowledge only one fMRI study has directly assessed alcohol AB. Testing recovering alcoholics using a dot probe task, researchers identified positive correlations between alcohol AB and brain activations in the inferior frontal gyrus (IFG), insula, precentral gyrus, anterior cingulate cortex (AnCC), the caudate, and putamen (Vollstädt-Klein et al. 2012).

There has also been research investigating the neural mechanisms of attentional bias to non-drug related reward cues. Investigating the role of reward related dopamine release in generalized AB,

Anderson et al (2017), found that dopamine release within the right anterior caudate predicted generalized reward conditioning in a sample of normal participants (Anderson et al. 2017). In another study, researchers used a version of the monetary incentive task to investigate the neural mechanisms of response to reward and threatening cues. They found increased activation of the dorsal AnCC and, bilaterally, midbrain/ventral tegmental area (VTA), caudate, putamen, nucleus accumbens and anterior insula to reward cue trials compared to non-rewarded trials (Choi et al. 2014), In a meta-analysis comparing general reward processing in obesity, substance addiction and non-substance addiction, general rewards (monetary reward, pleasant pictures/happy faces, pleasant interoceptive stimulation (soft touch) and food reward) where found to elicited a greater activation in drug-addicted individuals in several regions including the thalamus, anterior insula, superior and middle frontal gyri, basal ganglia (caudate/accumbens and putamen/pallidum), amygdala, posterior cingulate cortex and anterior cingulate/paracingulate cortex (García-García et al. 2014). Finally, Tang et al. (2012) found overlapping neural responses for food and drug cue reactivity in the orbitofrontal cortex (OFC), AnCC, DLPFC, insula, striatum, and amygdala (Tang et al. 2012). Significantly more research has focused on the neural mechanisms of drug cue compared to natural reward conditioning in humans but these studies provide neural region of interests to investigate to answer questions of the neural mechanisms of AB in humans.

Overlapping evidence from the preclinical literature and the neuroimaging findings on the neural mechanism of AB and reward conditioning highlight the role of key brain regions in the mesolimbic circuit in reward conditioning/processing and potentially AB in humans. It is known from animal models, that mesolimbic dopamine projections from the VTA to the NAc play a critical role in both Pavlovian conditioning and expression of conditioned responses, which are often conceptualized as a preclinical model of AB (Di Ciano et al. 2001; Parkinson et al. 2002). Furthermore, dopamine's role in conditioned responses is characterized by fast dopamine release events (dopamine transients) that occur at the onset of a conditioned cue (Day et al. 2007; Flagel et al. 2011). Investigations into the neural mechanisms of attentional processes, such as alerting, and orientating to stimuli, and even forms of executive control function rely on dopamine function (Geva et al. 2013).

In addition to the mesolimbic circuits role in Pavlovian conditioning and expression of conditioned responses non-human primate studies suggest that it plays another important role in reward processing. Studies have shown that signals of motivational significance of reward and reward cues first enter the mesolimbic circuit at the VTA. The VTA in turn sends signals to the PFC and NAc to trigger orienting toward and seeking of reward (Bromberg-Martin et al. 2010). The PFC also projects to VTA neurons in non-human primates (Frankle et al. 2006; Williams and Goldman-Rakic 1998), rodents (Sesack and Pickel 1992) and PFC stimulation in rodents can modulate the firing of VTA (Gao et al. 2007; Svensson and Tung 1989) and mesencephalic (Gariano and Groves 1988) dopamine neurons, and transcranial magnetic stimulation of the dorsolateral PFC (DLPFC) induces dopamine release in the striatum of normal healthy participants (Ko et al. 2008) and individuals with major depression (Ko et al. 2008). With the use of functional magnetic resonance imaging, human research has been able to support the findings of the preclinical literature that suggest the mesolimbic circuit plays a role in drug cue conditioning such as attentional bias. Neuroimaging investigations have revealed neural correlates of attentional bias in humans to be overlapped with those areas and regions discussed above that have been found to play an essential role in reward and drug cue conditioning. Neuroimaging findings, highlight increased activity in the cognitive control regions (i.e., lateral prefrontal and dorsal anterior cingulate) across addicted populations (Hester and Luijten 2014); measures of subjective craving during attentional bias correlated with brain activation in the insula and putamen (Luijten et al. 2011); and mesocorticolimbic reward system was found to trigger focused attention to substance-associated cues in alcoholic (Vollstädt-Klein et al. 2012). More recently in a human neuroimaging study using dynamic causal modeling, it has been shown that information about rewarding stimuli enters the mesolimbic circuit through the DLPFC and drives activity of the VTA and NaC (Ballard et al. 2011b). As AB reflects acquired motivational significance of previously neutral cues, it is probable that reward-driven AB involves altered connectivity among these brain areas and is modulated by the dopaminergic system. The combination of significant behavioral and neurobiological research in the area of AB and reward conditioning across specifics highlights its importance in field of addiction research. There remain significant gaps in our knowledge of

the underlying neural mechanisms of alcohol-related AB and reward conditioning and this dissertation aims to begin to address those gaps in the following chapters.

Summary of Aims

Attentional bias (AB) to addiction-related stimuli has been widely investigated in addiction and characterizes addiction (Field and Cox 2008; Weinstein and Cox 2006). Studies of AB to addiction cues have revealed its clinical relevance across multiple substances of abuse. However, significantly less research has been conducted on AB in subclinical substance using and abusing populations such as binge drinkers. The research described here will attempt to characterize alcohol attentional bias in a social drinking sample. A few studies have reported increased attentional bias to alcohol-related stimuli in heavy, binge drinkers. However the studies described in this dissertation will not only investigate the presence of AB in social drinkers, but investigate multiple forms of AB and probe the underlying neural mechanism and processes of AB with novel behavioral tasks, pharmacological manipulations, and resting state functional connectivity. Our findings will contribute to a growing body of knowledge on alcohol AB in subclinical hazardous drinkers

In Chapter 2, we specifically aim to identify and compare two forms of alcohol AB, selective attention capture and extending attentional hold, in a sample of light to moderate drinkers and heavy binge drinker. We will test the working hypothesis that heavy, binge drinkers will show elevated alcohol AB relative to light to moderate drinkers and these two distinct forms of AB, as measured by a traditional dot probe task (Figure 1-1) and modified attentional blink task (Figure 1-2) that has yet to be used in an alcohol drinking population. To further probe the relationship between AB to alcohol cues and drinking history, we will assess the role of current and past binge drinking behavior on alcohol AB. Finally to begin probing the underlying mechanisms of AB we will assess reward conditioning, a process that may potentially underlie AB, in a subset of female participants. We will investigate whether sensitivity to general reward conditioning predicts the magnitude of AB to alcohol-related cues, and whether the relationship between these two forms of AB interacts with binge drinking history.

In Chapter 3 we will continue our investigations of sensitivity to general reward conditioning in heavy binge and light to moderate social drinkers using a monetary reward conditioning task (Figure 1-3). Using this task we will investigate whether heavy binge drinkers display heightened sensitivity to reward conditioning compared to light to moderate social drinkers and evaluate whether adolescent binge alcohol exposure predicts sensitivity to reward conditioning in this sample, independent of current alcohol use. Given evidence for heightened sign-tracking effects in alcohol exposed female rats (Madayag et al. 2017), we chose to test females only in task.

In Chapter 4 we will probe the neural mechanisms of alcohol AB and reward conditioning utilizing pharmacological manipulations, resting state functional connectivity and the AB tasks used in the previous chapters in a new sample of male light to moderate and heavy, binge drinkers. We will measure functional connectivity between frontolimbic regions of interest (ROI) from brief, resting-state fMRI scans collected immediately before behavioral AB tests. We will assess the role of dopamine in functional connectivity and AB by administering a phenylalanine/ tyrosine (P/T) depleted amino acid (AA) beverage to pharmacologically manipulation dopamine levels and a control AA beverage in a double-blind, counter-balanced design. We hypothesize that alcohol AB involves altered connectivity among frontolimbic brain areas. Furthermore, we hypothesized that acute dopamine depletion will reduce AB to alcohol cues and to reward-conditioned cues, and would do so in proportion to changes in the functional connectivity of PFC subregions (OFC, DLPFC, AnCC, IFG, fronto-insular cortex (FIC) with the VTA. Furthermore, we further hypothesized that these effects would be magnified in heavy binge drinkers.

Task Figures

Dot Probe Task (Fig.1-1)

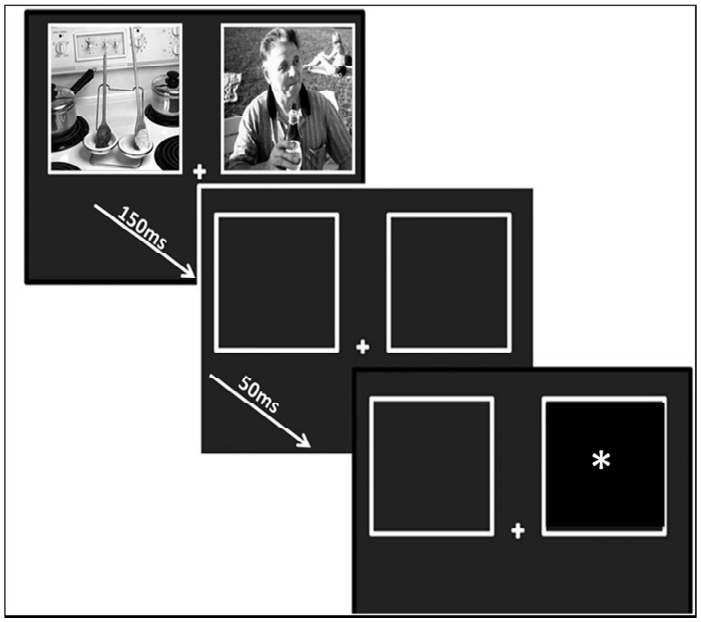

Fig.1-1 Dot Probe Task Procedure. An alcohol and neutral cue pair appears for either 150ms, followed by an ISI of 50ms, and then an asterisk target for 200ms. In this trial, the target appears in the location of the alcohol cue.

Modified Attentional Blink Task (Fig. 1-2)

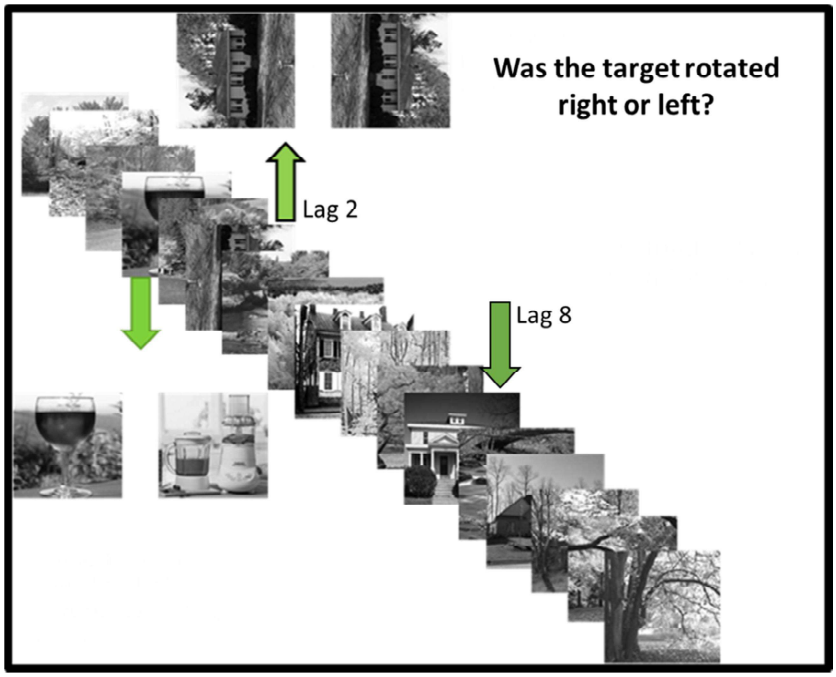

Figure 1-2 Modified Attentional Blink Task. Rapid Serial Visual Presentation (RSVP) of 17 grayscale photos for 100ms each, with a 0ms ISI. Stimuli within each stream consisted of neutral images, except for two images, and were all upright landscape/architectural photographs. Two images consisted of the critical distractor and the target stimulus. Half of the critical distractor images had neutral (kitchen related) content and the other half were alcohol-related images. Targets were presented 2 or 8 images after the distractor images in the stream, and were rotated 90° to the left or right. At the end of each trial, the response screen was presented for 2000ms and participants were instructed to indicate the orientation of the target image (left or right) by pressing one of two keys.

Reward Conditioning Task (Figure 1-3)

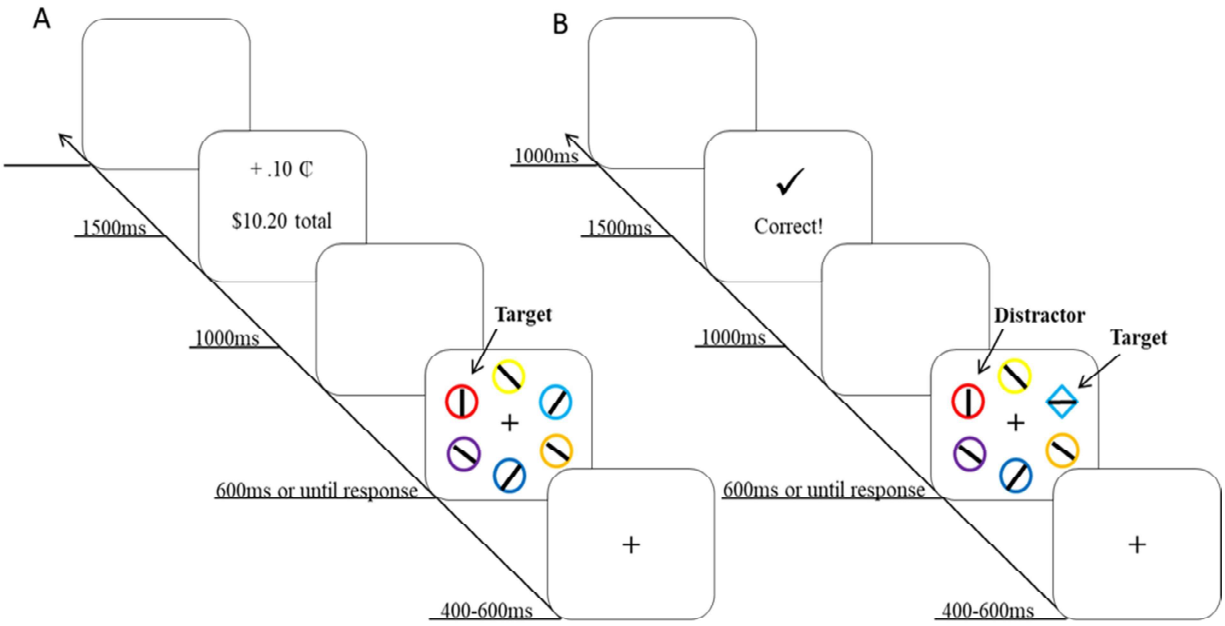

Figure 1-3. Reward Conditioning Task Procedure for a trial during the training phase (A) and test phase (B). During the training phase, participants visually searched for a target circle that was unpredictably red or green, and received a monetary reward for correctly reporting the orientation of a bar contained within the target (by pressing one of two keys). During the test phase, participants searched for a target defined as the unique shape (i.e., diamond among circles or circle among diamonds) and received accuracy feedback but no monetary reward. On two thirds of the trials, one of the non-target shapes was rendered in the color of a formerly reward-predictive target (red or green), which served as the reward-associated distractor.

CHAPTER 2:

ALCOHOL USE AND ATTENTIONAL BIAS TO REWARD CUES

Introduction

Attentional bias (AB) is defined as the excess allocation of attention toward particular stimuli and AB to addiction-related stimuli characterizes addiction (Field and Cox 2008; Weinstein and Cox 2006). Studies of AB to addiction cues have revealed its clinical relevance across multiple substances of abuse. For example, the relationship between addiction cue AB and addiction severity, (Bearre et al. 2007; Copersino et al. 2004; Nikolaou et al. 2013), craving (Attwood et al. 2008; Copersino et al. 2004; Manchery et al. 2017), and treatment outcome have each been reported (Marissen et al. 2006; Schoenmakers et al. 2007; Waters et al. 2003). Research studies of either individuals with alcohol use disorders (AUDs) or heavy binge drinkers have both found AB toward alcohol-related stimuli (Roberts and Fillmore 2015; Ryan 2002; Schoenmakers et al. 2007; Sharma et al. 2001; Townshend and Duka 2001). More specifically, AB's clinical relevance has been highlighted by studies showing that AB toward alcohol-cues positively correlates with craving and predicts relapse risk (Cox et al. 2002; Field et al. 2005b).

AB to addiction cues is thought to result from Pavlovian conditioning, whereby the repeated pairing of addiction related stimuli and the rewarding effects of the substance results in the attribution of incentive salience to alcohol cues (Berridge 2004; Berridge and Robinson 1998; Uslaner et al. 2006). Interestingly, decreased responses to natural rewards in people with substance use disorders (SUDs) has also been reported, which is thought to reflect an overall "hijacking" of the reward system by addiction cues in states of craving, withdrawal, and early abstinence (Goldstein and Volkow 2011). However, in people with no SUD history, pairing a monetary reward with neutral stimuli can also engender a

persistent AB towards these previously neutral stimuli, a phenomenon we refer to here as reward-driven attention capture (or AB) (Anderson et al. 2011b). Moreover, reward-driven AB has been found to be enhanced in an SUD population, specifically methadone-maintained opiate addicts, suggesting that substance misuse is associated with heightened sensitivity to reward conditioning (Anderson et al. 2013; Bjork et al. 2012). Together these studies highlight the importance and complex nature of drug related and non-drug reward related AB in addiction.

Several cognitive paradigms are commonly used to measure AB. Although AB can be elicited in each paradigm, some can provide insight into the distinct aspects of attention that underlie the AB. The spatial cuing, or "dot probe" tasks are thought to detect the automatic shifting of attention to a cue's spatial location (Maylor and Hockey 1985; Posner 1980). Faster reaction time to a neutral probe occurring in the prior location of a special (e.g. addiction-related) versus a neutral cue reflects selective attentional capture by those cues, a form of AB, although interpretation of reaction time effects depend on the interval between presentation of the cues and the probe (Field and Cox 2008). AB to drug or alcohol cues in dot probe tasks, has been correlated with increased craving in social alcohol drinkers and in individuals with AUDs (Manchery et al. 2017; Townshend and Duka 2001), and with treatment outcome in other SUDs (Ehrman et al. 2002). Another distinct form of AB is prolonged hold of attention, indicated by the failure to disengage attention from a stimulus. This form of AB can be revealed in rapid serial visual presentation tasks, which include imbedded targets in a stream of irrelevant stimuli. Specifically, a second target (T2) is more frequently missed when it follows a detected first target (T1) in close temporal proximity in a rapid visual stimulus stream. This phenomenon is referred to as an attentional blink (Chun and Potter 1995; Raymond et al. 1992). Attentional blink tasks have rarely been employed in the addiction setting, but (Chanon et al. 2010) found that when T1 is smoking related image, smokers are less likely to detect T2 than nonsmokers are, suggesting greater attentional hold by smoking cues in smokers. Similar to addiction related stimuli, this paradigm has also been modified to investigate the blink effect in the presence of emotional based distractors. In a study using emotionally negative stimuli (harmful, violent images) participants searched for a single target inside of 2 targets within the rapid serial visual stream of

images. Within that stream an irrelevant, emotionally negative or neutral picture preceded the target by either two or eight items. This study found that the shorter lag, negative pictures induced greater deficits in target processing than neutral pictures (Most et al. 2005). To our knowledge only 2 studies have looked at AB to alcohol related cues using an attentional blink paradigm (DePalma et al. 2017; Tibboel et al. 2010).

Few studies to date have administered multiple AB tasks to the same sample of participants (Chanon et al. 2010; Munafo et al. 2005). Although these studies were able to capture AB using multiple tasks, performance was not correlated across tasks, suggesting that the different forms of AB reflect different underlying mechanisms. Different aspects of attention appear to be influenced by the presence of drug related cues. By utilizing multiple tasks that assess different aspects of attention within a single sample, we can assess the relationship between different aspects of alcohol cue AB to particular sample characteristics, including current and past alcohol use.

AB is thought to reflect basic reward conditioning processes (Anderson 2016), and thus be akin to the conditioned orienting responses observed in preclinical Pavlovian conditioning paradigms, e.g. sign-tracking (Parker and Gaffan 1998; Robinson and Flagel 2009; Uslaner et al. 2008). While the preclinical literature suggests marked individual differences in the tendency to establish sign-tracking responses to reward conditioned cues (Meyer et al. 2012; Robinson and Flagel 2009; Robinson et al. 2014), and that a tendency toward greater sensitivity to reward conditioning is a risk factor for addiction in animal models (Flagel et al. 2008; Waselus et al. 2013), individual differences in susceptibility to reward conditioning has been little explored in human subjects. In addition to these individual differences, a recent study reported heightened sign-tracking effects in alcohol exposed female rats (Madayag et al. 2017), suggesting that there may also be gender differences in the reward conditioning. Investigating both AB to alcohol related cues and reward conditioning in the same sample would provide valuable insight into whether reward conditioning and AB to alcohol cues are related.

The objective of this study is to identify and compare two forms of alcohol AB in a sample of light to moderate drinkers and heavy binge drinkers. We tested the working hypothesis that heavy, binge drinkers

will show elevated alcohol AB relative to light to moderate drinkers and the two distinct forms of AB, as measured by the dot probe and attentional blink tasks. To further probe the relationship between AB to alcohol cues and drinking history, we will assess the role of current and past binge drinking behavior on alcohol AB. In a subset of female participants, we will investigate whether the magnitude of AB evoked by previously neutral reward-conditioned cues correlates with the magnitude of AB to alcohol-related cues, and whether the relationship between these two forms of AB interacts with binge drinking history.

Methods

Participants

Eighty two healthy male (n=33) and female (n=49) participants (ages 18-40 years; mean = 26.2) were recruited from the University of North Carolina, Chapel Hill (UNC) campus and surrounding communities. To include a broad spectrum of alcohol use, we recruited participants in two groups based on their alcohol drinking patterns: heavy, binge drinkers (HD; n=39) and moderate, social drinkers (MD; n=43). HD participants self-reported ≥14 alcoholic drinks/wk (≥7 alcoholic drinks/wk for females), and ≥12 binge episodes (≥5 drinks/2hrs for males, (≥4 drinks/2hrs for females) in the past 12 mos. MD participants self-reported <14 (7 for females) alcoholic drinks/wk, <10 lifetime binge episodes, and no binge episodes in the past 12 mos. Participants had no current or past history of neurological or psychiatric diagnoses. Additional exclusion criteria were use of psychoactive drugs or medication use (excepting moderate alcohol or caffeine intake), a history of treatment for a substance use disorder or a lifetime history of substance use disorder based on a structured clinical interview using DSM-IV criteria (Sheehan et al. 1998), except that alcohol dependence was not exclusionary for the BD group. All participants were native English speakers, right-handed, and had at least a high school education (or equivalent). Participants were screened for drug or alcohol use on the day of the scan via breathalyzer test (FC-10, Lifeloc Inc., Wheat Ridge, CO) and urine drug screen. (Biotechnostix, Inc., Markham, ON). Participants gave written, informed consent, as approved by the UNC Office of Human Research Ethics. Participants received monetary compensation per hour for participation.

General Procedure

Following screening, participants completed a single laboratory session, first completing a battery of standard questionnaires (see "Behavioral Inventories"), followed by brief training on the computerized tasks (see "Behavioral Tasks"), and finally completion of the behavioral tasks. One task, the reward conditioning task, was added to the procedure after several months of recruitment due to relevant and novel findings in the literature and as a result only a subset of participants completed that task

Behavioral Inventories

Participants completed standardized questionnaires to capture demographic information and to quantify factors that may account for individual differences in attentional bias to alcohol and sensitivity to reward conditioning. We quantified past and current drug and alcohol use and drinking motivations with the Alcohol Use Questionnaire (AUQ; Townshend and Duka 2002), the Carolina Alcohol Use Patterns Questionnaire (CAUPQ; see Appendix), the Drug Use Screening Inventory-Domain I (DUSI-I; Tarter 1990), the Alcohol Use and Disorders Inventory Test (AUDIT; Saunders et al. 1993), and Coopers Drinking Motivations Scale-Revised (DMQ-R; Cooper 1994). We used the NIAAA definition of binge drinking for males: 5 or more drinks in a 2 hour period, and females: 4 or more drinks in a 2 hour period (National Institute on Alcohol Abuse and Alcoholism, 2017). We used the AUQ binge drinking score (BDS), which is based on the speed of drinking, the frequency of intoxication in the past 6 months, and the percentage of time the individual becomes intoxicated when drinking, rather than a purely alcohol intake quantity measure (Townshend and Duka 2002). The CAUPQ assesses the age of drinking onset, and the frequency of binge drinking; three questions on the CAUPQ were used to assess binge drinking before age of 18, binge drinking between 18-21years, and current binge drinking frequency. Responses range from "Never" to "More than once a week" and are coded numerically from 0-6 (see Appendix). To assess the effect of familial history of alcohol abuse we administered the Family Tree Questionnaire (Mann et al. 1985). Impulsivity was measured by the Barrett Impulsivity Scale (BIS-11; Barratt 1994).

Behavioral Tasks

Dot Probe Task

We assessed selective attention capture using a dot probe task consisting of 48 trials (Fig. 1-1). Each trial began with a non-predictive white fixation cross that served as an orienting cue. Following the presentation of the orientation cue, two grayscale images (11.1°× 9.0°) images appeared simultaneously, one on each side of the fixation cross for 150ms. Grayscale images were used to avoid confounds in our results due to high salience of color (Theeuwes 1992; 1994; Figure 1-1). Following a 50 ms inter-stimulus interval (ISI), the target (a white asterisk, 36 pt font) appeared in one of the image locations and appeared for 200 ms. With 50 ms between cue offset and target onset, a 150-ms cue duration gave a 200-ms stimulus-onset asynchrony (SOA), which is well below the SOA where capture effects start to diminish (~300 ms; Posner and Cohen 1984a). In each trial, one image depicted alcohol-related content, while the other depicted neutral, kitchen-related content. Alcohol and neutral cues images were matched in terms of their basic visual properties. Left/right position of the alcohol images was pseudorandomly ordered (ratio 1:1). Each image was randomly drawn from a set of 20 alcohol or 20 neutral images. Subjects were instructed to respond to the target's location via keypress as quickly as possible. This design is modified from our previous study assessing AB toward smoking cues in cigarette smokers (Chanon et al. 2010).

Modified Attentional Blink Task

To measure extended attention hold, participants completed a modified attentional blink (Figure 1-2). The task consisted of four blocks of 48 trials, and each trial began with a non-predictive white cross hair (18pt font), followed by a rapid serial visual presentation of 17 grayscale photos (11.1°×9.0°) for 100 ms each, with a 0-ms ISI. Stimuli within each stream consisted of neutral images, except for two images, and were all upright landscape/architectural photographs. The remaining two images consisted of the critical distractor and the target stimulus. Half of the critical distractor images had neutral (kitchen related) content and the other half were alcohol-related images. Targets were presented 2 or 8 images after the distractor images in the stream, and were rotated 90º to the left or right. At the end of each trial, the response screen was presented for 2000ms and participants were instructed to indicate the orientation of

the target image (left or right) by pressing one of two keys. Participants' accuracy in reporting the target rotation was recorded for each trial, and mean accuracy for each task condition served as the dependent measure.

Reward Conditioning Task

We assessed each participant's reward conditioning sensitivity using a value driven attention capture task identical to that used in (Anderson et al. 2013), programmed in Matlab (The MathWorks Inc., Natick, MA, 2000) using the Psychtoolbox-3 extensions (Brainard 1997; Figure 1-3). Participants completed the task while seated at a computer in a darkened room. A visual search task was presented on a color LCD screen. The task was separated into two phases, a reward-conditioning phase, and a test phase. For the conditioning phase, each trial began with a fixation display for 400, 500, or 600 ms (randomly determined), followed by a visual search for a target circle among five non-target circles. The search array remained on the screen until a response was made, up to a limit of 1200 ms. Following the search array, a blank screen appeared for 1000 ms, and reward feedback was then displayed for 1500 ms, followed by a blank 1000 ms inter-trial-interval (ITI). The target circles were unpredictably red or green, and participants were rewarded for correctly reporting (via keypress) the orientation of a white bar (horizontal or vertical) appearing within the target circle. Participants received feedback in each trial (n=240) during the conditioning phase. One of the two target colors yielded a reward of 10¢ in 80% of trials, and 2¢ in the remaining 20% of trials (high-reward target); these contingencies were reversed for the other color target (low-reward target). Incorrect or omitted responses yielded 0¢. The high-reward color was red for half the participants and green for the other half. Participants completed 40 practice trials prior to beginning the task.

The test phase was structured similarly to the training phase, with a few keys differences. First, the search array included a target shape (diamond) among 5 non-target shapes (circles); participants disregarded shape color, and instead reported the orientation of the bar within the target shape. Second, feedback after the search array only informed participants if their response was correct (✓) or not (×); no monetary rewards were given. Third, the search array appeared for up to 1500 ms, followed by the

feedback screen for 1000 ms, and a blank ITI screen for 500 ms. Critically, 25% of trials included a red circle in the search array, 25% included a green circle in the search array, and the remaining 50% lacked any reward-conditioned distractor shapes. Both accuracy and reaction time (RT) were collected for each trial.

Statistical Analysis

For the dot probe task, the primary dependent measure of interest was the difference in RT between alcohol-cued and neutral-cued target trials. Faster RT values represent attentional bias toward alcohol-related cues via selective attention capture. Only RTs from correct trials were included in our analyses. We also excluded trials in which the RT was >2 standard deviations longer than the individual's mean RT for that condition, or <200ms. Due to large amounts of variability on a trial by trial basis in the task, a secondary AB measure was also calculated based on inverse efficiency. Inverse efficiency scores (IES) were calculated for each cue type (alcohol or neutral) using the formula: $RT_{AccOnly}/Accuracy_{overall.}$ This alternative measure accounts for the tendency of response selection speed to inversely vary with response selection accuracy by factoring both into the dependent measure.

For the modified attentional blink task, we calculated the accuracy of target responses, for each lag (2 or 8) and distractor type (kitchen or alcohol). The primary dependent measure of interest was the difference in the attentional blink effect (decreased accuracy lag 2 compared to lag 8) between the alcohol and neutral distractor trials. Smaller values (lower accuracy) represent greater attentional bias to alcohol cues (extended attentional hold by the critical distractor). Trials in which the RT was <200ms were excluded.

For the reward conditioning task, the primary dependent measure of interest was the difference in RT during the test phase between trials with a high reward distractor present (RT_{High}) and trials with no reward distractor present (RT_{Absent}) (Anderson et al. 2011b). Larger RT values represent greater reward conditioning. Only RTs from correct trials were included in our analyses. We also excluded trials in which the RT was >3 standard deviations longer than the individual's mean RT for that condition, or <200ms.

For each task, we will entered our dependent measures into 2×2 mixed model ANOVA to test for cue type × group interactions to assess whether there were differences in AB to alcohol cues or to reward-conditioned cues between groups.

We quantified bias for alcohol related images versus neutral images on the dot probe task according to the following equation: RT Bias Measure$_{\text{Neutral-Alcohol}}$ = ($RT_N - RT_A$), where RT_N and RT_A represent mean RT to targets appearing in the location of neutral, or alcohol images, respectively. Positive values of RT Bias Measure$_{\text{Neutral-Alcohol}}$ indicate AB to alcohol related images. Similarly, we quantified bias for the attentional blink tas according to the following equation: :Blink Bias Measure (Accuracy $_{\text{Alcohol8-Alcohol2}}$-Accuracy $_{\text{Neutral8-Neutral2}}$) - (Accuracy $_{\text{Alcohol8-Alcohol2}}$-Accuracy $_{\text{Neutral8-Neutral2}}$), where Accuracy $_{\text{Alcohol8-Alcohol2}}$ and Accuracy $_{\text{Neutral8-Neutral2}}$ represent the difference in accuracy for target identification appearing 2 or 8 lags after the neutral, or alcohol critical distractor images, respectively. Positive values of this measure also indicate AB to alcohol related images.

To assess whether reward conditioning predicted attentional bias to alcohol cues in either task, we used multiple linear regression analyses in SPSS. For each multiple regression analysis, we entered variables in a stepwise manner in the following order: block 1: age, and ethnicity; block 2: AUQ BDS, Binge frequency score 0-18yo, Binge frequency score 18-21yo; block 3: reward conditioning bias. Furthermore, to probe the relationship between different attentional mechanisms that are thought to drive attentional bias captured by the dot probe and modified attentional blink tasks (selective attention capture, and extended attentional hold) we correlated performance on these tasks. Lastly, to assess the significance of between group differences, we used unpaired, two-tailed *t* tests for continuous measures and χ^2 tests for categorical demographic measures.

Results

Demographic and Psychometric Data

Despite efforts to match our recruitment groups, they differed significantly in terms of demographics, reflecting younger age, and fewer years of education in our HD group. As these variables were highly co-linear, we therefore controlled for age in all subsequent analyses. Groups did not differ in terms of

familial alcoholism, but the HD group self-reported greater trait impulsivity (BIS), and differed from the MD group on all alcohol use measures, except for age at first drink (Table 2-1).

Attentional Bias Tasks Performance

Dot Probe Task Results

To test for differences in attentional bias to alcohol cues between the MD and HD groups, we used a 2 × 2 ANOVA (Cue Type × Group), comparing RT on neutral-congruent and alcohol-congruent trials. We detected a significant main effect of cue type ($F_{(1, 74)} = 4.038$, p=0.048), with slower RT in trials in which the target appeared in the location of an alcohol related cue (i.e. alcohol-congruent). There was no significant effect of group ($F_{(1, 74)} = 0.004$, p=0.948), nor a cue type × group interaction ($F_{(1,74)} = 0.2226$, p=0.636; Figure. 2-1a). Using the inverse efficiency score calculated for each trial type, we also detected no main effect of group ($F_{(1, 74)} = 0.335$, p=0.564), nor any cue type × group interaction ($F_{(1,734)} = 0.930$, p=0.38), and also failed to detect a main effect of cue type ($F_{(1, 73)} = 0.731$, p=0.395; Figure 2-1b). Due to the importance of a speed accuracy trade off effect in this task and differences in significance using the two calculations, we used IES for the remainder of our analyses as it accounts for both speed and accuracy.

Attentional Blink Task Results

To test for differences in the extended hold of attention by visual alcohol cues between the MD and HD groups, we used a modified attentional blink task. Using a mixed model ANOVA (Cue Type × Lag × Group), we tested for main and interacting effects of these factors on accuracy. Due to violations of normality, we applied an arcsine-root transformation to the data prior to analyses. We detected no significant main effects of group ($F_{(1, 70)} = .560$, p=0.457) or cue type ($F_{(1, 70)} = 0.011$, p=0.915) on accuracy, but did find a significant lag effect ($F_{(1, 70)} = 24.74$, p<0.001). Drinking group marginally interacted with cue type ($F_{(1, 70)} = 3.69$, p=0.059), but not with lag ($F_{(1, 70)} = 0.000$, p=0.994); however our main interaction of interest, cue type × lag × group, was statistically significant ($F_{(1,70)} = 4.66$, p=0.034), although contrary to our expectations, the MD group exhibited greater attentional hold by alcohol cues than did the HD group (Fig. 2-2).

Relationship between AB Measures from the Dot Probe and Modified Attentional Blink Tasks

The dot probe and modified attentional blink tasks are thought to reflect different forms of AB and as such potentially have different underlying cognitive basis (Chanon et al. 2010; Field and Cox 2008). To test for a potential relationship between the two forms of AB of measured by these two tasks, we performed nonparametric correlations between AB measures from each task. Performance in the dot probe and modified attentional blink tasks were not correlated across individuals (ρ= -.020, p= .862).

Exploratory Analysis

Additional non-parametric partial correlations were performed, controlling for age, education, and gender to explore relationships between psychometric variables and alcohol cue AB, the results of which are shown in Table 2-4. Within the sample as a whole, AB to alcohol cues in the attentional blink task negatively correlated with several drinking measures, including the AUDIT, the consumption and harm subscales of the AUDIT, current and adolescent binge drinking, and drinking for enhancement. We detected no significant correlations with alcohol cue AB in the dot probe task, and no significant correlations were detected within either drinking group alone (Table 2-4).

Reward Conditioning and Alcohol AB in Females

Lastly, we explored the relationship between alcohol AB in the dot probe task and reward conditioning in a subset of our sample that included only females. Specifically, we probed the relationship of current and adolescent binge exposure on in our analysis of the dot probe task as well. Using multiple linear regression, we entered the demographic variables of age and ethnicity in block 1, and for block 2, we added self-reported current binge drinking, self-reported frequency of binge drinking before age 18, and between ages 18-21, and magnitude of reward conditioning to determine which factors were predictors for alcohol AB. While the overall model predicting alcohol AB was not significant ($F_{(3,37)}$= 1.69 p =.187), reward conditioning was a significant independent predictor of cuing bias in the model (p=.048; Table 2-2). A greater degree of reward conditioning was associated with less AB to alcohol cues in the dot probe task.

We next performed an identical analysis for AB measured in the attentional blink task. Consistent

with our finding above that alcohol cue AB measures between the two tasks were uncorrelated, multiple regression analysis did not reveal significant predictive relationships between any of our independent variables and alcohol AB in this task ($F_{(3,37)} = 1.96$, $p = 0.138$; Table 2-3).

Discussion

AB to alcohol related cues has been widely reported in AUDs. Fewer studies have investigated the presence of attentional bias in heavy social drinking populations. In studies of AB in social drinking populations, AB has been shown to be greater in heavy binge drinkers compared to moderate or low social drinkers (Nikolaou et al. 2013; Townshend and Duka 2001; 2002; 2005). Here we assessed the presence of alcohol AB in heavy binge drinkers and light to moderate drinkers with two different tasks. Contrary to published data, we did not detect a significant difference in alcohol AB in heavy binge drinkers compared to moderate drinkers on the dot probe task. We did detect a statistically significant difference in alcohol AB between heavy, binge drinkers and to moderate drinkers on a modified attentional blink task; however, the direction of the effect was contrary to our hypothesis: alcohol cue AB was greater in the MD group relative to the HD group. Furthermore, we also failed to detect a relationship between current binge drinking and alcohol AB in the dot probe task when we instead used a continuous measure of binge drinking. Measures of adolescent binge drinking frequency also failed to predict AB to alcohol cues in the dot probe task. In contrast, consistent with our group results, both current and adolescent binge drinking measures negatively correlated with AB to alcohol cues in the attentional blink task. Moreover, attentional blink bias was also negatively correlated with the total AUDIT score and with the consumption and harm subscales of the AUDIT, and with self-reported "drinking for enhancement." Finally, to our surprise, AB toward alcohol cues in the dot probe task was inversely related to the magnitude of AB toward a reward-conditioned cue in a reward conditioning task; AB to alcohol cues in the attentional blink task was unrelated to reward conditioning.

Failure to detect AB to alcohol cues in a dot probe task: too little consumption?

Our sample of heavy binge drinkers differs in terms of alcohol consumption from previous studies that have reported alcohol attentional bias in heavy social drinking groups. We recruited heavy drinkers

according to the NIAAA standards of heavy drinking: 14 or more drinks per week for males, and 7 or more drinks per week for females. In contrast, previous studies that reported alcohol AB in 'social drinking' populations recruited drinkers with a weekly consumption of at least 20 drinks per week (Bruce and Jones 2004; Field et al. 2004; Townshend and Duka 2001). Our sample of heavy binge drinkers therefore reported a lower average number of drinks per week, 16.8, compared to these prior studies, in which average drinks per week were 53.1, 28.6, and 37.9, respectively. Thus, while our sample of HD met NIAAA criteria for hazardous drinking, higher intensity drinking patterns may be necessary for AB to alcohol cues to develop (Townshend and Duka 2001). In a study of AB with participants with similar drinking behavior as those in our sample, no relationship between social drinkers' attentional bias and the amount of alcohol that they habitually consumed was found (Field et al. 2005b). AB has been repeatedly shown to have a relationship with substance use frequency and quantity, with heavier users exhibiting greater rates of AB than lighter or non-users (Bruce and Jones 2004; Field et al. 2007; Field and Cox 2008). Together these findings support the theory that AB develops as a result of greater frequency and quantity of alcohol use. AB research in addicted and treatment seeking populations has repeatedly shown that those individuals with SUDs and greater addiction severity have significantly higher rates of AB (Copersino et al. 2004).

Failure to detect AB to alcohol cues in a dot probe task: task timing effects?

The dot probe task has been used in multiple variations to assess AB in addiction. A faster response time to a probe that appears in the same spatial location of a previously displayed addiction related image is thought to reflect AB. One of the key manipulations in this task is the timing of stimulus presentation or stimulus onset asynchrony (SOA). General studies of attention have varied the SOA from 17ms-2000ms and determined that SOAs up to 300 ms (short SOA) produce facilitation of processing at the cued location resulting in faster RTs, while longer SOAs do not (Posner and Cohen 1984). Facilitation of processing is thought to reflect quick, automatic capture of attention, or selective attention capture. This form of attentional capture has been well characterized, such that basic perceptual research studies have repeatedly shown that at short SOAs, it reflects initial orienting of attention (Theeuwes and Chen 2005).

While dot probe tasks aren't as commonly used in alcohol research as for addictions, studies using this task in either alcohol use disorders or other SUDs have revealed increased attentional capture by substance related stimuli in the context of a short SOA, motivating our use in this study (Bradley et al. 2004; Chanon et al. 2010; Field and Cox 2008; Hester and Luijten 2014; Luijten et al. 2011; Noel et al. 2006). In contrast to our use of a short SOA (200ms), previous studies of alcohol AB have used different timing and found different results. For example, (Townshend and Duka 2001) found a significant AB toward alcohol cues in heavy social drinkers using a 1000ms SOA, and Field et al. (2004), found similar results using a 500 and 2000ms SOA. These longer SOA are thought to reflect maintained attention, in part because the timing allows for the decay of the initial orienting of attention seen at shorter SOAs and multiple shifts of attention between addiction and neutral stimuli, reflecting a more voluntary attentional processes or delayed disengagement from addiction related material (Duncan et al. 1994; Field and Cox 2008; Theeuwes and Chen 2005). The combination of these studies in addiction using the short and long SOA provide support for the theory that short SOA is essential to detect automatic capture, however limited evidence on alcohol AB suggests that alcohol AB is captured by the long SOA. This may reflect increased development of the form of AB captured by the long SOA (maintained attention) compared to that of the short SOA (automatic attention capture).

It is apparent from the literature using the dot probe task to investigate AB in substance abusing populations that varying SOA is a key manipulation in capturing multiple forms of AB however these effects likely relay heavily on individuals reaching a threshold of heavy use before AB can be detected, which may have not been the case in our study.

Attentional Bias in Addiction: Mixed Results

Dot Probe Task

Large amounts of evidence suggest that AB towards addiction cues is common in addiction; however, when reviewing the literature on addiction related AB as a whole, the findings are fairly inconsistent. Using a variety of AB paradigms, researchers have been able to capture AB to alcohol related cues in social drinkers (Field et al. 2005b; Field et al. 2004; Townshend and Duka 2001) and individuals with

AUDs (Schoenmakers et al. 2010; Vollstädt-Klein et al. 2012); however, some studies have reported no AB, or inconsistent findings of alcohol related AB using similar tasks and samples. For example, alcohol cue AB was found only after the presentation of simple alcohol related images (Miller and Fillmore 2010), personalized alcohol images (Christiansen et al. 2015a), and only in males (Emery and Simons 2015). Instances in which AB was not detected, or only detected in a subset or participants or trial types, may stem from a variety of explanations, including insufficient addiction severity in the tested sample, ineffectiveness of the stimuli used, or simply the lack of internal validity and reliability of the dot probe paradigm. A meta-analysis using a sample of 7 studies examined the reliability of dot probe tasks and showed that they produce unreliable estimate of substance related AB (Ataya et al. 2012a). Moreover, studies that used a short SOA were found to be even more unreliable than those that used longer SOAs. Additionally, in a meta-analysis focused on the relationship between craving and substance related AB, the strength of the relationship between AB and craving was found to be mediated by treatment status, illicit drug use, and the use of direct measures of AB, such as those derived from eye tracking, compared to indirect measures, such RT as the dot probe task. Together, these results identify the complexities of using dot probe tasks to measure AB and how many factors in study and study sample may affect the likelihood of detecting substance related AB (Field et al. 2009b). Our finding that greater reward conditioning significantly predicted less cuing bias, while drinking behavior did not, suggests that selective attention capture by alcohol-related images does not reflect heightened sensitivity to reward conditioning, and could reflect diminished non-drug reward responsiveness. Future research is needed to test this possibility.

Attentional Blink Task

The attentional blink paradigm is a cognitive task originally used to investigate basic visual attention mechanisms, such as attentional capacity and interference (Chun and Potter 1995; Raymond et al. 1992; Shapiro et al. 1994; 1997). The attentional blink effect refers to a phenomenon of decreased detection of a second target (T2) when it follows a first target (T1) in close temporal proximity in a rapid visual stimulus stream. Significant research on the cognitive mechanisms associated with the attentional blink effect have

been conducted in normal healthy populations (Awh et al. 2004; Dell'acqua et al. 2009; Di Lollo et al. 2005; Dux et al. 2008; Dux and Marois 2009; Giesbrecht and Di Lollo 1998; Kelly and Dux 2011; Marois and Ivanoff 2005; Olivers and Meeter 2008; Raymond et al. 1995; Visser and Ohan 2011). The paradigm has also been commonly used in studies of assessing the effect of emotional valence on the blink effect. Research on the effect of emotional valence on attention includes the use of sexually explicit stimuli (Most et al. 2007) or threatening stimuli(Most et al. 2005), and shows that images that evoke emotional valence can cause or enhance the attentional blink effect in healthy and clinical populations (Keil and Ihssen 2004; Kennedy and Most 2012; McHugo et al. 2013; Smith et al. 2006). Despite the presumed emotional valence of drug related stimuli to addicts and users, to date, attentional blink paradigms have been used in only a handful of studies of substance related AB, two in heavy or binge drinkers (DePalma et al. 2017; Tibboel et al. 2010). Using an AB paradigm with alcohol related images, no AB was found for alcohol targets in a sample of binge drinkers, however higher self-reported hazardous drinking was associated with smaller ABs to alcohol-related targets in binge drinkers suggesting that alcohol images may have been processed more efficiently (DePalma et al. 2017).Moreover Tibboel et al (2010) also found an attenuation of the AB in heavy social drinkers compared to light drinkers. Furthermore three other studies used a dual version of the AB paradigm in other substance abusing populations (Chanon et al. 2010; Munafo et al. 2005; Waters et al. 2007). These latter three studies employed a dual task version of the attentional blink paradigm where participants were required to identify two targets appearing 2-6 images apart. Using this version of the blink paradigm resulted in mixed findings in smoking populations, ranging no AB effect (Munafó et al. 2005) to increased AB in smokers compared to nonsmokers (Chanon and Boettiger 2008). These inconsistent findings across multiple substance abusing populations is interesting as they suggest a potential hyper-vigilance of attention for addiction related cues resulting in either prioritized encoding or processing for such cues leading to increased accuracy or prioritized processing leading to extended attentional hold of cues in a variety of addicted populations.

Another version of the attentional blink paradigm has also been used to assess AB, the single task blink paradigm. For the single task, participants are required to view a stream of rapidly appearing images

and identify the orientation or rotation of a target image with in the stream at the end of each trial. Embedded in the stream are critical distractor images that can be addiction or neutral either in close (2 lags) or distant (8 lags) temporal proximity to the single target (Most et al. 2005). The single task attentional blink paradigm used in this study is thought to allow detection of extended attentional hold, with decreases in accuracy for targets in close temporal proximity to the critical distractor reflecting extended attentional hold by the critical distractor. Using such a paradigm, we found AB towards alcohol-related cues only in the moderate drinking group, and in fact AB was inversely related to binge drinking and other consumption measures. Although surprising, this finding may be similar to traditional studies of the blink effect for emotional valence. For example, increased AB among our moderate drinkers may result from the salience of alcohol images, as most moderate drinkers were exposed to and consumed alcohol however this should also be the case in our binge drinkers. The lack of AB in heavy drinkers may result from deficits in attentional processing or associative learning around alcohol related cues due to the effects of binge drinking on neural mechanisms required for these cognitive processes (intoxication during learning, learning impairment due to binge drinking early in life). Future studies may benefit from probing cognitive markers of general associate learning in both groups to determine if deficits reflect differences in AB.

Reward Conditioning Task

The reward conditioning task was administered to only females in our study due to it being added to the battery of assessments after the beginning of data collection. While other results from this task are reported in Chapter 3, here we investigated whether generalized reward conditioning predicted alcohol AB in either task. Multiple regression analyses revealed that reward conditioning significantly predicted cuing bias, with greater AB toward alcohol cues being associated with less reward conditioning (β= -.348). This relationship may reflect changes in generalized reward conditioning as a result of increased hazardous drinking behavior. Cuing bias has been repeatedly shown to increase with addiction severity (Roberts et al. 2014); and reactivity to generalized rewards has been shown to decrease with addiction (Volkow and Morales 2015). In contrast, we observed no relationship between reward conditioning and

AB toward alcohol cues in the attentional blink task. This distinction is consistent with the notion that AB measured in these two tasks reflects impacts on distinct cognitive processes. The attentional blink effect theories suggest that it arises from limited capacity of attentional resources for processing stimuli. Those attentional resources may not be greatly influenced by prior reward conditioning but possibly of current state or other personality traits.

Study Limitations

There were several limitations in this study, the first being the drinking levels of our HD group. Although our HD group met heavy drinking criteria established by the NIAAA, the group's drinking levels were substantially lower than that seen in the alcohol AB literature (Field et al. 2005a; Field et al. 2004; Nikolaou et al. 2013; Tibboel et al. 2010; Townshend and Duka 2001). Second, while the dot probe task we used have been commonly used in the assessment of AB, it has been shown to have low internal validity and reliability (Ataya et al. 2012a). In the future methodological changes to the dot probe task could be used to improve its reliability, such as using personalized stimuli or including more direct measures of AB (eye tracking) (Ataya et al. 2012b; Christiansen et al. 2015a).

Another limitation of this study may have been our inability to fully characterize extended attentional hold on the blink task using the single task paradigm. Our task utilized only 2 lags and did not reveal an effect, however studies using multiple lags (2-5) captured AB to addiction related stimuli on multiple lags (2 and 3) (Chanon and Boettiger 2008). As such increasing the number of lags may enable us to better characterize the nature of attentional hold. Due to the rapid presentation of images in the attentional blink task it may be possible that AB can be captured efficiently in lags after lag2 as they reflect 300-500ms timeframes, the same timing thought to reflect maintained attention in the dot probe task. Including additional lags may provide us with increased ability to capture and characterize this form of AB.

Lastly, we were limited in our assessment of reward conditioning in this study due to only collecting this data in a subset of female participants. As such, the relationship between reward conditioning and alcohol AB remains to be fully explored.

Conclusions

Our findings add to a growing body of literature on AB to alcohol cues in nonclinical drinking populations. The development of AB is thought to reflect extensive Pavlovian conditioning and has been shown to be related to addiction severity (Field and Cox 2008; Field et al. 2009b; Franken 2003; Robbins and Ehrman 2004). Our data support previous findings suggesting that social drinkers must meet a minimum level of heavy drinking before demonstrating AB to alcohol related cues (Field et al. 2005b). Specifically, weekly drinking rates under 20 units of alcohol appear insufficient to elicit AB to alcohol cues. The lower drinking rates in this study may have undermined our ability to detect AB here. Moreover, our finding of blink bias in only moderate drinkers driven by decreases in the attentional blink after neutral images, suggest future studies utilize blink paradigms that are better able to distinguish between extended attentional hold and hyper-vigilance of the attention system in heavy drinkers. These data suggest that future research of AB in hazardous social drinkers should focus on levels of high consumption and probe factors that may influence individual differences in AB, such as adolescent binge alcohol exposure, frontal lobe function, and past and current perceptions of alcohol use. Given the inconsistency in AB findings in the literature using cognitive paradigms, direct measures of AB such as eye tracking should be utilized in future studies to better identify and characterize the nature of AB in social binge drinking populations and what role reward conditioning plays, if any, in its development.

Table 2-1. Demographics & Psychometric Measures in Moderate and Heavy Drinkers

Demographics	MD (n=41)	HD (n=38)	Statistic (79)	*p* value
General	Moderate	Heavy		
Gender	24 (16males)	21 (15males)		
Age (yrs)	29.7	22.6	7.06	**.000**
Education (yrs)	17.6	15.7	3.93	**.000**
Family History Density	15%	14%	18.36	.366
Substance Use Measures				
Binge Score	5.3	44.2	-10.49	**.000**
Age of Onset	16.8	15.9	.460	.691
Binge 0-18yrs age	.11	1.9	-3.68	**.002**
Binge 18-21yrs age	.9	4.4	-7.56	**.000**
Adolescent Binge	.9	5.6	-7.11	**.000**
DMQR Social	12.4	19.4	-6.51	**.000**
DMQR Enhance	9.6	17.4	-8.03	**.000**
DMQR Coping	6.9	11.4	-5.83	**.000**
DMQR Conformity	6.4	8.7	-3.01	**.004**
AUDIT Total	2.5	12.9	-11.13	**.000**
AUDIT Consumption	2.1	7.7	-14.12	**.000**
AUDIT Dependence	.1	1.5	-4.91	**.001**
AUDIT Harm	.4	3.6	-6.13	**.000**
Barratt Impulsiveness Scale	61.3	66.6	-2.04	**.046**

Table 2-2. Multiple Regression Analyses: Factors Predicting Cuing Bias

Variable	*B*	*SE B*	*B*
Step 1			
(Constant)	5.921	35.278	
Age	-0.365	1.327	-0.046
Ethnicity	-4.929	5.973	-0.138
Step 2			
(Constant)	-11.908	34.864	
Age	0.470	1.334	0.059
Ethnicity	-4.148	5.729	-0.116
Reward Conditioning	-612.123	298.335	-0.346*

Note: R^2 =.022 for Step 1; Δ R^2= 1.08 for Step 2 $F_{(3,37)}$ = 1.69 p =.187, R^2 = .130;
*p < .05 *B*: beta value; *SE B*: beta value standard error; β: standardized beta; current binge drinking score, binge drinking frequency for 0-18, and 18-21 years of age were also included and did not explain significant variance.

Table 2-3. Multiple Regression Analyses: Factors Predicting Attentional Blink

Variable	*B*	*SE B*	*B*
Step 1			
(Constant)	-0.115	0.086	
Age	0.005	0.003	0.262
Ethnicity	0.020	0.014	0.220
Step 2			
(Constant)	-0.094	0.089	
Age	0.004	0.003	0.215
Ethnicity	0.019	0.015	0.211
Reward Bias Conditioning	0.700	0.757	0.154

Note: $\Delta R^2 = .216$ for Step 1; $\Delta R^2 = .046$ for Step 2; $F_{(6,41)} = 2.074$ $p = .082$, $R^2 = .262$;
B: beta value; *SE B*: beta value standard error; β: standardized beta; current binge drinking score, binge drinking frequency for 0-18, and 18-21 years of age were also included and did not explain significant variance.

Table 2-4. Attentional Bias Tasks and Psychometric Correlations

Psychometric Measures	**Blink Bias Rho (*p*)**			**Cuing Bias Rho (*p*)**		
	All	**HD**	**MD**	**All**	**HD**	**MD**
Barratt	-.067 (.586)	-.024 (.892)	-.029 (.858)	-.054 (.636)	.008 (.962)	-.038 (.814)
Barratt – Attention	-0.205 (.076)	-.136 (.435)	-.125 (.435)	-.036 (.754)	.138 (.408)	-.144 (.369)
Barratt – Motor	-.048 (.681)	.024 (.890)	-.039 (.807)	.010 (.933)	.060 (.719)	.027 (.867)
Barratt – Planning	.054 (.644)	.077 (.662)	153 (.340)	-.080 (.486)	.044 (.794)	-.130 (.418)
AUDIT	**-.277 (.016)**	-.122 (.486)	-.147 (.360)	-.042 (.716)	.101 (.548)	.033 (.837)
AUDIT – Consumption	**-.272 (.017)**	-.196 (.259)	-.075 (.642)	-.017 (.879)	.147 (.378)	.075 (.642)
AUDIT – Dependence	-.178 (.125)	.058 (.742)	-.154 (.335)	-.026 (.821)	.165 (.322)	-.237 (.135)
AUDIT – Harm	**-.235 (.041)**	-.041 (.815)	-.115 (.474)	-.026 (.820)	.059 (.727)	.107 (.504)
DMQ-R – Social	-.083 (.478)	.034 (.845)	.046 (.778)	-.091 (.426)	-.076 (.648)	.044 (.785)
DMQ-R – Coping	-.181 (.119)	.151 (.387)	-.163 (.316)	-.138 (.227)	.091 (.587)	-.157 (.334)
DMQ-R – Enhancement	**-.241 (.037)**	-.150 (.390)	-.111 (.494)	-.015 (.897)	-.006 (.973)	.190 (.240)
DMQ-R –	-.046	.156	.092	-.085	.095	-.150

Conformity	(.697)	(.370)	(.571)	(.460)	(.571)	(.355)
Binge Score	**-.352**	-.200	-.301	.033	.201	.252
	(.002)	(.249)	(.056)	(.771)	(.227)	(.113)
Binges 0-18	**-.230**	-.134	-.178	.092	.198	.068
	(.046)	(.444)	(.267)	(.420)	(.234)	(.674)
Binges 18-21	**-.259**	-.106	-.076	-.004	-.006	.178
	(.024)	(.544)	(.637)	(.974)	(.972)	(.266)

Bold values= $p<.05$

Figure 2-1

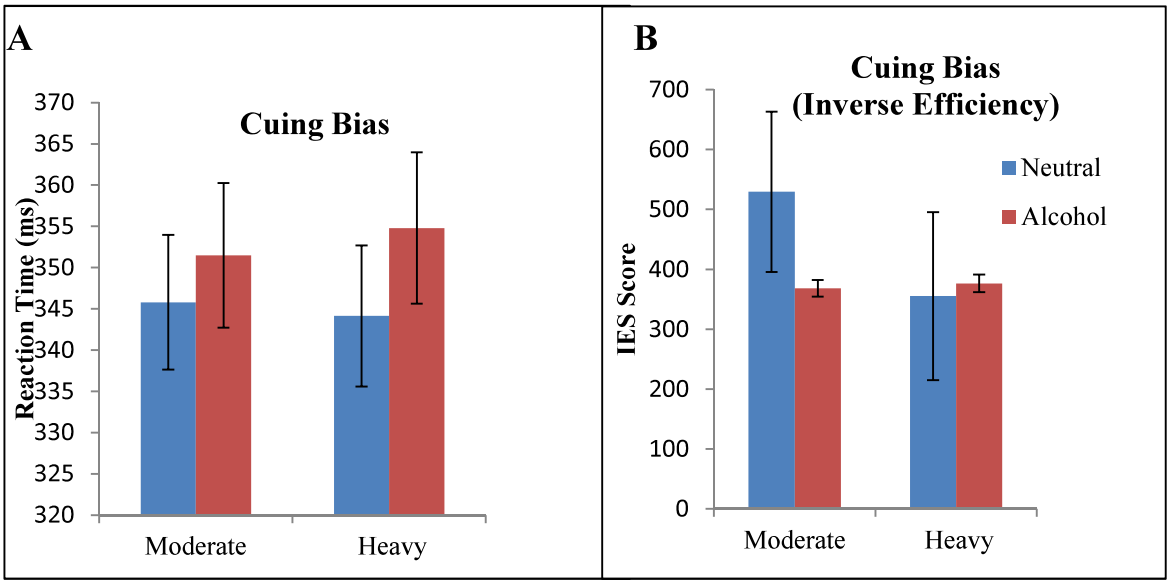

Figure 2-1. Dot Probe Task: Differences in attentional bias to alcohol cues between the moderate and heavy drinking groups. Average Reaction times identifying a target after presentation of alcohol-related or neutral images (spatial cuing). a. No significant group × cue interaction was present (MD b. Using inverse efficiency, we did not detect significant group × cue interaction was present). Error bars reflect the within-subjects SEM.

Figure 2-2.

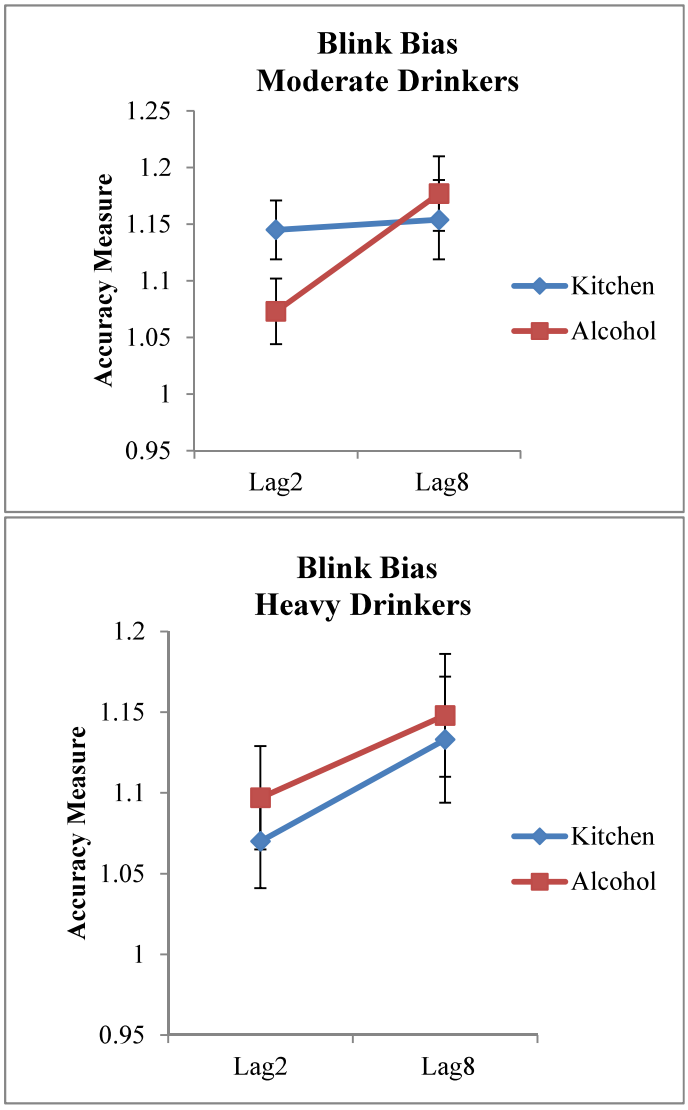

Figure 2-2. Attentional Blink Task: Moderate drinkers exhibited greater AB alcohol cues than did heavy drinkers. Accuracy identifying a target after presentation of an alcohol-related or neutral distractor. Targets appeared either 2 lags or 8 lags after the distractor. Moderate drinkers exhibited a significant blink bias with lower detection rates of the target when it was 2 lags after an alcohol related distractor compared to lag 8. Heavy drinkers did not exhibit this bias towards in the presence of alcohol. Error bars reflect the within-subjects SEM.

CHAPTER 3:

ASSOCIATION BETWEEN ADOLESCENT BINGE DRINKING AND SENSITIVITY TO REWARD CONDITIONING IN FEMALES

Introduction

Reactivity to addiction related cues has been widely investigated, with a subset of this work focused on attention effects of such cues. For example, presentation of addiction related cues in a laboratory setting can reveal an excess allocation of attention to these cues. This excess allocation of attention is termed attentional bias (AB) and has been reported in a wide variety of addictions, including opiates (Liu et al. 2008; Lubman et al. 2000; Marissen et al. 2006), nicotine (Bradley et al. 2004; Bradley et al. 2003; Chanon et al. 2010; Mogg et al. 2003; Munafo et al. 2005; Waters et al. 2003), cocaine (Copersino et al. 2004; Ersche et al. 2010; Goldstein et al. 2009; Hester et al. 2006; Liu et al. 2011), and alcohol (Bruce and Jones 2004; Cox et al. 2002; Field et al. 2004; Ryan 2002; Sharma et al. 2001; Townshend and Duka 2001; Wiers et al. 2011). Physiological and behavioral reactions to drug related cues have also been correlated with drug use (Robbins et al. 1999; Tapert et al. 2004), craving (Attwood et al. 2008; Monti et al. 2000), treatment outcome (Garland et al. 2010), and relapse (Marissen et al. 2006). In addition to these clinical links, AB to alcohol cues has also been detected among heavy social drinkers (Bruce and Jones 2004; Field et al. 2005b; Melaugh McAteer et al. 2015; Townshend and Duka 2001). AB to addiction cues is thought to result from Pavlovian conditioning, whereby the repeated pairing of addiction related stimuli and reward, results in the attribution of incentive salience to alcohol cues (Berridge 2004; Berridge and Robinson 1998; Uslaner et al. 2006). Such AB is thought to reflect basic reward conditioning processes (Anderson 2016), and thus be akin to the conditioned orienting responses observed in preclinical Pavlovian conditioning paradigms, e.g. sign-tracking (Parker and Gaffan 1998; Robinson and Flagel 2009; Uslaner et al. 2008). While the preclinical literature suggests marked

individual differences in the tendency to establish sign-tracking responses to reward conditioned cues (Meyer et al. 2012; Robinson and Flagel 2009; Robinson et al. 2014), and that a tendency toward greater sensitivity to reward conditioning is a risk factor for addiction in animal models (Flagel et al. 2008; Waselus et al. 2013), individual differences in susceptibility to reward conditioning has been little explored in human subjects.

Although studies with humans have found decreased responsiveness to monetary reward associated with addiction (Goldstein et al. 2007; Madden et al. 1997; Parvaz et al. 2012), greater sensitivity to reward conditioning has been observed in abstinent opiate users (Anderson et al. 2013). It is not yet known whether heightened sensitivity to reward conditioning occurs in other forms of addiction or substance abuse, particularly whether this sensitivity may be present at early stages of substance abuse. Studies of reward conditioning in both addicted and substance abusing populations may shed light on the underlying bases of AB. To date there has been no investigation of generalized sensitivity to reward conditioning as a function of drinking behavior. The reported presence of AB to alcohol cues in social drinking populations may reflect ordinary conditioning by alcohol reward, but could alternatively be a product of heightened reward conditioning due to their alcohol exposure and drinking patterns. To begin addressing this question, here we assessed sensitivity to general reward conditioning in heavy binge and light social drinkers using a monetary reward conditioning task. Given evidence for heightened sign-tracking effects in alcohol exposed female rats (Madayag et al. 2017), we chose to test females only for the present study. Moreover, numerous lines of evidence indicate that adolescent binge alcohol exposure plays an important role in the development of hazardous drinking behavior and AUDs in adulthood. For example, in preclinical studies, exposure to binge-like levels of ethanol during adolescence led to persistent neurobiological changes in key reward processing regions and increased risk taking behavior in adulthood (Boutros et al. 2014; Crews et al. 2016; Lerma-Cabrera et al. 2013; Spoelder et al. 2015; Vargas et al. 2014; Vetreno and Crews 2015). Furthermore binge drinking in adolescence predicts risk for alcoholism in adulthood (Viner and Taylor 2007). Thus, we also evaluated whether adolescent binge

alcohol exposure predicted sensitivity to reward conditioning in this sample, independent of current alcohol use.

Methods

Participants

Forty-one healthy female participants (ages 18-40 years; mean = 25.7) were recruited from the University of North Carolina, Chapel Hill (UNC) campus and surrounding communities. To include a broad spectrum of alcohol use, we recruited participants in two groups based on their alcohol drinking patterns: heavy, binge drinkers (HD; *n*=19) and moderate, social drinkers (MD; *n*=22). HD participants self-reported ≥7 alcoholic drinks/wk, and ≥12 binge episodes (≥4 drinks/2hrs) in the past 12 mos. MD participants self-reported <7 alcoholic drinks/wk, <10 lifetime binge episodes, and no binge episodes in the past 12 mos. Participants had no current or past history of neurological or psychiatric diagnoses. Other exclusion criteria were use of psychoactive drug or medication use (excepting moderate alcohol or caffeine intake), a history of treatment for a substance use disorder or a lifetime history of alcohol or other drug dependence based on a structured clinical interview using DSM-IV criteria (Sheehan et al., 1998). All participants were native English speakers, right-handed, and had at least a high school education (or equivalent). Participants were screened for drug or alcohol use on the day of the scan via breathalyzer test (FC-10, Lifeloc Inc., Wheat Ridge, CO) and urine drug screen. (Biotechnostix, Inc., Markham, ON). Participants gave written, informed consent, as approved by the UNC Office of Human Research Ethics. Participants received monetary compensation for participation.

Behavioral Inventories

Participants completed standardized questionnaires to capture demographic information, and to identify factors that may account for individual differences in sensitivity to reward conditioning. We quantified past and current drug and alcohol use and drinking motivations with the Alcohol Use Questionnaire (AUQ) (Townshend and Duka 2002), Carolina Alcohol Use Patterns Questionnaire (CAUPQ), Drug Use Screening Inventory-Domain I (DUSI-I; Tarter 1990), the Alcohol Use and Disorders Inventory Test (AUDIT; Saunders et al. 1993), and Coopers Drinking Motivations Scale-

Revised (DMQ-R; Cooper 1994). We used the NIAAA definition of binge drinking for females: 4 or more drinks in a 2 hour period. We used the AUQ binge drinking score (BDS), which is based on the speed of drinking, the frequency of intoxication in the past 6 months, and the percentage of time the individual becomes intoxicated when drinking, rather than a purely alcohol intake quantity measure. The CAUPQ assesses the age of drinking onset, and the frequency of binge drinking; three questions on the CAUPQ were used to assess binge drinking before age of 18, binge drinking between 18-21years, and current binge drinking frequency. Responses range from "Never" to "More than once a week" and are coded numerically from 0-6 (see Appendix). To assess the effect of familial history of alcohol abuse we administered the Family Tree Questionnaire (Mann et al. 1985). Familial alcoholism was quantified by dividing the number of possible and definite problem drinkers in the immediate family by all immediate family members. Socioeconomic status was determined by reported occupation and highest level of completed education (Hollingshead 1975). Impulsivity was measured by the Barrett Impulsiveness Scale (BIS-11; Patton et al. 1995).

Reward Conditioning Task

We assessed each participant's reward conditioning sensitivity using a value driven attention capture task identical to that used in (Anderson et al. 2013), programmed in Matlab (The MathWorks Inc., Natick, MA, 2000) using the Psychtoolbox-3 extensions (Brainard 1997; Fig. 1). Participants completed the task while seated at a computer in a darkened room. A visual search task was presented on a color LCD screen. The task was separated into two phases, a reward-conditioning phase, and a test phase. For the conditioning phase, each trial began with a fixation display for 400, 500, or 600 ms (randomly determined), followed by a visual search for a target circle among five non-target circles. The search array remained on the screen until a response was made, up to a limit of 1200 ms. Following the search array, a blank screen appeared for 1000 ms, and reward feedback was then displayed for 1500 ms, followed by a blank 1000 ms inter-trial-interval (ITI). The target circles were unpredictably red or green, and participants were rewarded for correctly reporting (via keypress) the orientation of a white bar (horizontal or vertical) appearing within the target circle. Participants received feedback in each trial (n=240) during

the conditioning phase. One of the two target colors yielded a reward of 10¢ in 80% of trials, and 2¢ in the remaining 20% of trials (high-reward target); these contingencies were reversed for the other color target (low-reward target). Incorrect or omitted responses yielded 0¢. The high-reward color was red for half the participants and green for the other half. Participants completed 40 practice trials prior to beginning the task.

The test phase was structured similarly to the training phase, with a few keys differences. First, the search array included a target shape (diamond) among 5 non-target shapes (circles); participants disregarded shape color, and instead reported the orientation of the bar within the target shape. Second, feedback after the search array only informed participants if their response was correct (✓) or incorrect (×); no monetary rewards were given. Third, the search array appeared for up to 1500 ms, followed by the feedback screen for 1000 ms, and a blank ITI screen for 500 ms. Critically, 25% of trials included a red circle in the search array, 25% included a green circle in the search array, and the remaining 50% lacked any reward-conditioned distractor shapes. Both accuracy and reaction time (RT) were collected for each trial.

Statistical Analysis

For the reward conditioning task, the primary dependent measure of interest was the difference in RT during the test phase between trials with a high reward distractor present (RT_{High}) and trials with no reward distractor present ($RT_{Absent)}$ (Anderson et al. 2011b). This difference was calculated using the formula: RT_{High}-$RT_{Absent,}$ such that larger values represent greater reward conditioning. Only RTs from correct trials were included in our analyses. We also excluded trials in which the RT was >3 standard deviations longer than the individual's mean RT for that condition, or <200ms. To assess which variables had the greatest predictive value in estimating reward conditioning, we used multiple linear regression analyses in SPSS. For each multiple regression analysis, we entered variables in a stepwise manner in the following order: block 1: ethnicity, age, and years of education; block 2: AUQ BDS, BDS 0-18yo, BDS 18-21yo. To assess the significance of between group differences, we used unpaired, two-tailed *t* tests for continuous measures and χ^2 tests for categorical measures.

Results

Demographic, Psychometric Data

Despite efforts to match our recruitment groups, they differed significantly in terms of demographics, reflecting younger age, fewer years of education, and a lower proportion of non-white participants in our HD group. Therefore, we controlled for these variables in all subsequent analyses. Groups did not differ in terms of familial alcoholism or socioeconomic status. Measures of impulsivity (BIS) did not differ significantly between groups. The groups did differ on all alcohol use measures, including drinking motivations, except for age at first drink (Table 3-1).

Reward Conditioning Task Performance

We first tested for differences in acquisition of reward conditioning between the MD and HD groups. Using a 2 × 2 ANOVA (Reward Type × Group), we compared RT on low and high reward color trials during the training phase of the task. We detected no significant main effects of reward type ($F_{(1, 39)}$ = 0.372, p=.545), or group ($F_{(1, 39)}$ =1.01, p=.321), nor any reward type × group interaction ($F_{(1,39)}$= 2.19, p=.147; Fig. 2). We next tested for group differences in the test phase with a 2 × 2 ANOVA (Distractor type × Group), and found no significant main effects of distractor type (high reward or absent; $F_{(1, 38)}$ =.003, p =.959), or group ($F_{(1, 38)}$ =.733, p =.397), and no significant Distractor type × group interaction ($F_{(1, 38)}$ =.000, p=.998; Fig. 3A). We also calculated reward bias during the test phase according to the following formula: RT_{High}-RT_{Absent}, and found no significant difference in reward bias between groups (t=.681, p=.504; Fig. 3B).

Reward Conditioning and Adolescent Binge Drinking

Given our finding that current drinking behavior did not predict differences in sensitivity to reward conditioning, we next probed whether binge alcohol exposure in adolescence predicted such sensitivity. To test the relationship between adolescent binge drinking and sensitivity to reward conditioning, we used two self-reported measures of binge drinking prior to age 21: frequency of binge drinking before age 18, and between 18-21 years (see Methods) as predictors for reward conditioning. Using multiple linear regression, we also controlled for demographic variables, and for current binge drinking behavior (Table

2). Multiple regression analysis indicates that the sole factor predicting reward conditioning in this sample is adolescent binge drinking frequency before age 18 ($F_{(4, 35)} = 2.678$, $p = .048$; Table 2).

Discussion

Although amplified reward conditioning has been reported in heroin addicts, and in animal models of addiction or of adolescent alcohol exposure, it was unknown whether increased sensitivity to reward conditioning occurs in other substance abusing populations, particularly those at the less severe end of the spectrum, or whether such sensitivity varies with intensity of adolescent alcohol exposure. Here we quantified the magnitude of reward conditioning in heavy binge and light social drinkers with a range of adolescent alcohol exposure using a monetary reward conditioning task. To our surprise, we did not detect a statistically significant difference in reward conditioning between heavy, binge drinkers and light to moderate drinkers. In contrast, we did detect a significant relationship between frequency of adolescence binge drinking and reward conditioning. Specifically, a greater frequency of binge drinking before age 18 predicted significantly greater expression of reward conditioning, independent of current binge alcohol use.

Increased reward conditioning, and adolescent alcohol: possible mediators

A simple interpretation of these findings is that adolescent binge drinking heightens sensitivity to reward. However, that interpretation is challenged by data showing that blunted reward sensitivity to non-drug related rewards evolves over the course of addiction (Freeman et al. 2015; Goldstein et al. 2007; Lubman et al. 2009; Parvaz et al. 2012; Volkow and Morales 2015; Volkow et al. 2010). Thus, it seems unlikely that this form of substance abuse (binge drinking) increased reward sensitivity. Instead, sensitivity to reward conditioning has been previously found to negatively correlate with working memory capacity and to positively correlate with impulsivity (Anderson et al. 2013; Yantis et al. 2012). Moreover similar working memory and reward conditioning relationships are present in other clinical disorders thought to share similar neurocognitive features of addiction (Coppin et al. 2014; Gearhardt et al. 2011; Smith and Robbins 2012). The prefrontal cortex plays a critical role in processing task relevant and ultimately in ignoring task irrelevant information (Otis et al. 2017; Rushworth et al. 2005). Moreover,

individuals with substance use disorders who show decreased ability to ignore task irrelevant stimuli have decreased neural activity in the prefrontal cortex (Hester and Luijten 2014; Roberts and Garavan 2013). Taken together, these data suggest that heightened reward conditioning may result from an inability to ignore irrelevant, previously rewarded stimuli, an executive impairment suggesting frontal dysfunction.

Adolescent binge alcohol and frontal impairment

The idea that frontal impairment might underlie enhanced reward conditioning associated with more frequent adolescent binge-drinking is consistent with a variety of evidence demonstrating that the adolescent prefrontal cortex is particularly vulnerable to the damaging effects of alcohol (Crews et al. 2007). Models of adolescent binge drinking in animals have revealed significant reductions in neurogenesis (Vetreno and Crews 2015) and increased risk taking behavior and alcohol consumption in adulthood (Boutros et al. 2014; Crews et al. 2016). Adolescence is a period in which significant changes to reward neurocircuitry occur (Luciana 2013; Wahlstrom et al. 2010), and exposure to alcohol during this period is associated with significant changes in brain activity (Cservenka et al. 2015). Thus, it seems likely that frontal damage mediates the relationship reported here between adolescent binge drinking frequency and sensitivity to reward conditioning. Future studies that include measures of frontal function are needed to test this hypothesis.

Sensitivity to reward conditioning: sign-tracking?

Individual differences in reward conditioning are often seen in preclinical studies. Animals can be classified as either sign- or goal-trackers (Robinson and Flagel 2009). This classification is determined by the animal's behavior after undergoing Pavlovian conditioning. Sign-trackers more readily approach the cue paired with reward whereas goal-trackers approach the reward delivery mechanism, rather than the cue. While these individual differences occur naturally, exposure to alcohol (Spoelder et al. 2015; Srey et al. 2015), nicotine (Palmatier et al. 2013; Stringfield et al. 2017), heroin (Peters and De Vries 2014), or cocaine (Uslaner et al. 2006) can all promote sign-tracking behavior. Most relevant to the present findings, adolescent binge-like drinking increases sign-tracking behavior in adult animals (Madayag et al. 2017; McClory and Spear 2014).

Study Limitations

One limitation of our study was the inclusion of only females, so we may not generalize these findings to males, particularly as recent studies in rodents have shown sex-specific effects in reward conditioning, although findings in the literature conflict (Madayag et al. 2017) (McClory and Spear 2014). Future research specifically comparing male and females are needed to shed light on whether there are sex effects on reward conditioning. Another limitation is the lack of effective reward conditioning across the sample as a whole. This finding conflicts with prior studies showing robust reward conditioning in healthy controls ((Anderson et al. 2016b; Anderson et al. 2017; Anderson et al. 2011b), HIV positive participants (Anderson et al. 2016a), and heroin addicts (Anderson et al. 2013). Our sample size was larger than many of these prior studies, suggesting that this study was not simply underpowered (Anderson et al. 2013; Anderson et al. 2017). A prior study also reported that more impulsive participants showed more reward conditioning (Anderson et al. 2013), and while our sample did show similar levels of impulsivity to those in that study, we did not replicate that finding in this sample. One difference between our study and those published previously is that our participants were paid a base rate for participation in addition to the bonus amounts of money earned in the task. This procedural difference may have rendered the monetary reward in the conditioning task less valuable, and thus less effective in conditioning reward-paired stimuli. Finally, retroactive reporting of adolescent binge drinking may be unreliable. Therefore, future longitudinal studies are needed to more accurately assess the relationship between adolescent binge drinking and susceptibility to reward conditioning.

Conclusions

Our findings support evidence from the rodent literature that adolescent binge drinking heightens Pavlovian reward conditioning. Our data also add to mounting evidence that adolescence is a time of particular vulnerability to the effects of alcohol, leading to persistent neural and behavioral sequelae (Boutros et al. 2014; Crews and Boettiger 2009; Crews et al. 2016; Liu and Crews 2015; Vetreno and Crews 2015). Specifically, we find that more frequent binge drinking before age 18 is associated with heighted susceptibility to reward conditioning in females. This suggests persistent effects of adolescent

binge alcohol on the circuits engaged in our attention task, including circuits that process reward cues. Given that adolescent binge drinking predicts risk for AUD in adulthood (Viner and Taylor 2007), our findings provide a platform for brain-based investigations that may help identify AUD risk biomarkers.

Table 3-1. Demographics

Demographics	HD (*n*=22)	MD (*n*=22)	Statistic (44)	*p* value
General				
Age (yrs)	21.3	29.7	6.634	.000
Education (yrs)	15.6	17.4	3.292	.002
Ethnicity (% non-white)	23	41	11.65†	.050†
FTQ Density	15%	16%	.217	.829
Socioeconomic Status	43.2	47.4	4.92	.177
Substance Use Measures				
Binge Score	35.6	5.5	-8.503	.000
Age of Onset (yrs)	16.4	16.8	.460	.649
Binge Frequency Score 0-18 yrs age	1.6	.1	-3.680	.000
Binge Frequency Score 18-21 yrs age	4.1	.8	-7.568	.000
DMQ-R Social	18.7	12	-4.439	.000
DMQ-R Enhancement	16.2	9.1	-5.216	.000
DMQ-R Coping	11	7.3	-3.377	.002
DMQ-R Conformity	8.1	6.1	-2.449	.019
AUDIT Total	10.5	2.5	-9.151	.000
AUDIT-Consumption	6.7	2.0	-11.573	.000
AUDIT-Dependence	1.1	.1	-3.742	.001
AUDIT-Harm	2.7	.5	-5.269	.000
Barratt Impulsiveness Scale	62.1	63.1	.348	.730

Reported *p* values represent the results of unpaired two-tailed comparisons between groups, except where noted. FTQ, Family Tree Questionnaire; HD, heavy binge drinkers; MD, moderate light drinkers; DMQ-R, Cooper's Drinking Motivation Scale-Revised; AUDIT, Alcohol Use Disorders Identification Test. †represents results of a $_{X}^{2}$ test.

Table 3-2 Multiple Regression Analyses: Factors Predicting Reward Conditioning

Variable	*B*	*SE B*	*B*
Step 1			
Constant	.020	.037	
Ethnicity	-.001	.003	-.059
Age	.002	.001	.418*
Education	-.004	.003	-.267
Step 2			
Constant	.001	.037	
Ethnicity	-.002	.003	-.107
Age	.002	.001	.537**
Education	-.004	.002	-.266
Binge Drinking Frequency 0-18yo	.007	.003	.340*

Note: R^2 =.141 for Step 1; ΔR^2= .099 for Step 2. *$p < .05$, **$p < .01$

$F_{(4,35)} = 2.678$, p =.048, R^2 = .240

B: beta value; *SE B*: beta value standard error; β: standardized beta; current binge drinking score, and binge drinking frequency for 18-21 years of age were also included and did not explain significant variance.

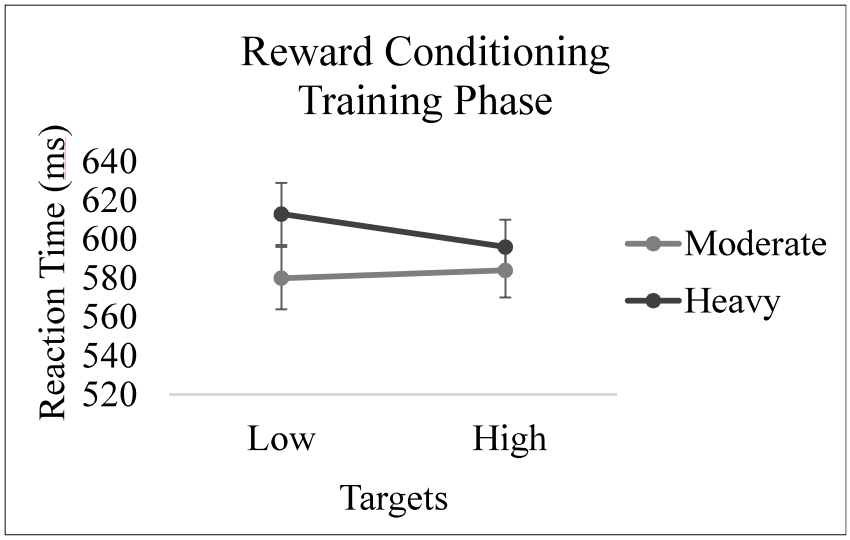

Figure 3-1. Reward Conditioning Training Phase: Effects of reward type. Reaction time to identify high- and low-reward targets during the training phase of the task (Fig. 2). Faster reaction times to high-reward targets indicate learning of the reward contingencies. Error bars reflect the within-subjects SEM.

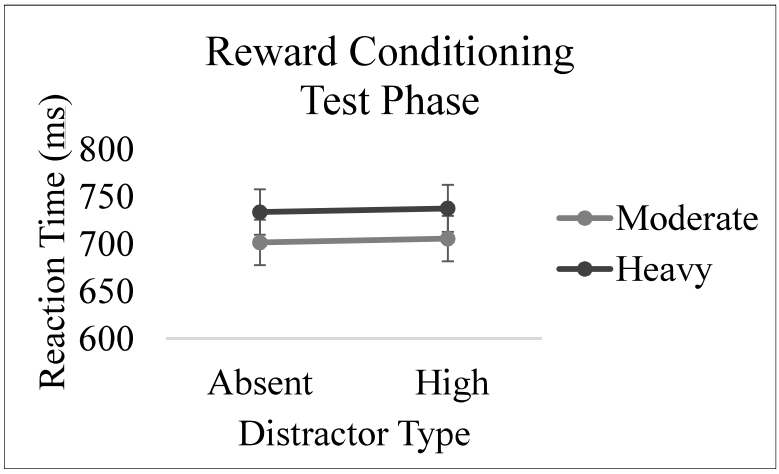

Figure 3-2a. Reward Conditioning Test Phase: Effects of Distractor Type. Reward conditioning effects during the Test phase. A) Reaction time across distractor conditions during the test phase. Error bars reflect the within-subjects standard error of the mean. B) Average reward bias (RT_{High}-RT_{Absent}) for each group during the Test phase. RT, reaction time. Error bars reflect SEM.

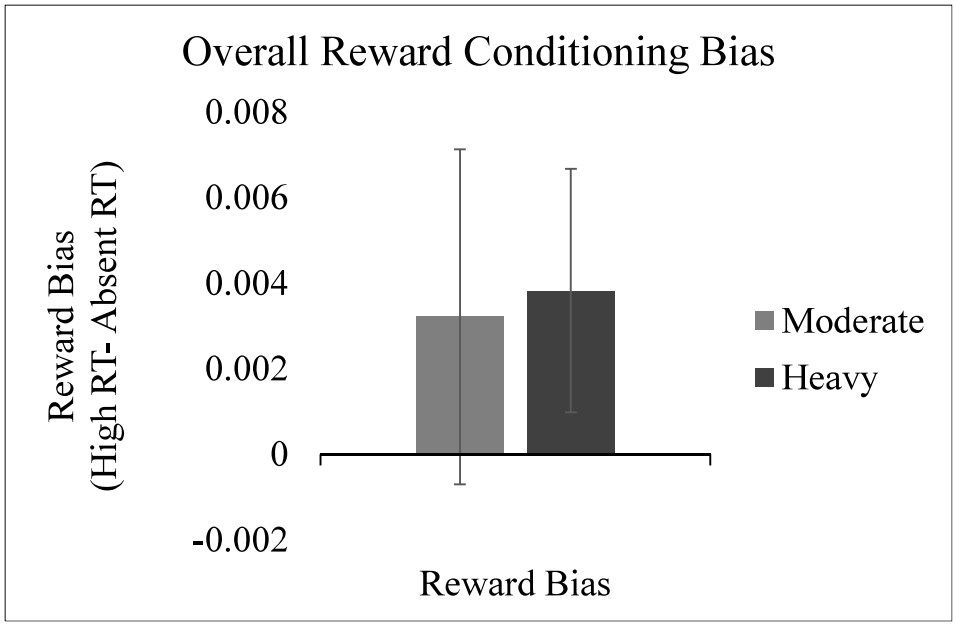

Figure 3-2b. Reward Conditioning Test Phase: Bias Measurement. Reward conditioning effects during the Test phase. A) Reaction time across distractor conditions during the test phase. Error bars reflect the within-subjects standard error of the mean. B) Average reward bias (RT_{High}-RT_{Absent}) for each group during the Test phase. RT, reaction time. Error bars reflect SEM.

CHAPTER 4:

EFFECT OF ACUTE DOPAMINE PRECURSOR DEPLETION ON FRONTOLIMBIC FUNCTIONAL CONNECTIVITY AND ATTENTIONAL BIAS TO ALCOHOL CUES: MODERATION BY BINGE DRINKING HISTORY

Introduction

Attentional bias (AB) towards alcohol-related stimuli is a common finding in AUDs, often with the strength of AB predicting relapse risk (Cox et al. 2002; Marissen et al. 2006; Waters et al. 2003), alcohol craving (Field et al. 2005b), and future alcohol drinking (Field and Eastwood 2005). The development of AB to addiction-cues is thought to reflect Pavlovian learning, resulting in drug reward-predicting cues eventually acquiring the capacity to initiate drug seeking and consumption (Robinson and Berridge 1993; Tiffany 1990). Decreased response to natural rewards in people with SUDs have been reported and is thought to reflect an overall "hijacking" of the reward system by addiction cues in states of craving, withdrawal, and early abstinence (Goldstein and Volkow 2011). However, recent data show that AB to non-drug rewards is heightened in abstinent addicts, suggesting that substance misuse more generally associates with heightened sensitivity to reward conditioning (Anderson et al. 2013; Bjork et al. 2012). The relationship between alcohol-related AB and general reward AB is unknown.

Despite the prevalence and apparent clinical relevance of AB, the neural bases of this phenomenon remain unclear, both in terms of neural circuit dysfunction and neuromodulation. With the help of neuroimaging, researchers have begun to probe the neural correlates of addiction AB in humans. For example, in a functional magnetic resonance (fMRI) study of smokers, AB toward smoking cues positively correlated with activation in response to these cues in the dorsolateral prefrontal cortex (DLPFC), putamen, posterior cingulate gyrus (PCC), and primary motor cortex (Kang et al. 2012). In another study of smoking related AB, using an addiction Stroop task, increases in RT to identify the color in which smoking-related words were displayed was associated with increased activity in the insula,

amygdala, hippocampus, parahippocampal gyrus in active smokers (Janes et al. 2010). To our knowledge only one fMRI study has directly assessed alcohol AB. Testing recovering alcoholics using a dot probe task, researchers identified positive correlations between alcohol AB and brain activations in the inferior frontal gyrus (IFG), insula, precentral gyrus, anterior cingulate cortex (AnCC), the caudate, and putamen (Vollstädt-Klein et al. 2012). These findings suggest a potentially strong role of the frontolimbic in AB to addiction related cues, and provide support for further investigations into the neural mechanisms of addiction AB.

Many aspects of human addiction research have been based on and supported by the findings in animal models. While AB is difficult to model in rodents, much is known about Pavlovian conditioned responses (CRs) to reward-predictive cues. For example, mesolimbic dopamine projections from the ventral tegmental are (VTA) to the nucleus accumbens (NAc) play a critical role in both Pavlovian conditioning and expression of CRs (Di Ciano et al. 2001; Parkinson et al. 2002). In addition, fast dopamine release events (dopamine transients) commence at the onset of a conditioned cue (Day et al. 2007; Flagel et al. 2011). Pavlovian CRs to alcohol cues in rodents have provided a model of alcohol AB that allows direct measurements and mechanistic manipulations of the neural circuitry that underlies AB. Evidence from these rodent studies indicates that dopaminergic pathways play a key role in mediating response to alcohol related cues (Löf et al. 2010; Shnitko and Robinson 2015; Sparks et al. 2014). Moreover, in studies of human participants, the use of acute dopamine depletion provides additional support of the role of dopamine in response to addiction related cues (Barrett et al. 2008; Hitsman et al. 2008) and cognitive functions vulnerable to addiction (Kelm and Boettiger 2013). Taken together, these findings highlight dopamine's important role in response to addiction related cues.

While the role of dopamine and dopaminergic pathways in reactivity to addiction related cues is clear, and this reactivity appears to mirror AB in humans, key questions remain unanswered regarding the neural circuit bases of alcohol AB. For example, whether diminishing dopamine signaling reduces alcohol AB and alters brain functional connectivity. These unanswered questions can be explored using dietary dopamine depletion methods in human subjects. The precursor-deficient amino acid (AA) beverage

(dopamine depletion) method has been safely used for many years, and its effects in the brain are well established (Moja et al. 1996; Sheehan et al. 1996). Consuming AA beverages induces protein synthesis, and if the beverage lacks the AA precursors for dopamine, phenylalanine (P) and tyrosine (T), it will deplete P/T reserves and decrease brain P/T concentrations (Booij et al. 2003), and PET studies showing a corresponding decrease in striatal dopamine levels (Leyton et al. 2004; Montgomery et al. 2003). This method has been shown to reduce AB toward smoking cues in smokers (Hitsman et al. 2008). Thus, the dopamine depletion method may aid in investigating the neural circuit bases of alcohol AB.

An *a priori* neural circuit of interest that may be involved in this process includes the VTA, and key PFC regions, which are anatomically connected to the VTA and play essential roles in motivated behaviors (Berridge and Robinson 1998; Goto and Grace 2005; Miller and Cohen 2001; Schultz 1998; Watanabe and Sakagami 2007; Wise 2004). However, the direction of reward cue information through this circuit is not yet resolved. Hypotheses based largely on primate studies suggest that motivationally significant signals first enter this circuit at the VTA, which sends signals to the PFC and NAc to trigger orienting toward and seeking of reward (Bromberg-Martin et al. 2010). However, the PFC projects to the VTA neurons (Frankle et al. 2006; Sesack and Pickel 1992; Williams and Goldman-Rakic 1998), and PFC stimulation can modulate dopamine neuron firing (Gao et al. 2007; Gariano and Groves 1988; Svensson and Tung 1989), and transcranial magnetic stimulation of the dorsolateral PFC (DLPFC) induces dopamine release in the striatum (Ko et al. 2008; Pogarell et al. 2006). Moreover, recent human neuroimaging data indicate that reward information enters the circuit at the DLPFC, which in turn modulates the VTA and NAc (Ballard et al. 2011). As alcohol AB reflects acquired motivational significance of previously neutral cues, we hypothesized that alcohol AB involves altered connectivity among these brain areas. Furthermore, we hypothesized that acute dopamine depletion would reduce AB to alcohol cues and to reward-conditioned cues, and would do so in proportion to changes in the functional connectivity of PFC subregions (OFC, DLPFC, AnCC, IFG, fronto-insular cortex (FIC) with the VTA. Finally, we hypothesized that these effects would be magnified in heavy binge drinkers. To test these hypotheses, we recruited light to moderate drinkers (n=19) and heavy, binge drinkers (n=15). We

measured functional connectivity between frontolimbic regions of interest (ROI) from brief, resting-state fMRI scans collected immediately before behavioral AB tests. These data were collected under two conditions for each participant: after consuming a P/T depleted AA beverage, and after consuming a control AA beverage, with a double-blind, counter-balanced design.

Methods

Participants

34 healthy male participants (ages 22-40 years; mean = 26.3) were recruited from the University of North Carolina, Chapel Hill (UNC) campus and surrounding communities. To include a broad spectrum of alcohol use, we recruited participants in two groups based on their self-reported alcohol drinking patterns: heavy, binge drinkers (HD; *n*=15) and moderate, social drinkers (MD; *n*=19). HD participants self-reported ≥14 alcoholic drinks/week and ≥12 binge episodes (≥5 drinks/2hrs for males in the past 12 months. MD participants self-reported <14 alcoholic drinks/week, <10 lifetime binge episodes, and no binge episodes in the past 12 months. Participants had no current or past history of neurological or psychiatric diagnoses, no contradictions for MRI or the amino acid depletion manipulation. Additional exclusion criteria were the use of psychoactive drugs or (including medications), excepting moderate alcohol or caffeine intake, a history of treatment for a substance use disorder, or a lifetime history of substance use disorder based on a structured clinical interview using DSM-IV criteria (Sheehan et al., 1998). For the HD group only, meeting current or past criteria for an alcohol use disorder was not exclusionary. All participants were native English speakers, right-handed, and had at least a high school education (or equivalent). Participants were screened for drug or alcohol use on the day of each testing session via breathalyzer test (FC-10, Lifeloc Inc., Wheat Ridge, CO) and urine drug screen. (Biotechnostix, Inc., Markham, ON). Participants gave written, informed consent, as approved by the UNC Office of Human Research Ethics. Participants received monetary compensation for participation.

General Procedure

This study was a double blinded, within subjects design consisting of two laboratory visits lasting approximately 8hrs. Each laboratory session was identical and began with urine, alcohol and health

screening. Following screening, participants' blood pressure was measured and saliva and initial blood samples were collected. Immediately after the blood draw, the dopamine depletion beverage (see "Dopamine Depletion Procedure") was administered and participants had up to 30mins to consume the beverage. After beverage consumption, participants had 4-5 hours of free time to complete a battery of standard questionnaires (see "Behavioral Inventories"), followed by a resting state functional connectivity (rs-fcMRI) scan. Finally, after the rs-fcMRI, behavioral tasks were completed (see "Behavioral Tasks"). Participants were dismissed after being offered a high protein snack, and were compensated for participation at the end of the second visit.

Dopamine Depletion Procedure

Subjects followed a low protein diet (<20 g) for 24 hrs prior to each test session and fasted from midnight until session onset (~8 A.M.). The depletion procedure began with participant's providing a written account of their diet in the last 24hrs. Following completion of the diet sheet, researchers administered an amino acid (AA) beverage deficient in the dopamine precursors, phenylalanine (P) and tyrosine (T), to initiate the acute dopamine depletion process (Karobath and Baldessarini 1972). The AA mixes were prepared by SHS International (Liverpool, UK). The balanced/control beverage consisted of (g): alanine, 4.1; arginine, 3.7; cysteine, 2.0; glycine, 2.4; histidine, 2.4; isoleucine, 6; leucine, 10.1; lysine, 6.7; methionine, 2.3; phenylalanine, 4.3; proline, 9,2; serine, 5.2; threonine, 4.9; tryptophan, 3.0; tyrosine, 5.2; and valine, 6.7. The P/T-depleted beverage had the same composition except that P and T were omitted. Beverages were mixed with cold water and a lemon-lime flavor packet from Nutricia (Gaithersburg, MD) in an 11 oz sterile container.

Behavioral Inventories

Participants completed standardized questionnaires to capture demographic information, and to quantify factors that may account for individual differences in attentional bias to alcohol, sensitivity to reward conditioning, or brain connectivity. We quantified past and current drug and alcohol use with the Alcohol Use Questionnaire (AUQ; Townshend and Duka 2002), the Carolina Alcohol Use Patterns Questionnaire (CAUPQ; see Appendix), the Drug Use Screening Inventory-Domain I (DUSI-I; Tarter

1990), the Alcohol Use and Disorders Inventory Test (AUDIT; Saunders et al. 1993), and drinking motivations with Coopers Drinking Motivations Scale-Revised (DMQ-r; Cooper 1994). We used the NIAAA definition of binge drinking for males: 5 or more drinks in a 2 hour period (National Institute on Alcohol Abuse and Alcoholism, 2017). We also used a more refined measure of binge drinking, the AUQ binge drinking score (BDS), which is based on the speed of drinking, the frequency of intoxication in the past 6 months, and the percentage of time the individual becomes intoxicated when drinking, rather than a purely alcohol intake quantity measure (Townshend and Duka 2002). The CAUPQ assesses the age of drinking onset, and the frequency of binge drinking. Binge drinking frequency was assessed in three questions on the CAUPQ, addressing binge drinking before age of 18, binge drinking between 18-21 years, and current binge drinking frequency. Responses range from "Never" to "More than once a week," and are coded numerically from 0-6 (see Appendix). To assess the effect of familial history of alcohol abuse we administered the Family Tree Questionnaire (Mann et al. 1985). Impulsivity was measured by the Barrett Impulsivity Scale (BIS-11; Barratt 1994) and anxiety and stress was assessed by the DASS (citation (Lovibond and Lovibond 1993)).

Resting State Functional Connectivity

We acquired continuous whole-brain blood oxygenation level dependent (BOLD) signal resting-state fMRI data as 243 T2*-weighted images (EPI) on a Siemens 3T Prisma magnetic resonance imaging scanner equipped with a TEM send-receive radio frequency (RF) head coil, using a 1-shot gradient-echo EPI pulse sequence. Acquisition parameters were: TR=2s, TE=25ms, flip angle=50°, 35 slices tilted at 30° from horizontal; FoV=192×192mm; voxel size=3×3×4mm with a 0.5mm inter-slice gap. The fMRI acquisition was preceded by 11s of dummy gradient RF pulses to achieve steady-state tissue magnetization and minimize startle-induced motion. Duration was approximately 8 min. In addition to the resting state BOLD images, we acquired a low-resolution T1-weighted coplanar image for each participant, and a high-resolution magnetization prepared rapid gradient echo (MPRAGE) T1-weighted image. Head movement was comfortably restricted with cushions to minimize motion. An LCD projector displayed stimuli onto a rear projection screen, which the subjects viewed via a head coil mounted mirror.

During the scan, participants were directed to stay awake, look at the fixation crosshair on the screen, and to "let their minds wander" and not focus on any particular thoughts.

Behavioral Tasks

Dot Probe Task

We assessed selective attention capture using a dot probe task consisting of 48 trials. Each trial began with a non-predictive white fixation cross that served as an orienting cue. Following the presentation of the orientation cue, two grayscale images (11.1° × 9.0°) appeared simultaneously, one on each side of the fixation cross, for 150ms (Figure 1-1). Grayscale images were used to avoid confounds in our results due to high salience of color (Theeuwes 1992; 1994). Following a 50 ms inter-stimulus interval (ISI), the target, a white asterisk in 36 pt font, appeared in one of the image locations and appeared for 200 ms. With 50 ms between cue offset and target onset, a 150-ms cue duration gave a 200-ms stimulus-onset asynchrony (SOA), which is well below the SOA where capture effects start to diminish (~300 ms; Posner and Cohen 1984). In each trial, one image depicted alcohol-related content, while the other depicted neutral, kitchen-related content. Alcohol and neutral cues images were matched in terms of their basic visual properties. Left/right position of the alcohol images was pseudo-randomly ordered (ratio 1:1). Each image was randomly drawn from a set of 20 alcohol or 20 neutral images. Subjects were instructed to respond to the target's location via keypress as quickly as possible. This design is modified from our previous study assessing AB toward smoking cues in cigarette smokers (Chanon et al. 2010).

Modified Attentional Blink Task

To measure extended attention hold, participants completed a modified attentional blink. The task consisted of four blocks of 48 trials each. Each trial began with a non-predictive fixation crosshair white cross hair (18pt font), followed by a rapid serial visual presentation of 17 grayscale photos (11.1°×9.0°) for 100 ms each, with a 0-ms ISI. Stimuli within each stream consisted of neutral images, except for two images, and were all upright landscape/architectural photographs. The remaining two images consisted of the critical distractor and the target stimulus. Critical distractor images were either a neutral content (kitchen) image or an alcohol-related image (ratio: 50:50). Targets were occurred 2 or 8 images after the

distractor images within the stream, and were rotated either 90° left or right. At the end of each trial, the response screen was presented for 2000ms and participants were instructed to indicate the target orientation by pressing one of two keys in response to the query "Was the target rotated right or left." Participants' accuracy in reporting the target rotation (left or right) was recorded for each trial. We calculated the accuracy of target responses, for each lag (2 or 8) and distractor type (kitchen or alcohol). The primary dependent measure of interest was the difference in the attentional blink effect (decreased accuracy lag 2 compared to lag 8) between the alcohol and neutral distractor trials. Lower lag 2 accuracy relative to lag 8 accuracy indicates a greater attentional blink, with a greater blink following an alcohol distractor representing greater attentional bias to alcohol cues.

Reward Conditioning Task

We assessed each participant's reward conditioning sensitivity using a value driven attention capture task identical to that used in (Anderson et al. 2013), programmed in Matlab (The MathWorks Inc., Natick, MA, 2000) using the Psychtoolbox-3 extensions (Brainard 1997). (Figure 1-3) Participants completed the task while seated at a computer in a darkened room. A visual search task was presented on a color LCD screen. The task was separated into two phases, a reward-conditioning phase, and a test phase. For the conditioning phase, each trial began with a fixation display for 400, 500, or 600 ms (randomly determined), followed by a visual search for a target circle among five non-target circles. The search array remained on the screen until a response was made, up to a limit of 1200 ms. Following the search array, a blank screen appeared for 1000 ms, and reward feedback was then displayed for 1500 ms, followed by a blank 1000 ms inter-trial-interval (ITI). The target circles were unpredictably red or green, and participants were rewarded for correctly reporting (via keypress) the orientation of a white bar (horizontal or vertical) appearing within the target circle. Participants received feedback in each trial (n=240) during the conditioning phase. One of the two target colors yielded a reward of 10¢ in 80% of trials, and 2¢ in the remaining 20% of trials (high-reward target); these contingencies were reversed for the other color target (low-reward target). Incorrect or omitted responses yielded 0¢. The high-reward color was red for half the participants and green for the other half. Participants completed 40 practice trials prior to

beginning the task.

The test phase was structured similarly to the training phase, with a few keys differences. First, the search array included a target shape (diamond) among 5 non-target shapes (circles); participants disregarded shape color, and instead reported the orientation of the bar within the target shape. Second, feedback after the search array only informed participants if their response was correct (✓) or not (×); no monetary rewards were given. Third, the search array appeared for up to 1500 ms, followed by the feedback screen for 1000 ms, and a blank ITI screen for 500 ms. Critically, 25% of trials included a red circle in the search array, 25% included a green circle in the search array, and the remaining 50% lacked any reward-conditioned distractor shapes. Both accuracy and reaction time (RT) were collected for each trial.

Statistical Analysis

For the dot probe task, the dependent measure was RT on alcohol-cued and neutral-cued target trials after acute dopamine depletion. Faster RT values in alcohol-cued trials represent attentional bias toward alcohol-related cues via selective attention capture. We quantified bias for alcohol related images versus neutral images according to the following equation: RT Bias $\text{Measure}_{\text{Neutral-Alcohol}} = (RT_N - RT_A)$, where RT_N and RT_A represent mean RT to targets appearing in the location of neutral, or alcohol images, respectively. Positive values of RT Bias $\text{Measure}_{\text{Neutral-Alcohol}}$ indicate AB to alcohol related images. Only RTs from correct trials were included in our analyses. We also excluded trials in which the RT was >2 standard deviations longer than the individual's mean RT for that condition, or <200ms.

For the modified attentional blink task, our dependent measure was the accuracy of target responses, for each lag (2 or 8) and distractor type (kitchen or alcohol). We quantified bias for alcohol related distractors versus neutral distractor according to the following equation: Accuracy Bias $\text{Measure}_{((A)-(N))} = (\text{Accuracy}_{\text{Alcohol8-Alcohol2}}\text{-Accuracy}_{\text{Neutral8-Neutral2}})$, where A8 and A and N represent difference in accuracy to targets appearing 2 or 8 lags after of neutral, or alcohol images. Positive values of Accuracy Bias $\text{Measure}_{((A)-(N))}$ indicate AB to alcohol related images. Trials in which the RT was <200ms were excluded.

For the reward conditioning task, we assessed RT during the test phase between trials with a high reward distractor present (RT_{High}) and trials with no reward distractor present (RT_{Absent}) (Anderson et al. 2011b) after dopamine depletion. Larger RT values in the trials with a High reward distractor present relative to trials with no distractor present represent greater AB to reward conditioned cues. Only RTs from correct trials were included in our analyses. We also excluded trials in which the RT was >3 standard deviations longer than the individual's mean RT for that condition, or <200ms.

For multifactorial comparisons, we used repeated-measures ANOVA. To ensure the validity of parametric statistical tests, we used an arcsine-root transformation of the blink task accuracy data before statistical analyses and age was entered as a covariate in all analysis.

To assess whether dopamine depletion predicted a change in AB to alcohol cues, we calculated a change in AB equation for each task: Dot probe task change in AB equation: [(Depleted($RT_{Neutral\text{-}Alcohol}$) - Control($RT_{Neutral\text{-}Alcohol}$)] and Attentional blink task change in AB equation:[(Depleted(Accuracy $_{Alcohol8\text{-}Alcohol2}$-Accuracy $_{Neutral8\text{-}Neutral2}$))] – [(Control(Accuracy $_{Alcohol8\text{-}Alcohol2}$-Accuracy $_{Neutral8\text{-}Neutral2}$))]. We used AB measures to perform multiple linear regression analyses in SPSS. For each multiple regression analysis, we entered variables in a stepwise manner in the following order: block 1: age, beverage order, and AUQ BDS; block 2: Binge frequency before age 18, Binge frequency between ages 18-21.

Neuroimaging Analysis

Imaging data was processed using Statistical Parametric Mapping (SPM8 (version 5236; Welcome Department of Cognitive Neurology, London, UK). We used the artifact detection toolbox (ART; http://www.nitrc.org/projects/artifact_detect) to identify time points with high amounts of noise according to head motion and global signal intensity measures. Preprocessing included the following steps: reorientation, slice time correction, realignment, coregistration, MPRAGE segmentation, artifact detection, and normalization to a standard template in Montreal Neurological Institute (MNI) space, using both a 12-parameter affine transformation and a nonlinear transformation using cosine basis functions. The images were resampled into $2mm^3$ voxels, and spatially smoothed with an isotropic Gaussian kernel of 5mm.

Subject-specific realignment parameters and a matrix containing the ART-detected outlier volumes were included as first-level nuisance covariates. A temporal filter of 0.009 and 0.08 Hz was applied to focus on low-frequency fluctuations.

Following preprocessing, connectivity analyses were performed using Analysis of Functional Neuroimages (AFNI (R. W. Cox, 1996), version 16.2.07), Matlab2013a, SPSS 24, and Microsoft Excel. Mean time series data was extracted using AFNI for the following *a priori* regions of interests (ROI): dorsolateral prefrontal cortex (dlPFC), AnCC, lateral orbitofrontal cortex (LOFC), fronto-insular cortex (FIC), inferior frontal gyrus, pars opercularis (IFGop), medial orbitofrontal cortex (mOFC), amygdala, VTA, limbic striatum, executive striatum, sensorimotor striatum. All ROI were selected using coordinates from published research findings or from recent unpublished relevant findings from the Boettiger lab (Table 4-1). ROI connectivity values for each beverage condition were compared to assess the overall effect of DA depletion on functional connectivity. To do so, for each VTA-frontolimbic ROI pair, we calculated Pearson correlation values which were then Fisher-Z transformed then entered these functional connectivity values into 2×2 mixed model ANOVA to test for main and interacting effects of beverage condition and group with age entered as a covariate. All resulting significance values were corrected for multiple corrections using false discovery rate procedures in SPSS.

To capitalize on possible variance in beverage effects, we also assessed the relationship between dopamine depletion effects on AB and changes in functional connectivity. To do so, we conducted Spearman's correlations using the change in connectivity between each ROI pair ($ROI\text{-}ROI_{Depleted}\text{-}ROI\text{-}ROI_{Control}$) and change in AB ($ABMeasure_{Depleted}\text{-}ABMeasure_{Control}$).

Results

Demographic and Psychometric Data

Drinking groups were equated on age, years of education, ethnicity, and familial alcoholism. Although age did not differ between groups, we controlled for age in all subsequent analyses due to known age dependent declines in dopamine signaling (Volkow et al. 1998). Heavy binge drinkers differed

significantly from moderate drinkers on several psychometric measures (Table 4-2). Heavy drinkers reported higher rates of current and past binge drinking (between 18-21 yrs of age) and significantly more hazardous drinking behavior based on AUDIT scores. Heavy and moderate drinkers also differed significantly in their self-reported motivations to drink alcohol. Motivations are classified into 4 categories: social (drinking to be sociable, to celebrate), coping (drinking to forget about problems), enhancement (drinking to feel great), and conformity (drinking to fit in). Heavy drinkers reported significantly greater motivation to drink for enhancement or for social reasons, compared to moderate drinkers (Table 4-2). These results indicate that the binge drinking groups are reward-based drinkers, rather than relief-based drinkers (Cooper 1994; Roos et al. 2017).

Effects of Dopamine Depletion on Attentional Bias Measures

Dot Probe Task

We assessed the effects of acute dopamine depletion and group (HD versus MD) on AB to alcohol cues in the dot probe task using a mixed model ANOVA to test for main and interacting effects of beverage, cue type, and group on RT (Figure 4-1a,b). To assess and visually inspect AB responses change under the depleted vs neutral conditions across individuals, we calculated the RT Bias Measure$_{\text{Neutral-Alcohol}}$ for each condition for each group as well (Fig. 4-1c,d). We did not detect significant main effects of acute dopamine depletion ($F_{(1, 28)} = 1.15$, p=0.292), group ($F_{(1, 28)} = .466$, p=0.500), or cue type ($F_{(1, 28)} =.257$, p=0.616). We further probed the effect of dopamine depletion by assessing the interaction of beverage with group ($F_{(1, 28)} =1.65$, p=0.209) and with cue and group ($F_{(1, 28)} = .384$, p=0.541) and did not detect any statistically significant effects.

To increase our power to detect effects, rather than using binge drinking behavior to define binary groups, we instead considered binge drinking as a more continuous measure. Specifically, we used multiple linear regression to test whether measures of current or adolescent binge drinking predicted effects of dopamine depletion on AB toward alcohol cues in this task. Taking the change in AB measured by the dot probe task [(Depleted($RT_{\text{Neutral-Alcohol}}$) - Control($RT_{\text{Neutral-Alcohol}}$)] as our dependent measure, we entered independent variables in a stepwise manner in the following order consistent with the previous

analysis: block 1: age, beverage order, current binge drinking behavior (BDS); block 2: frequency of binge drinking before age 18, and between 18-21 years (see Methods for details on binge drinking measures). We found that frequency of binge drinking before age 18 significantly predicted the change in AB after dopamine depletion ($F_{(4,27)}$= 3.37, p=0.026; Table 4-3a). More frequent binge drinking prior to age 18 predicted a greater decline in AB to alcohol cues following acute dopamine depletion. This relationship was present within each group, reaching statistical significance in the MD group ($F_{(4,14)}$=3.599, p=.046; Table 4-3b), and trend level significance in the HD group ($F_{(4,12)}$=3.177, p=.077), albeit with a larger effect size (Table 4-3c). We note that beverage order had similar predictive power in terms of depletion effects on AB to alcohol cues (Table 4-3a-c), indicating that dopamine depletion had less effect on alcohol cue AB when depletion occurred in Session 1. This likely reflects session effects on AB, as AB tended to increase from Session 1 (RT Bias $Measure_{Neutral\text{-}Alcohol}$ mean = -11.32) to Session 2 (RT Bias $Measure_{Neutral\text{-}Alcohol}$ mean = 5.066).

Attentional Blink Task

We assessed the effect of acute dopamine depletion and group (HD versus MD) on AB to alcohol cues in the attentional blink task using a mixed model ANOVA to test for main and interacting effects (Beverage Type × Cue Type × Lag × Group) on accuracy. Results revealed a significant main effect of lag on target accuracy ($F_{(1, 29)}$ = 18.28 p<0.001). Decreased accuracy on lag 2 trials compared to lag 8 trials indicated an overall attentional blink effect (Figure 4-2). We did not, however, detect significant main effects of beverage type ($F_{(1, 29)}$ = 0.280, p=0.601), cue type ($F_{(1, 29)}$ = 1.042, p=0.316), or group ($F_{(1, 29)}$ = 0.616, p=0.439). We did not find a significant beverage × cue × lag × group interaction ($F_{(1, 29)}$ = .146, p=0.705), nor a cue × lag × group ($F_{(1, 29)}$ =.707, p=.407), or cue × lag × beverage interaction ($F_{(1, 29)}$ = .078, p=0.782). We also found no other interacting effects of cue, lag, beverage, or group on accuracy (max. F=0.760, min. p=0.95).

For the spatial cuing data, we also conducted analyses considering binge drinking behavior as a continuous, rather than a dichotomous, variable. Following the same multiple regression procedure as described for the spatial cuing data, but taking the change in AB calculated from the blink task

[(Depleted($Accuracy_{Alcohol8\text{-}Alcohol2}$-$Accuracy_{Neutral8\text{-}Neutral2}$))] – [(Control($Accuracy_{Alcohol8\text{-}Alcohol2}$-$Accuracy_{Neutral8\text{-}Neutral2}$))], we used several binge drinking measures to predict the change in our AB following dopamine depletion. While the overall model did not reach significance ($F_{(4,28)}$= 2.477, p=0.071), several independent predictors did significantly predict the change in AB (Table 4-4a-c). Age, depletion order, current binge drinking, and binge drinking frequency between the ages 18-21 years significantly predicted the change in AB to alcohol cues after dopamine depletion. The latter three effects appeared to be driven by the HD group, as when we repeated these analyses separately for each group, we found similar results in the HD group (Table 4-4b). Specifically, current binge drinking score significantly predicted the change in AB after DA depletion, reflecting a greater increase of AB to alcohol cues following dopamine depletion associated with heavier binge drinking behavior. In contrast, more frequent binge drinking between ages 18 and 21 predicted a greater decline in AB to alcohol cues following acute dopamine depletion. Finally, dopamine depletion had less effect on AB on this task when it occurred in Session 1, likely reflecting the fact that AB tended to increase from Session 1 ($ACC_{Alcohol8\text{-}Alcohol2}$-$ACC_{Neutral8\text{-}Neutral2}$ mean= -0.011) to Session 2 ($ACC_{Alcohol8\text{-}Alcohol2}$-$ACC_{Neutral8\text{-}Neutral2}$ mean =0.011). In contrast, none of these relationships were observed in the MD group (Table 4-4c).

Reward Conditioning Task

We assessed the effects of acute dopamine depletion and group (HD versus MD) on reward conditioning using a mixed model ANOVA to test for main and interacting effects of beverage, cue type, and group on RT. Similarly to the alcohol AB tasks, using a 2×2×2 ANOVA (Beverage Type × Cue Type × Group), we did not detect significant main effects of acute dopamine depletion ($F_{(1, 16)}$ = .504, p=0.488), cue ($F_{(1, 16)}$ = 1.97, p=0.179), or group ($F_{(1, 16)}$ = .599, p=0.450), nor a significant depletion × cue × group interaction ($F_{(1, 16)}$ = .702, p=0.414). In addition to this ANOVA, we also considered binge drinking behavior as a semi-continuous measure, and used multiple regression analysis to identify significant predictors of the change in AB to the high reward cue after dopamine depletion using the change in AB [(Depleted($RT_{High\text{-}Absent}$)-Control($RT_{High\text{-}Absent}$)] as our dependent measure. This analysis

found that neither current binge drinking, nor adolescent binge drinking significantly predicted changes in AB to the high reward cue ($F_{(3,15)}$= 1.12, p=0.381) (Table 4.5a-c). We also detected no depletion order effect for this task.

Dopamine Depletion Effects on Frontolimbic Functional Connectivity

Using an ROI to ROI approach, we assessed the change in connectivity between ROI following acute dopamine depletion. We calculated functional connectivity values for each all ROI pairs for each condition (depleted and control) and performed a 2 × 2 ANOVA (Beverage Type × Group) to assess the overall effect of dopamine depletion. While we did see trends for a main effect of group in the connectivity between the AnCC and FIC, and between the IFGOp and sensorimotor striatum, these effects did not survive correction for multiple comparisons. Trends suggested increased functional connectivity between the AnCC and FIC, and between the IFGOp and sensorimotor striatum in HD compared to MD. Interestingly, these areas have repeatedly been shown to be involved in addiction related behaviors. The AnCC and FIC are major hubs of the salience network which aids in conditioning and assigning incentive salience to drugs and drug-related cues (Goldstein and Volkow 2011). These trends may suggest increased intrinsic salience network connectivity as a result of drinking status. We also observed trends for group × depletion interactions between the mOFC and both the executive striatum and the FIC, but these interactions also did not survive correction for multiple comparisons (Figure 4-4). The group × depletion interaction trend of the mOFC and executive striatum suggests that acute dopamine depletion decreased functional connectivity of these regions in HD, while it tends to increase connectivity of these regions in the MD group. Moreover the group × depletion interaction trend of the mOFC and FIC suggests that acute dopamine depletion increases the functional connectivity of the mOFC and FIC in HD, while it tends to decrease connectivity of these regions in MD. It is suggests that the FIC in conjunction with other regions of the salience network facilitates access to attention and working memory resources when a salient event is detected and regulates reactivity to salient stimuli (Menon 2011; Menon and Uddin 2010). Potential changes in functional connectivity in HD between the mOFC, a region shown to

involved in attentional control as well as craving in addiction, and the FIC, as a result of dopamine depletion may suggest underlying differences in attention and salience processing in these individuals that effects AB.

Individual Differences in Dopamine Depletion Effects on Functional Connectivity

Dopamine depletion did not appear to cause overall changes in functional connectivity between our frontolimbic ROI, however, we observed substantial variability in the effects of depletion on both behavioral and connectivity measures. Thus, we evaluated whether dopamine depletion effects on AB correlated with depletion effects on functional connectivity. To do so, we conducted Spearman's correlations using the change in ROI-ROI functional connectivity ($ROI\text{-}ROI_{Depleted}\text{-}ROI\text{-}ROI_{Control}$) and change in AB ($ABMeasure_{Depleted}\text{-}ABMeasure_{Control}$; Table 4-6). This analysis found two correlations that survived correction for multiple comparisons. First, the extent to which dopamine depletion increased AB toward alcohol cues in the dot probe task was associated with the magnitude of increase in functional connectivity between the VTA and the executive striatum (ρ=0.542, p=0.002; Figure 4-5a). Second, the extent to which dopamine depletion increased AB toward alcohol cues in the attentional blink task was associated with the magnitude of increase in function connectivity between the VTA and dlPFC (ρ=0.458, p=0.008); however this effect was driven solely by the moderate drinkers (ρ=0.600, p=0.008; Figure 4-5b).

Discussion

Despite the prevalence and clinical importance of alcohol AB, the neural base of this phenomenon remains unclear. Specifically, it is unknown whether dopamine modulates AB and dopaminergic pathways of the VTA and PFC intrinsic functional connectivity play a role in AB. Here we quantified the magnitude of alcohol AB and reward conditioning in heavy binge and light to moderate social drinkers after acute dopamine depletion using a dopamine depletion beverage and 3 behavioral tasks. We also assessed whether functional connectivity between the VTA and key frontolimbic regions was altered after dopamine depletion, and if those changes predicted significant changes in AB. To our surprise, we did not

detect a statistically significant difference in AB after dopamine depletion, nor did we find group differences in AB between heavy, binge and light to moderate drinkers. However, multiple linear regressions revealed that frequency of binge drinking prior to age 18 negatively correlated with changes in attentional capture by alcohol cues after dopamine depletion. Current and past binge drinking significantly predicted change in attentional hold by alcohol cues, but only in heavy drinkers. Furthermore, current binge drinking was directly related to blink bias while adolescent binge drinking was inversely related to this measure. Our neuroimaging analysis did not reveal a significant difference in functional connectivity after depletion. However, we did find a statistically significant relationship between the depletion-induced change in functional connectivity and change in alcohol AB. Specifically, increased AB measured by the dot probe task was positively correlated with increased functional connectivity of the VTA and executive region of the striatum. In addition, AB measured on the attentional blink task was positively correlated with increased functional connectivity of the VTA and DLPFC. We did not see overall effect of dopamine depletion on functional connectivity in our ROI-ROI analysis however there was a significant relationship between the change in functional connectivity and change in AB on tasks after depletion. The change in functional connectivity between the VTA and the executive control region of the striatum, which roughly corresponds to the caudate, was positively correlated with the change in AB on the dot probe task. Furthermore, the change in functional connectivity between the VTA and the DLPFC positively correlated with the change in AB on the attentional blink task.

Dopamine Depletion and Behavioral Changes

While the use of acute dopamine depletion has previously been found to produce significant changes in behavior, including significant changes in responsiveness to addiction- related cues (Hitsman et al. 2008; Leyton et al. 2007; Venugopalan et al. 2011), its effects have also been found to be widely variable. Kelm and Boettiger (2013) found no overall effects of dopamine depletion on delay discounting behavior, but observed a strong relationship between a genetic biomarker of PFC dopamine levels and depletion, suggesting that some effects of dopamine manipulation depends on individual differences in frontal lobe

dopamine tone or levels. Acute dopamine depletion was also found to not have an effect on RTs or interact with incentive value during a monetary incentive delay task, despite depletion-induced changes in neural activity in the NAc were present after depletion (Bjork et al. 2014). The inconsistencies in these findings may indicate that acute dopamine depletion methods are most effective in very specific populations and that individual differences play a strong role in depletion effects. Given our small sample size, we may have been unpowered to detect significant depletion effects. Moreover, individual differences, such as baseline DA levels, gender, and genetic factors were not explored in this study, but may play a role in the depletion effects as seen in previous studies. Individual differences in baseline dopamine levels have been shown to be important in studies using pharmacological manipulations of dopamine. For example, greater baseline dopamine synthesis capacity predicted better reward-based reversal learning in healthy participants (Cools et al. 2009). Moreover, dopamine depletion was found to significantly improve punishment-based reversal learning only in females, who are known to have higher baseline DA levels than males (Robinson et al. 2010). These individual differences, including withdrawal or craving states, may play a large role in the effectiveness of acute dopamine depletion, as dopamine has been shown to play a role in these addiction states (Franken 2003; Freeman et al. 2015; Robinson and Berridge 1993). Future studies may benefit from assessing withdrawal and craving measures or inducing these states by priming with alcohol before behavioral testing to assess their roles in mediating the acute of effects of dopamine depletion.

Dopamine Depletion Effects on Attentional Capture by Alcohol Cues

Our findings of the relationship between adolescent binge drinking and the change in AB captured on the dot probe task also suggests individual differences in past binge drinking behavior may effect dopamine depletion. Given our findings in Chapters 2 and 3, it is somewhat surprising that increased adolescent drinking behavior negatively predicted the change in AB on these tasks while current binge drinking status predicted a positive change in AB on the attentional blink task. Models of adolescent and adult binge-like drinking exposure in animals have revealed different neural effects. In animals, binge-

like exposure in adolescence produces significant reductions in neurogenesis (Vetreno and Crews 2015), an increased risk taking behavior (Boutros et al. 2014) and alcohol consumption in adulthood. Adolescence is a period in which significant changes to reward neurocircuitry occur (Luciana 2013; Wahlstrom et al. 2010), and exposure to alcohol during this period is associated with significant changes in brain activity (Cservenka et al. 2015). Our finding that increased frequency of adolescent binge exposure predicts the change in the form of AB thought to reflect selective attention capture to alcohol cues after dopamine depletion supports the animal literatures that suggest the adolescent prefrontal cortex is particularly vulnerable to the damaging effects of alcohol and leads to changes in adult neural mechanisms of cognition in adulthood (Crews et al. 2007).

Binge Drinking History and Attentional Hold by Alcohol Cues

We found that current binge drinking status predicted a positive change in AB on the attentional blink task. In adult animals, binge like drinking exposure has been shown to lead to deficits in spatial memory (Fernandez et al. 2017) decreases cognitive flexibility and disruption of OFC function (Badanich et al. ; Nimitvilai et al. 2016). Our heavy binge drinkers also had frequent adolescent binge exposure, significantly more than moderate drinkers between the age of 18 and 21, likely compounding the effects of current binge drinking. The relationship between current binge drinking and AB on the attentional blink task may indeed reflect the continual insult of binge drinking to regions such as the OFC. Taken together, these findings emphasize the potential role of past and current binge drinking in changes to the neural mechanisms that maintain or hold AB to alcohol related stimuli.

Finally, we did not see significant differences in behavior between heavy, binge and moderate social drinkers in a previous study sample (see Chapters 2 and 3). We theorized that the HD group's drinking patterns and history may not have been severe enough to develop reliably stable forms of AB. This may also play a role in this sample as the inclusion criteria was the same; participants may have not been greatly affected by the depletion manipulation because the underlying neural mechanisms were not abnormal.

Phasic Dopamine Release, Cue Reactivity, and Functional Connectivity

Although a wealth of data indicates that resting state connectivity closely resembles connectivity during active tasks, it is possible that dopamine depletion produces undetectable changes in resting state functional circuit connectivity. We hypothesized that acute dopamine depletion would result in a change in behavioral responses to alcohol related cues. This theory is grounded in the preclinical literature that highlighted phasic dopamine release in response to cues associated with reward (Shnitko and Robinson 2015; Spoelder et al. 2015). Our current model lacked the ability to capture the response to cues as our behavioral tasks were performed after the resting state functional connectivity scan. It is possible that there may be changes in the activity in frontolimbic ROI as a result of dopamine depletion that are most optimally captured using event related fMRI. Using event-related fMRI procedures, dopamine depletion has been found to decrease reward related brain activation during anticipation of rewards or loss (da Silva Alves et al. 2011; Nagano-Saito et al. 2012). These findings suggest that utilizing event related fMRI during the alcohol AB tasks and measuring task-specific changes in connectivity may provide greater insight into the role of dopamine in AB to alcohol cues.

Despite not finding an effect of beverage on overall functional connectivity, our data did reveal a significant relationship between the change in functional connectivity of the VTA and the executive control region of the striatum and changes in AB on the dot probe task. The relationship between the VTA and the executive region of the striatum is not surprising given the role of the striatum in response to drug related cues (Grusser et al. 2004; Volkow and Morales 2015; Volkow et al. 2006). The executive region of the striatum has been shown to facilitate executive function, goal directed behavior and cognition. Additionally, this striatal region plays a role in goal directed behavior and evaluating action selection (de Wit et al. 2012; Tanaka et al. 2008; Tanaka et al. 2004) which may be mediated by dopamingeric function in this region.

We also saw a significant relationship between the VTA and DLPFC and changes in AB on the attentional blink task. The DLPFC has been found to be particularly vulnerable to substance use and plays

a critical role in addiction, specifically in response to drug related cues (Goldstein and Volkow 2011). Moreover, general (non-addiction) AB measured in the blink task was found to decrease following anodal TMS to the left DLPFC in normal participants with large baseline AB (London and Slagter 2015). Our findings suggest that dopamine may be playing a role in the functional changes of the DLPFC via connectivity with the VTA in the face of AUDs, SUDs, and hazardous drinking (Goldstein and Volkow 2011; Lefaucheur et al. 2014).

Besides using additional imaging modalities, different analytical approaches to the imaging data may provide significant additional insight into the role of dopamine in the neural circuit bases of alcohol AB. Our *a priori* hypothesis informed our ROI selection for connectivity analyses. These results provide us the clear ability to explore the effect of dopamine depletion on these specific connections, but each of these connections is part of large neural networks. With our limited sample size it may not be feasible to detect specific ROI to ROI changes in functional connectivity. However, large scale network changes may be more sensitive methods to reveal dopamine depletion effects and provide insight into the role of dopamine in alcohol AB and reward conditioning. One study utilizing network analysis and graph theory found that dopamine depletion reduced global and local efficiency of the whole brain network, reduced regional efficiency in limbic areas, reduced modularity of brain networks, and resulted in greater connection between the normally anti-correlated task-positive and default-mode networks (Carbonell et al. 2014). These widespread neural network changes would not have been captured in our current analyses plan, but point to an intriguing future direction for analysis.

Study Limitations

One limitation of this study is the small sample size. Power analysis revealed a sample size of 50 would be sufficient for finding significance. As our study is a little over half of this figure, it lacked sufficient power to detect significant main and interacting effects of depletion and drinking group. We did see several significant functional connectivity changes in our analysis, but after correcting for multiple comparisons these findings were no longer significant. This result suggests that possibly using a whole

brain, voxel based analysis to identify regions that change as a result of acute depletion, then moving forward with fewer analyses may an alternative approach to investigate the functional connectivity after depletion.

The significant relationship between changes in AB and changes in functional connectivity speak to the possibility that there are effects of depletion and connectivity but we may be under powered to detect those. Another limitation of this study is the lack of variability in adolescent binge drinking. Preclinical research on adolescent binge drinking has provided significant evidence of the deleterious effects of binge like drinking exposure on neural development (Boutros et al. 2014; Crews et al. 2016; Liu and Crews 2015; Vetreno and Crews 2015; Vetreno et al. 2016). Our groups did not differ on their adolescent binge drinking measures and as a result it is possible that our heavy binge drinking group did not have enough exposure to result in the neural changes that lead to differences in functional connectivity and DA modulation of AB.

Conclusions

Our findings support evidence from neuroimaging studies that show although no behavioral or overall neural changes are seen with acute dopamine depletion; the changes in neural patterns of activations as a result of dopamine depletion show a relationship with behavioral task changes (Mehta et al. 2005). Specifically, we found that changes in functional connectivity between the VTA and DLPFC after depletion are strongly correlated with changes in a form of alcohol attentional bias thought to reflect extended attentional hold and that changes in functional connectivity of the VTA and the executive control region of the striatum and changes in a form of alcohol attentional bias thought to reflect selective attention capture. These functional connectivity and behavioral change findings suggest that dopamine is in some way playing a role in functional connectivity of these frontolimbic regions and as such, may be facilitating AB. Furthermore, our findings of the relationship between current binge drinking status and change in extended hold, and adolescent binge drinking frequency and change in selective attention capture highlight the importance of assessing past and current drinking patterns as they may provide

insight into behavioral and neural changes after depletion. Our findings provide a first step at investigating the role of frontolimbic connectivity and dopamine in AB in non-clinical drinking populations and increasing our knowledge in this clinical relevant area of addiction related research.

Table 4-1. Regions of Interests

Region of Interest	MNI Coordinates	Sources
VTA	Probabilistic atlas	(Murty et al. 2014)
DLPFC	Left DLPFC: -48, -18, 44 Right DLPFC: 48, -18, 44	(Uddin et al. 2011)
ACC	-8,-24,34	(Ma et al. 2010)
LOFC	Left: -27, 39, -6 Right: 27, 39, -6	(Ma et al. 2010)
FIC	Left: -38, -24, -8 Right: 34, -24, -8	(Uddin et al. 2011)
IFGop	Left: -58, 16, 10 Right: 54, -16, 10	Harvard-Oxford cortical and subcortical atlases
mOFC	28,-28,-16	(Kveraga et al. 2007)
Amyg	Left: -20, 6, 10 Right: 20, 6, -12	(Uddin et al. 2011)
Limbic Striatum	Probabilistic atlas	(Tziortzi et al. 2014)
Executive Striatum	Probabilistic atlas	(Tziortzi et al. 2014)
Sensorimotor Striatum	Probabilistic atlas	(Tziortzi et al. 2014)

Table 4-2. Imaging Study Demographics

Demographics	MD (*n*=19)	HD (*n*=15)	Statistic (34)	*p* value
General				
Age (yrs)	27± 5.0	25.4± 5.2	0.868	0.392
Education (yrs)	16.9±2.2	16.5± 1.6	0.551	0.586
Familial Alcohol Density	12% ± .15	18% ± .18	1.017	0.317
Substance Use Measures				
Binge Score	8.01±5.2	32.27±28.04	-3.26	**<0.001**
Age of Onset	15.9±3.3	15.8±3.3	.071	0.994
Binge 0-18yrs age	0.53±1.1	0.80±1.3	-.658	0.516
Binge 18-21yrs age	1.89±1.7	3.33±1.7	-2.47	**0.019**
DMQR Social	11.79±3.9	15.33±3.8	-2.66	**0.012**
DMQR Enhancement	10.05±4.2	14.00±3.5	-2.98	**0.005**
DMQR Coping	7.31±3.4	9.06±3.8	-1.41	0.170
DMQR Conformity	7.47±3.9	7.46±2.2	0.07	0.995
AUDIT	4.05±2.7	12.6±3.7	-7.55	**<0.001**
Barratt Impulsiveness Scale	57±9.5	61.2±8.7	-1.36	0.184

Table 4-3a. Multiple Regression Analyses: Factors Predicting Cuing Bias

Variable	*B*	*SE B*	*β*
Step 1			
(Constant)	14.315	29.389	
Age	-0.092	1.004	-0.018
Beverage Order	-9.585	9.813	-0.194
Binge Drinking Score	0.182	0.205	0.174
Step 2			
(Constant)	21.763	24.865	
Age	0.647	0.876	0.128
Beverage Order	-21.572	9.036	-0.436*
Binge Drinking Score	0.109	0.175	0.104
Binge Frequency, Ages 0-18 years	-12.784	3.888	-0.609*

Note: $\Delta R^2 = .074$ for Step 1; $\Delta R^2 = .296$ for Step 2. *$p < .05$, **$p < .01$
$F_{(4,27)} = 3.373$, $p = .026$, $R^2 = .370$
B: beta value; *SE B*: beta value standard error; *β*: standardized beta; binge drinking frequency for 18-21 years of age was also included and did not explain significant variance.

Table 4-3b. Multiple Regression Analyses: Factors Predicting Cuing Bias in Moderate Drinkers

Variable	*B*	*SE B*	*β*
Step 1			
(Constant)	105.257	46.988	
Age	-2.545	1.446	-0.455
Beverage Order	-22.323	13.172	-0.437
Binge Drinking Score	-0.683	1.232	-0.139
Step 2			
(Constant)	90.339	39.355	
Age	-1.258	1.306	-0.225
Beverage Order	-29.762	11.311	-0.582*
Binge Drinking Score	-0.957	1.025	-0.195
Binge Frequency, Ages 0-18 years	-14.625	5.940	-0.585*

Note: $\Delta R^2 = .342$ for Step 1; $\Delta R^2 = .248$ for Step 2. *$p < .05$, **$p < .01$
$F_{(4,14)} = 3.599$, $p = .046$, $R^2 = .590$
B: beta value; *SE B*: beta value standard error; *β*: standardized beta; binge drinking frequency for 18-21 years of age was also included and did not explain significant variance.

Table 4-3c Multiple Regression Analyses: Factors Predicting Cuing Bias for Heavy Drinkers

Variable	*B*	*SE B*	*β*
Step 1			
(Constant)	-39.881	36.508	
Age	2.066	1.556	0.462
Beverage Order	-12.475	16.288	-0.267
Binge Drinking Score	0.260	0.240	0.318
Step 2			
(Constant)	-16.505	28.847	
Age	3.062	1.230	0.684
Beverage Order	-32.724	14.301	-0.699*
Binge Drinking Score	0.028	0.199	0.034
Binge Frequency, Ages 0-18 years	-13.638	4.899	-0.755*

Note: ΔR^2 =.239 for Step 1; ΔR^2= .614 for Step 2. *$p < .05$, **$p < .01$
$F_{(4,12)} = 3.17$, p =.077, R^2 = .374
B: beta value; *SE B*: beta value standard error; *β*: standardized beta; binge drinking frequency for 18-21 years of age was also included and did not explain significant variance.

Table 4-4a. Multiple Regression Analyses: Factors Predicting Change in Attentional Blink

Variable	*B*	*SE B*	*β*
Step 1			
(Constant)	-0.281	0.242	
Age	0.012	0.008	0.279
Beverage Order	-0.100	0.079	-0.233
Binge Drinking Score	0.002	0.002	0.228
Step 2			
(Constant)	-0.175	0.233	
Age	0.017	0.008	0.382*
Beverage Order	-0.184	0.085	-0.429*
Binge Drinking Score	0.004	0.002	0.424*
Binge Frequency, Ages 18-21 years	-0.057	0.028	-0.461*

Note: R^2 =.165 for Step 1; Δ R^2= .127 for Step 2. *$p < .05$, **$p < .01$
$F_{(4,28)} = 2.477$, p =.071, R^2 = .292
B: beta value; *SE B*: beta value standard error; *β*: standardized beta; binge drinking frequency for 0-18 years of age was also included and did not explain significant variance

Table 4-4b Multiple Regression Analyses: Factors Predicting Change in Attentional Blink for Heavy Drinkers

Variable	*B*	*SE B*	*β*
Step 1			
(Constant)	-0.346	0.406	
Age	0.008	0.017	0.177
Beverage Order	-0.038	0.181	-0.076
Binge Drinking Score	0.003	0.003	0.396
Step 2			
(Constant)	0.400	0.292	
Age	0.010	0.010	0.212
Beverage Order	-0.296	0.121	-0.593*
Binge Drinking Score	0.005	0.002	0.618*
Binge Frequency, Ages 18-21 years	-0.145	0.033	-0.952*

Note: ΔR^2 =.171 for Step 1; ΔR^2= .581 for Step 2. *$p < .05$, **$p < .01$
$F_{(4,12)} = 3.17$, p =6.09, R^2 = .015
B: beta value; *SE B*: beta value standard error; *β*: standardized beta; binge drinking frequency for 0-18 years of age was also included and did not explain significant variance.

Table 4-4c Multiple Regression Analyses: Factors Predicting Change in Attentional Blink for Moderate Drinkers

Variable	*B*	*SE B*	*B*
Step 1			
(Constant)	-0.210	0.340	
Age	0.014	0.010	0.347
Beverage Order	-0.119	0.092	-0.325
Binge Drinking Score	-0.006	0.009	-0.165

Note: R^2 =.304 for Step 1 *$p < .05$, **$p < .01$
$F_{(3,15)} = 1.746$, p =.211, R^2 = .304
B: beta value; *SE B*: beta value standard error; β: standardized beta; binge drinking frequency for 0-18 and 18-21 years of age were also included and did not explain significant variance

Table 4-5a. Multiple Regression Analyses: Factors Predicting Reward Conditioning

Variable	*B*	*SE B*	*B*
Step 1			
(Constant)	0.094	0.070	
Age	-0.002	0.002	-0.268
Beverage Order	-0.030	0.023	-0.326
Binge Drinking Score	0.001	0.001	0.228

Note: R^2 =.218 for Step 1 *$p < .05$, **$p < .01$

$F_{(3,15)} = 1.12$, p =.381, R^2 = .218

B: beta value; *SE B*: beta value standard error; β: standardized beta; binge drinking frequency between 0-18yo and18-21 years of age was also included and did not explain significant variance.

Table 4-5b. Multiple Regression Analyses: Factors Predicting Reward Conditioning, Moderate Drinkers

Variable	*B*	*SE B*	*B*
Step 1			
(Constant)	-0.107	0.100	
Age	0.003	0.003	0.477
Beverage Order	-2.116E-05	0.026	0.000
Binge Drinking Score	0.002	0.002	0.349

Note: R^2 =.347 for Step 1 *p < .05, **p < .01
$F_{(3,8)}$ = .887, p =.508, R^2 = .347
B: beta value; *SE B*: beta value standard error; β: standardized beta; binge drinking frequency between 0-18yo and18-21 years of age was also included and did not explain significant variance.

Table 4-5c. Multiple Regression Analyses: Factors Predicting Reward Conditioning, Heavy Drinkers

Variable	*B*	*SE B*	*B*
Step 1			
(Constant)	0.172	0.118	
Age	-0.007	0.006	-0.667
Beverage Order	-0.013	0.062	-0.104
Binge Drinking Score	0.001	0.002	0.318

Note: R^2 =.542 for Step 1 *p < .05, **p < .01
$F_{(3,6)}$ = 1.19, p =.446, R^2 = .542
B: beta value; *SE B*: beta value standard error; β: standardized beta; binge drinking frequency between 0-18yo and18-21 years of age was also included and did not explain significant variance.

Table 4-6.Correlations between the Change in Functional Connectivity and AB after Depletion

	Δ in Blink Task ρ (pvalue)			**Δ in Dot Probe Task ρ (pvalue)**		
Δ in Functional Connectivity	**Total**	**MD**	**HD**	**Total**	**MD**	**HD**
VTA-dlPFC	.458 (**.008**)	.600 (**.008**)	.204 (.483)	-.131 (.484)	.100 (.701)	-.464 (.095)
VTA-ACC	.025 (.894)	.154 (.542)	-.086 (.771)	-.152 (.414)	-.005 (.985)	297 (.303)
VTA-LOFC	-.254 (.161)	-.400 (.100)	-.051 (.864)	.356 (.049)	.368 (.1477)	.349 (.221)
VTA-FIC	.262 (.148)	.205 (.416)	.292 (.311)	-.166 (.373)	.154 (.554)	-.468 (.091)
VTA-IFGop	-.029 (.873)	-.220 (.380)	.138 (.637)	-.007 (.971)	-.093 (.722)	.055 (.852)
VTA-mOFC	-.063 (.731)	.174 (.491)	-.059 (.840)	-.300 (.102)	-.292 (.256)	-.327 (.253)
VTA-Amy	-.054 (.768)	-.087 (.732)	-.182 (.533)	.149 (.424)	.409 (.103)	.037 (.899)
VTA-limbic	-.162 (.376)	-.182 (.470)	-.081 (.782)	-.411 (.022)	-319 (.213)	-.552 (.041)
VTA-executive	.023 (.899)	.145 (.567)	-.042 (.887)	.542 (**.002**)	.493 (.045)	.609 (.021)
VTA-Sensorimotor	.073 (.692)	.043 (.864)	.138 (.637)	-.260 (.158)	-.424 (.090)	-.090 (.759)

Values are reported as ρ between the change in functional connectivity of the VTA and ROIs (Depleted-Control) and change in attentional bias on tasks (Depleted-Control).
Reported *p* values represent the results of Spearman's correlations between connectivity changes and attentional bias changes. HD, heavy binge drinkers; MD, moderate light drinkers;
VTA: Ventral Tegmental Area, dlPFC: Dorsolateral PFC, ACC: Anterior Cingulate Cortex, LOFC: lateral Orbital Frontal Cortex, FIC: Fronto-Insular Cortex,
IFGOp: Inferior Frontal Gyrus Opercularis, mOFC: medial Orbital Frontal Cortex, Amy: Amygdala, Limbic: Striatum Limbic region, Executive: Striatum Executive region, Sensorimotor: Striatum Sensorimotor region.

Figure 4-1. Dot Probe Interaction

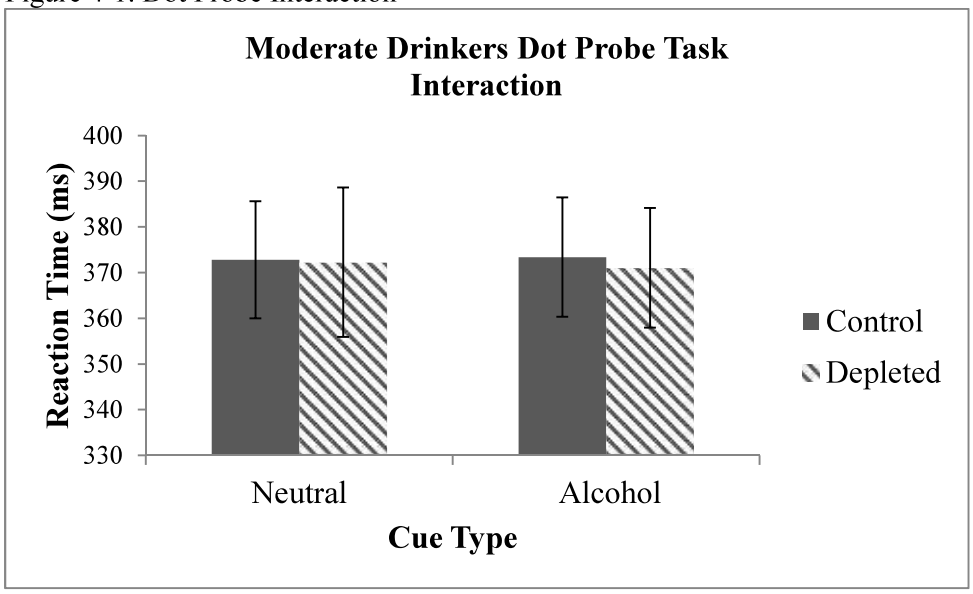

Figure 4-1a. Effect of DA depletion on Dot Probe AB Bias. Comparison of average RT in the control and DA depletion conditions for the moderate drinkers.ms:milliseconds

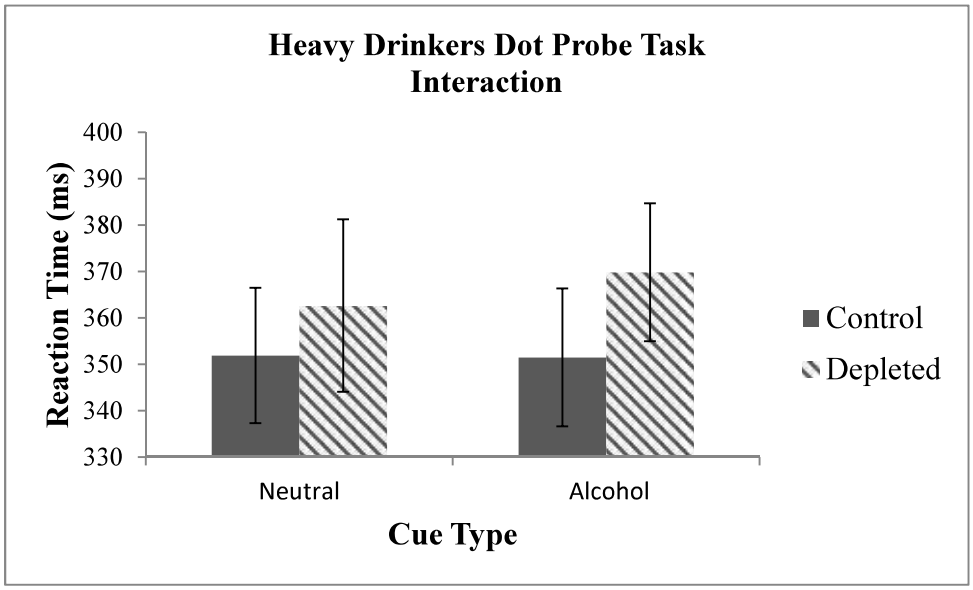

Figure 4-1b Comparison of average RT in the control and DA depletion conditions for the heavy drinkers. No significant effect of beverage, cue type, or group. ms:milliseconds

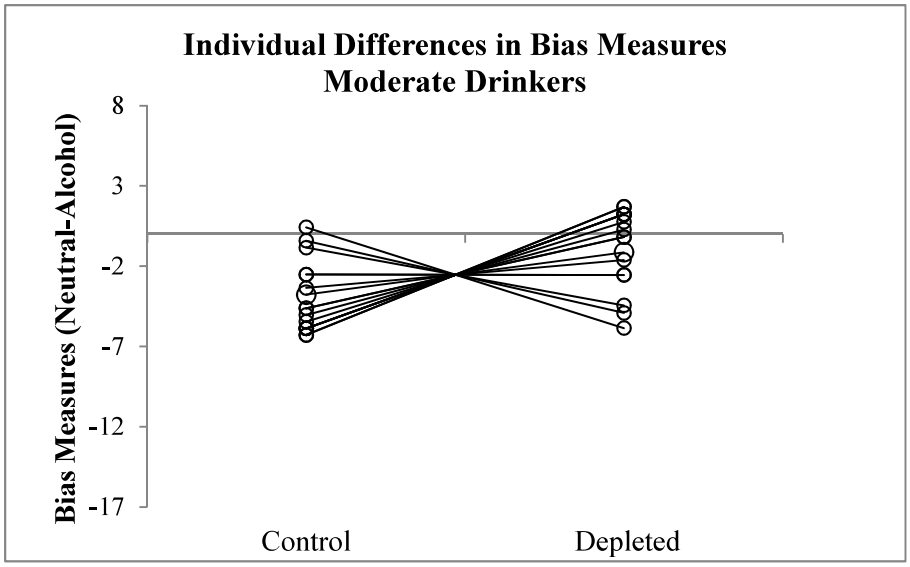

Figure 4-1c. Dot Probe Task Bias Measures between Conditions in Moderate Drinkers. Bias Measure is calculated from $RT_{Neutral}$-$RT_{Alcohol}$ for each condition (Control and Depleted) for moderate drinkers. Values >0 represent greater AB to alcohol related cues.

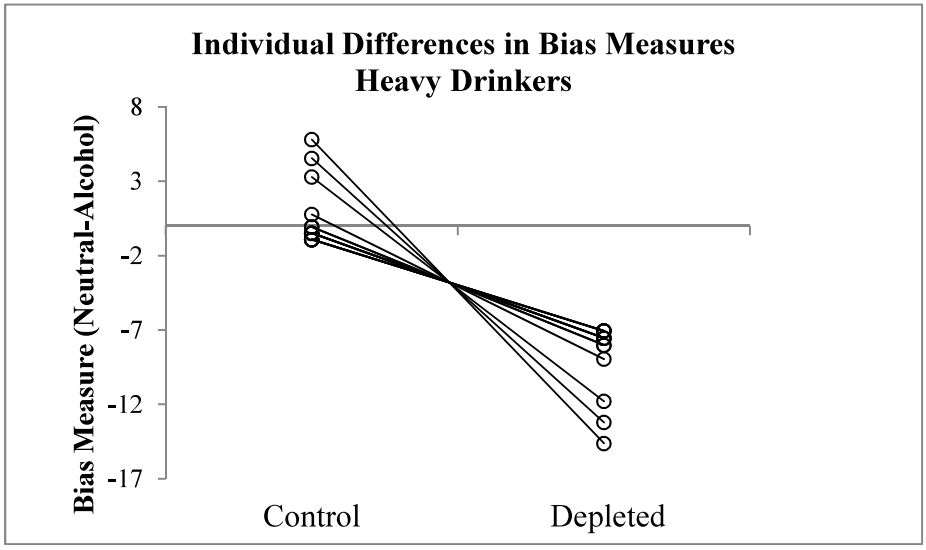

Figure 4-1d. Dot Probe Task Bias Measures between Conditions in Heavy Drinkers. Bias Measure is calculated from $RT_{Neutral}$-$RT_{Alcohol}$ for each condition (Control and Depleted) for heavy drinkers. Values >0 represent greater AB to alcohol related cues.

Figure 4-2.Attentional Blink Task Performance: Effect of DA Depletion

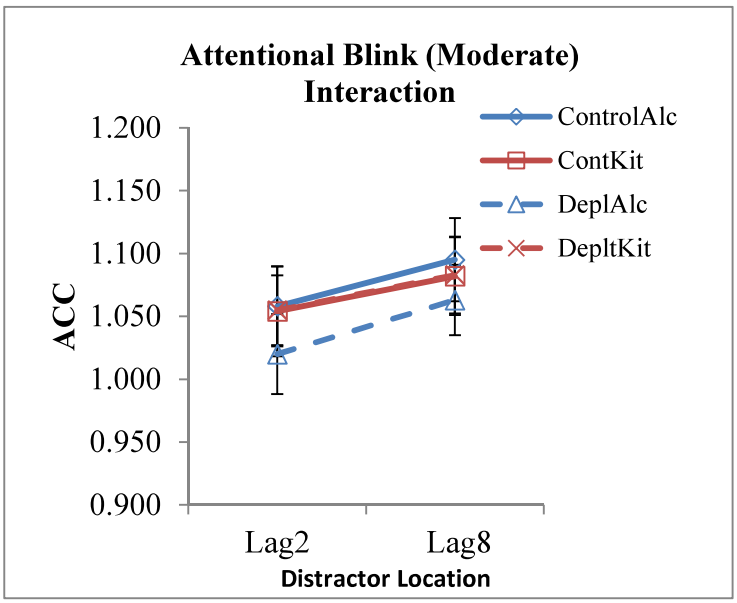

Figure 4-2a. Effect of DA depletion on Attentional Blink AB Bias in Moderate Drinkers. Comparison of average accuracy for each cue type (Alcohol and Kitchen) in the control and DA depletion conditions for the moderate drinkers. No significant interaction between beverage, cue, lag, and group present.ACC:accuracy, ControlAlc:Control Beverage, Alcohol related cue; ControlKit: Control Beverage, Kitchen related cue DepAlc: Depleted Beverage, Alcohol related cue DeplKit: Control Beverage, Kitchen related cue.

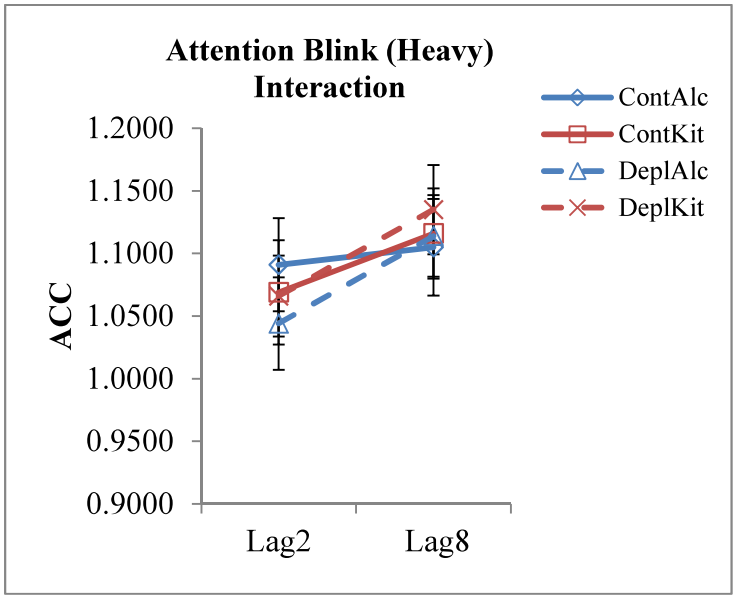

Figure 4-2b. Effect of DA depletion on Attentional Blink AB Bias in Heavy Drinkers. Comparison of average accuracy for each cue type (Alcohol and Kitchen) in the control and DA depletion conditions for the heavy drinkers. No significant interaction between beverage, cue, lag, and group present. ACC:accuracy, ControlAlc:Control Beverage, Alcohol related cue; ControlKit: Control Beverage, Kitchen related cue DepAlc: Depleted Beverage, Alcohol related cue DeplKit: Control Beverage, Kitchen related cue

Figure 4-3. Reward Conditioning Task Performance

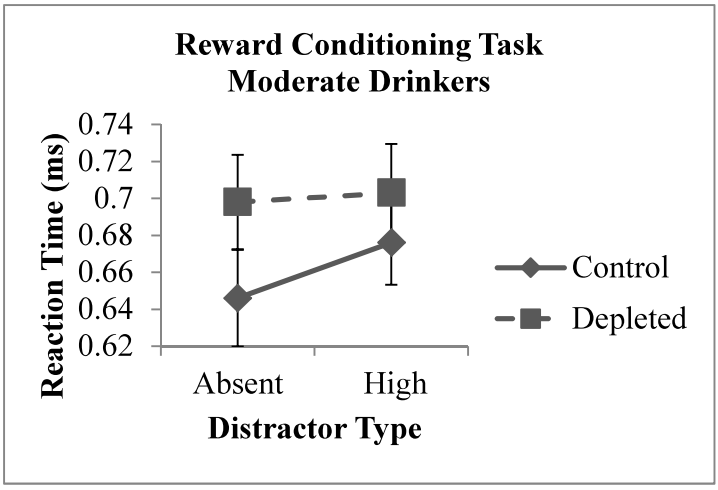

Figure 4-3a. Effect of DA depletion on Reward Conditioning Task in Moderate Drinkers. Comparison of average RT for each distractor trial type (Absent and High) in the control and DA depletion conditions for the moderate drinkers. No significant interaction between beverage, cue, and group present.ms: millisecond

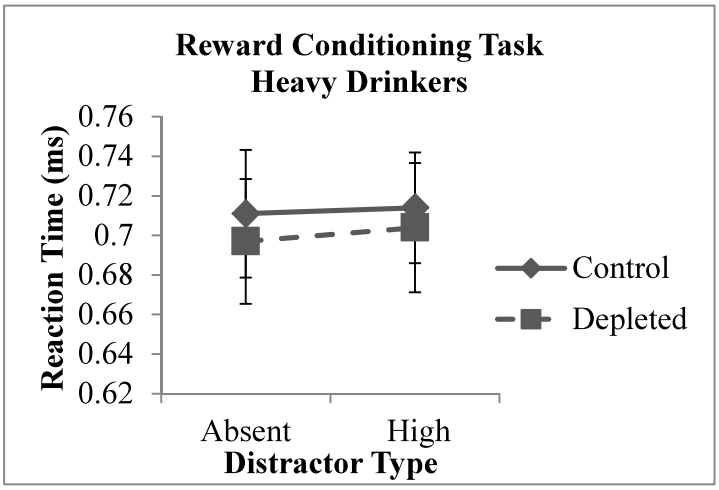

Figure 4-3b. Effect of DA depletion on Reward Conditioning Task in Heavy Drinkers. Comparison of average RT for each distractor trial type (Absent and High) in the control and DA depletion conditions for the heavy drinkers. No significant interaction between beverage, cue, and group present.ms: millisecond

Figure 4-4a Dopamine Depletion Effects on Frontolimbic Functional Connectivity

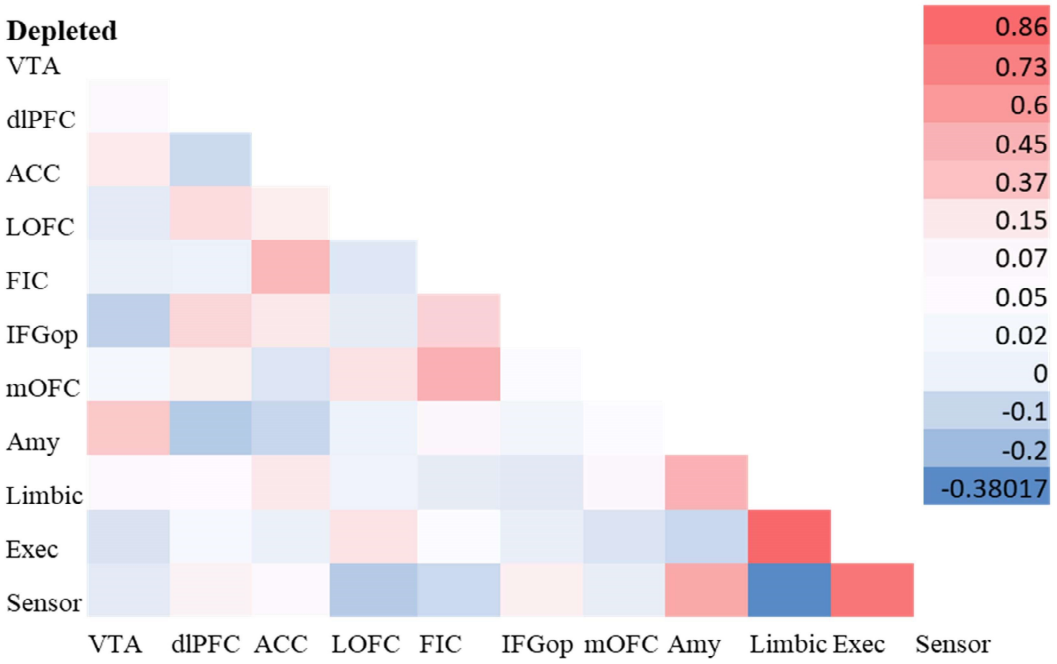

Figure 4-4b Control Beverage Effects on Frontolimbic Functional Connectivity

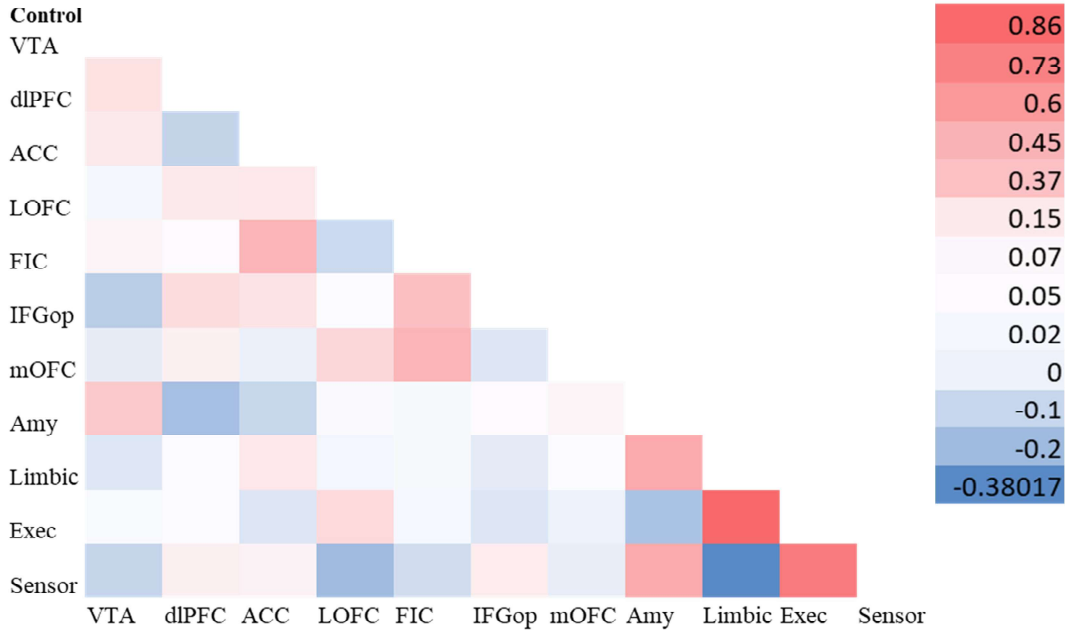

Figure 4-4c Dopamine Depletion Effects on Frontolimbic Functional Connectivity

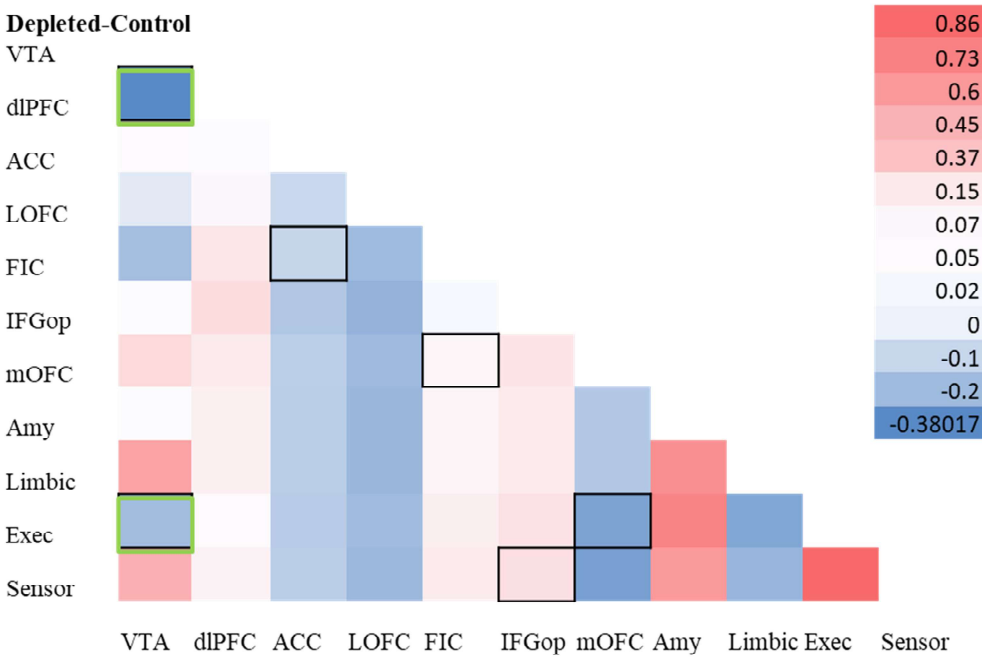

Figure 4-4. Functional connectivity region-of-interest (ROI)-pair analysis of DA depletion effect. Z-score correlation matrices for (a) Depleted, (b) Control beverage condition, as well as the (c) difference between Depleted and Control Z-scores among each region-of-interest (ROI) pair (DEP–CON). The red color indicates increased connectivity, and the blue color indicates decreased connectivity. There were no significant differences in functional connectivity between the conditions that survived correction for multiple corrections but cells outlined in green represent significant correlation with behavioral change (VTA-Exec Fig.4-5a; VTA-DLPFC Fig.4-5b) cells outlined in black represent significant main or interacting effects before correction (main effect of group: ACC-FIC, IFGOp-Sensor; beverage × condition group interaction: mOFC-FIC;; mOFC-Exec). VTA: Ventral Tegmental Area, dlPFC: Dorsolateral PFC, ACC: Anterior Cingulate Cortex, LOFC: lateral Orbital Frontal Cortex, FIC: Fronto-Insular Cortex, IFGOp: Inferior Frontal Gyrus Opercularis, mOFC: medial Orbital Frontal Cortex, Amy: Amygdala, Limbic: Striatum Limbic region, Exec: Striatum Executive region, Sensor: Striatum Sensorimotor region.

Figure 4-5. Correlation between Change in Functional Connectivity and Change in AB Tasks

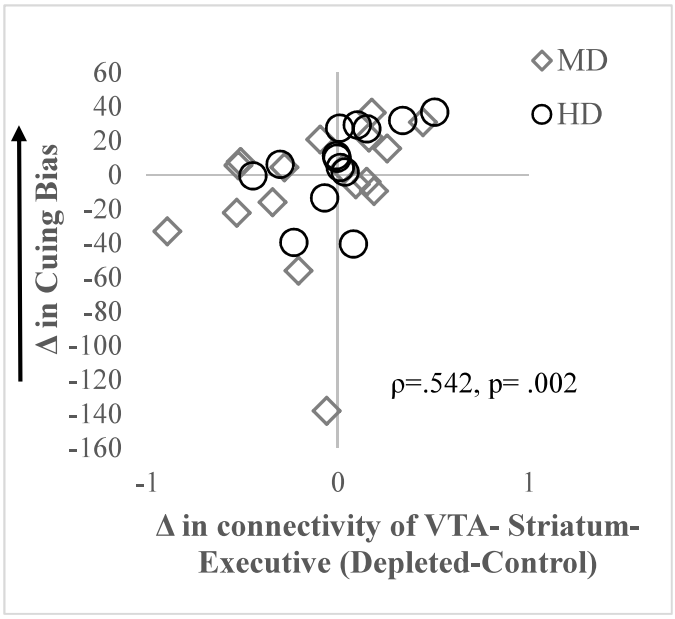

Figure 4-5a. Correlation between change in functional connectivity between the VTA and Striatum and change in AB toward alcohol cues after acute dopamine depletion. Changes in attentional bias and changes in functional connectivity of the VTA and Striatum were positively correlated (ρ=.542, p=.002). Increased bias on the attentional blink task positively correlated with increased functional connectivity of the VTA and DLPFC. MD: Moderate drinkers, HD: Heavy drinkers, VTA: Ventral Tegmental Area.

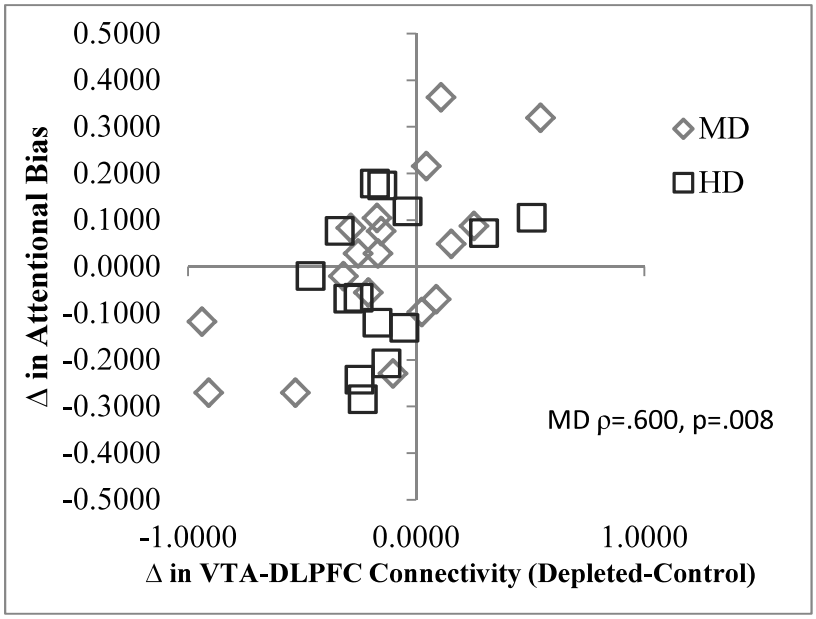

Figure 4-5b. Correlation between change in functional connectivity between the VTA and DLPFC and change in AB toward alcohol cues after acute dopamine depletion. Changes in attentional bias and changes in functional connectivity of the VTA and DLPFC were positively correlated (ρ=.458, p=.008). Increased bias on the attentional blink task positively correlated with increased functional connectivity of the VTA and DLPFC. MD: Moderate drinkers, HD: Heavy drinkers, VTA: Ventral Tegmental Area, DLPFC: Dorsolateral Prefrontal Cortex.

CHAPTER 5:

GENERAL DISCUSSION

Summary of Experiments

The experiments within this dissertation investigated the presence and underlying neural mechanisms of alcohol AB in heavy binge and light to moderate social drinkers using two different AB tasks thought to reflect two different forms of AB, selective attention capture and extended attentional hold. To characterize both forms of alcohol AB in this sample, the relationship between sensitivity to reward conditioning and past and current binge drinking behavior was quantified and used to predict the magnitude alcohol AB captured by the tasks. Focusing on alcohol AB and general reward conditioning, the neural mechanisms associated with these behaviors, specifically the role of dopamine and the functional connectivity of the frontolimbic network, were probed using an acute dopamine depletion manipulation and resting state functional connectivity analysis. We hypothesized that heavy binge drinkers would exhibit increased AB to alcohol related cues compared to light to moderate drinkers. Furthermore, we also expected heavy binge drinkers to show increased reward conditioning to monetary rewards, and that sensitivity to reward conditioning (general reward AB) would predict the magnitude of both forms alcohol AB (alcohol related AB) across individuals but be magnified in heavy binge drinkers. Finally, we hypothesized that AB to alcohol and reward-conditioned cues would be modulated by dopaminergic signaling in frontolimbic circuits and as such that acute dopamine depletion would decrease in AB in proportion to changes in functional connectivity within frontolimbic circuitry, particularly connections including the VTA.

General Discussion

Chapter 2: Alcohol Use, Selective Attention Capture and Reward Conditioning

We investigated two forms of AB to alcohol related cues and found that AB did not differ significantly between heavy, binge and light to moderate social drinkers. Similarly, there were no significant differences in reward conditioning between the two groups. To explore the relationship between general reward conditioning and alcohol AB, we used current and past binge drinking patterns and reward conditioning as predictors of AB. Multiple linear regression did not reveal a significant overall relationship between of these variables, however reward conditioning did significantly predict AB as captured by the dot probe task. The dot probe task models selective attention capture, a form of AB that is characterized by quick and automatic capture of attention. Interestingly, this relationship was in the opposite direction of our hypothesis, with a decrease in reward conditioning significantly predicting an increase in alcohol AB.

We attempted to identify another form of alcohol AB by using the attentional blink task. The attentional blink task thought to model extended attentional hold. While we did not find an overall group difference in alcohol AB on this task, we did find a significant interaction of group, cue type, and lag. This significant finding was also contrary to our hypothesis with moderate drinkers exhibiting more attentional blink bias than heavy binge drinkers. Neither reward conditioning nor drinking measures significantly predicted alcohol AB captured by the attentional blink paradigm. Our analysis also revealed no significant relationship between the two AB tasks and no significant drinking group correlations. However, when both groups were combined, AB was negatively correlated with several drinking measures. The AUDIT, consumption and harm subscale of the AUDIT, past and current binge drinking, as well as drinking motivations of enhancement were all negatively correlated with the blink task reflecting an inverse relationship of bias and drinking status, driven by the heavy binge drinkers.

In Chapter 2, we aimed to identify and compare two forms of alcohol AB in a sample including both light to moderate and heavy binge drinkers. Few studies have presented evidence of AB in social drinkers, but none to our knowledge, have attempted to distinguish two forms of AB in the same study (Manchery

et al. 2017; Nikolaou et al. 2013; Tibboel et al. 2010; Townshend and Duka 2001). The spatial cuing, or "dot probe," task is thought to detect the automatic shifting of attention to a cue's spatial location (Maylor and Hockey 1985; Posner 1980). Contrary to our hypothesis, we did not detect a significant difference of alcohol AB in heavy binge drinkers compared to moderate drinkers on the dot probe either task. This finding was surprising given the widespread prevalence of AB in both social drinking and alcohol addicted individuals but evidence from AB studies also indicate that addiction severity and craving (Copersino et al. 2004), active drug or alcohol use (Bradley et al. 2003; Bruce and Jones 2004), and treatment status (Gardini et al. 2009) all play a role in AB. Our sample of heavy binge drinkers differed in alcohol consumption from those studies that have previously identified alcohol AB in heavy social drinking groups. Our sample's weekly drinking rates are classified as heavy according to the standards put forth by NIAAA, however previous studies that found alcohol AB in social drinking populations recruited drinkers with a weekly consumption of at least 20 drinks per week, while our minimum was 14 drinks per week (Bruce and Jones 2004; Field et al. 2004; Townshend and Duka 2001).While our standards of drinking may correspond to problematic drinking behavior and health outcomes, they may not be sufficient drinking patterns to elicit the development alcohol AB (Townshend and Duka 2001). Another factor that may have played a role in our findings was the exclusion criteria of individuals that previously or currently are seeking treatment alcohol use problems. There was no exclusion for meeting criteria for an AUD, which may mean that our heavy binge drinking group varied significantly on many factors (addiction severity, craving, withdrawal) that have previously been reported to have a strong relationship with AB (Copersino et al. 2004; Field et al. 2014; Field et al. 2005b). Including individuals that may potentially have varying levels of these factors could increase variability in our sample making it difficult to capture alcohol AB in this sample. While we used behavioral questionnaires to address drinking motivations and a subset of one questionnaire focused on problem drinking behavior and consequences there were no direct measures of craving or withdrawal. Moreover, the participant's own feelings about alcohol use were not assessed outside of the drinking motivations questionnaire. Having more information on alcohol use perceptions may have helped us characterize AB more clearly. For

example, collecting information on lifetime drinking habits to establish if participants ever attempted to cut down on their drinking or had failed quit attempts would provide insight on their perception of their drinking behavior and possibly highlight why our sample of heavy drinkers seemed biased away from alcohol. Measures such as the Timeline Follow Back (Sobell et al. 1986) can provide insight alcohol consumption patterns from the onset of regular drinking (Skinner and Sheu 1982). Furthermore, in studies of AB in SUDs, treatment status (treatment seeking vs non treatment seeking) has played a significant role in the presentation of AB. In cocaine users, treatment seekers exhibited AB to cocaine related words while non treatment seekers did not. Moreover the treatment seekers also reported less usage than the non-treatment seeking group (Vadhan et al. 2007). While in another study of treatment seeking cocaine users, users did not exhibit AB to cocaine related stimuli but there was significant variability in the group, similar to our sample (Carpenter et al. 2012). Although there are clearly different neural effects associated with different drugs of abuse, AB to addiction related stimuli is thought to result from Pavlovian conditioning, whereby the repeated pairing of addiction related stimuli and reward, results in the attribution of incentive salience to addiction related cues (Berridge 2004; Berridge and Robinson 1998; Uslaner et al. 2006) and as such we can generalize findings across addiction. These findings highlight the potential importance of factors such as past or current treatment status or contemplation of treatment on AB.

Another factor associated with treatment status and AB is that bias away from alcohol related stimuli has been reported in studies of heavy drinkers after treatment. The biasing away appears to be a conscious attempt to divert attentional resources away from or ignore alcohol cues (Garland et al. 2010; Schoenmakers et al. 2007; Schoenmakers et al. 2010; Wiers et al. 2011).While it is unlikely that all our heavy drinkers fell into this category, it may be possible that the variability in our sample's drinking status, lifetime drinking history (quit attempts or desire to drink less), and possible internal perceptions of their alcohol use effected responsiveness to alcohol related cues and the negative bias phenomenon was present in our sample.

In addition to the discussion above on addiction severity and frequency of use, versions of AB tasks used in our study differed slightly from those used in the field that elicited AB. Research has shown that when complex images, such as bar and party scenes showing people consuming alcohol were used, adult alcohol drinkers did not exhibit AB (Miller and Fillmore 2010). In this study, all images were complex alcohol related images which may have played a role in the lack of AB captured by the task. The use of less complex stimuli may have elicited an AB but cautious must be used in applying this method. If AB is to be used a biomarker of clinical relevance and interpretation, the use of stimuli that is most reflective of the actual environmental stimuli that drinkers encounter is important.

Another difference in our study was the length of our dot probe task. The version of the task used in the current study had significantly fewer trials than in our previous study that captured AB to smoking related cues in active smokers (Chanon and Boettiger 2008). In that study of AB in active smoker, AB to smoking related cues was only captured on short SOA trials. As discussed extensively in Chapter 2, the short SOA reflects selective attention capture and was the SOA we used as well. All other aspects of the tasks were identical outside of the category of images (smoking vs alcohol) and it may be that we merely did not have enough trials to capture AB in this study.

Our investigation of the relationship between general reward conditioning and alcohol AB, revealed a trend of reward conditioning predicting selective attention capture on the dot probe task, but not in the direction we would have hypothesized. AB appeared to increase as reward conditioning decreased. This suggests a potential inverse relationship of selective attention capture to alcohol-related images and generalized reward conditioning. We hypothesized that generalized reward conditioning may underlie AB but it may also be the case that as AB to alcohol related stimuli increases, propensity to generalized reward conditioning decreases. Evidence from studies on the change in reactivity to cues suggests that throughout the course of addiction the value of non-drug related rewards is diminished (Goldstein et al. 2008; Parvaz et al. 2012). However this does not appear to explain our findings because there were no differences in the acquisition of reward conditioning on the training phase of the task.

As discussed in Chapter 2, there were several limitations present including lower levels of heavy drinking in our sample compared to what has been previously reported in the literature, the use of AB paradigms that may have lacked the ability to capture AB and the lack of more in depth assessment of the severity of alcohol related problems in our sample may have limited our ability to capture AB using this task. These limitations can be addressed in future studies in a number of ways. Future studies may benefit from increasing the quantity of drinks per week that are considered for inclusion into the heavy drinking group. This would allow for better assessment of addiction or problem drinking severity as well as be more consistent with previous findings in the literature. Additional behavioral questionnaires could be utilized to probe past drinking behavior and perceptions of alcohol allowing for the assessment of personal drinking behaviors and internal feelings towards alcohol. Future studies could also benefit from modifying the dot probe task to have more trials and piloting of AB tasks in a general population of alcohol drinking individuals to provide evidence of which tasks are most reliable in a population of social drinkers.

Chapter 2: Alcohol Use, Extended Attentional Hold and Reward Conditioning

We attempted to identify another form of alcohol AB by using the attentional blink task. The attentional blink task thought to model extended attentional hold. While we did not find an overall group difference in alcohol AB on this task, we did find a significant interaction of group, cue type, and lag. This significant finding was also contrary to our hypothesis with moderate drinkers exhibiting more attentional blink bias than heavy binge drinkers. Moreover AB on the blink task was negatively correlated with several measures of drinking behavior. AB on this task was negatively correlated with adolescent binge drinking frequency, total AUDIT (Harm and Consumption subscales as well) and drinking to enhance experience. Taken into context with the larger body of literature on the attentional blink, these finding may be similar to traditional studies of the blink effect for emotional valence. As discussed in Chapter 2 increased AB among our moderate drinkers may result from the salience of alcohol images however this should also be the case in our binge drinkers. The lack of AB in heavy drinkers may result from deficits in attentional processing or associative learning around alcohol related cues due to the

effects of binge drinking on neural mechanisms required for these cognitive processes (intoxication during learning, learning impairment due to binge drinking early in life). Another explanation may be that binge drinkers experience more negative states (hangovers, blackouts) associated with drinking reducing associative learning to alcohol cues. While our current data set does not support that theory because albeit not significant AB captured on the attentional blink is negatively correlated with our one measures negative consequences of drinking, AUDIT Harm subscale. As mentioned in our discussion of selection attention capture above future studies may benefit from probing lifetime drinking histories to better characterize drinking behavior, perceptions in both groups. Moreover, our findings on the blink task suggest cognitive markers of general associate learning in both groups may be helpful in to determining if deficits reflect differences in AB due to other underlying processes.

Our modified attentional blink task has not been used in a population of social drinkers; however other versions of the attentional blink task have been used in addiction research. Using other versions of the attentional blink paradigm, researchers have been able to identify what is thought to be two different forms of AB. The blink paradigm can be used to probe extended attentional hold or the priority processing of addiction related cues by the attention system (Chanon and Boettiger 2008; Munafó et al. 2005). Addiction severity and drinking frequency may have affected the results on this task as well, however using one of the blink paradigms that have been used in the literature to look at one or both of these forms of AB may have elicited a significant signal of AB. Our findings of AB in Chapter 2 add to a growing body of literature on AB in social drinking populations. Taken together, AB appears to be a complex cognitive phenomenon that is greatly influenced by individual differences. While widely reported in the addiction, tasks that are used to captured AB, in any form, have mixed findings. Great care should be taken to validate AB paradigms in population of interest to optimize the ability to capture AB. Additionally when researching AB in social drinkers, findings from the literature suggests care must be taken to recruit individuals with heavy alcohol consumption and potentially high levels of addiction severity.

Chapter 3: Reward Conditioning

In Chapter 3, we investigated the presence of increased reward conditioning in our sample and did not find a significant reward conditioning effect as in previous studies (Anderson and Folk 2010; Anderson et al. 2011a; b; Yantis et al. 2012). We found that a greater frequency of binge drinking before age 18 predicted significantly greater expression of reward conditioning, independent of current binge alcohol use. Our findings using the reward conditioning task support evidence from the rodent literature that adolescent binge drinking heightens Pavlovian reward conditioning. These data suggest that adolescent binge alcohol exposure alters systems vital to our attention system, including circuits that process reward cues.. Furthermore, this finding supports the preclinical literature on adolescent binge-like alcohol exposure leading to neural development changes and persistent impairments. The idea that frontal impairment might underlie enhanced reward conditioning associated with more frequent adolescent binge-drinking is consistent with a variety of evidence demonstrating that the adolescent prefrontal cortex is particularly vulnerable to the damaging effects of alcohol (Crews et al. 2007). Models of adolescent binge drinking in animals have revealed significant reductions in neurogenesis (Vetreno and Crews 2015) and increased risk taking behavior and alcohol consumption in adulthood (Boutros et al. 2014; Crews et al. 2016). Adolescence is a period in which significant changes to reward neurocircuitry occur (Luciana 2013; Wahlstrom et al. 2010), and exposure to alcohol during this period is associated with significant changes in brain activity (Cservenka et al. 2015). Thus, frontal insult may mediate the relationship reported here between adolescent binge drinking frequency and sensitivity to reward conditioning. Future studies that include measures of frontal function are needed to test this hypothesis.

One follow up study to Chapters 2 and 3 would involve equating male and females in the sample to assess whether there is a relationship between gender and reward conditioning, specifically if adolescent binge drinking is related to increased reward conditioning in females compared to males. In addition to the dot probe and attentional blink tasks, tasks that assess frontal lobe function and working memory can be included in future studies to assess their relationship with AB and reward conditioning (BERG 1948; D'Esposito et al. 2006; Stuss and Alexander 2000). More in-depth analysis of personality traits and life

experiences could also be included to assess what may or may not be playing a role AB or reward conditioning. For example, assessment of childhood traumatic experience has been found to be a predictor of AUDs and hazardous drinking behavior (Bernstein et al. 1994; Gerhant and Olajossy 2016; Lotzin et al. 2016). Including measures such as these may shed light on important traits and predictors of AB not revealed in our current study.

Chapter 4: Neural Mechanisms of AB

Chapter 4 of this dissertation explored the role of dopamine and frontolimbic neural circuitry on AB and reward conditioning. We quantified the magnitude of alcohol AB and reward conditioning in heavy binge and light to moderate social drinkers before and after acute dopamine depletion using a dopamine depletion beverage and using the same 3 behavioral tasks as Chapters 2 and 3. We focused our functional connectivity analysis on the VTA and key frontolimbic regions and whether these connections were altered after dopamine depletion and if those changes predicted significant changes in AB.

Group Effects on Selective Attention Capture

Contrary to our findings in Chapter 2 and 3, we did not find many significant differences in demographics in this sample. Heavy drinkers differed significantly from moderate drinkers in current binge score, adolescent binge frequency between the ages of 18-21, total AUDIT, and social and enhancement drinking motivations, exhibiting higher scores on all these measures. It is surprising that adolescent binge drinking before the age of 18 did not significantly differ in our groups as it did Chapter 2. Adolescent binge drinking has been shown to alter systems vital to our attention system, including circuits that process reward cues and lead to neural development changes and persistent impairments. It is not clear when in adolescence binge drinking has the most deleterious effects but the lack of significant difference in binge drinking between our groups during this time period may suggest that alterations of neural systems of this group of heavy binge drinkers may be different from those of heavy drinkers that initiated binge drinking earlier in life.

We did not detect a statistically significant difference in AB on the dot probe between our groups on the control beverage. These findings mirror those in Chapter 2 as AB on the control beverage should

reflect the individual's normal AB to alcohol related stimuli. Perform across samples, in Chapter 2 and the current sample, was not significantly different although moderate drinkers in this sample appear to have slower RT. Similar to our findings in Chapter 2, limitations include, heavy binge drinkers has lower drinking levels than seen in other studies of heavy binge drinking, completed the same battery of questionnaires that may not account for important past drinking behavior, and completed the same version of the dot probe task which may benefit from the addition of more trials.

Group Effects on Extended Attentional Hold

We also did not detect a statistically significant difference in AB on the attention blink task between our groups on the control beverage. Heavy drinker's performance on the attentional blink task was similar to that which we saw in Chapter 2 but there was no capture of AB in the moderate drinking group. As suggested in our discussion of Chapter 2, the lack of findings of AB may reflect levels of drinking behavior below the threshold for alcohol AB.

Baseline Functional Connectivity of the Frontolimbic Network

Our analysis of functional connectivity under the control beverage condition did not reveal a significant effect, however we did see trends for a main effect of group in the connectivity between the AnCC and FIC, and between the IFGOp and sensorimotor striatum, these effects did not survive correction for multiple comparisons.

Trends suggested increased functional connectivity between the AnCC and FIC, and between the IFGOp and sensorimotor striatum in HD compared to MD. These regions have all been repeatedly shown been shown to be involved in addiction related behaviors. The AnCC and FIC are major hubs of the salience network which aids in conditioning and assigning incentive salience to drugs and drug-related cues (Goldstein and Volkow 2011). These trends may suggest increased intrinsic salience network connectivity as a result of drinking status. It is possible with more subjects these findings may have reached the level of significance supporting the role of drinking status in alterations in functional connectivity of the salience and key frontolimbic networks.

Another consideration when looking at just the group effects in this data set is whether the differences in functional connectivity under control conditions predicts individual differences in AB. Although overall group effects may not be present differences in connectivity under the control condition may reflect alterations in the system that facilitates AB and as such predicts individual differences in AB.

Acute Dopamine Depletion Effects on Selective Attention Capture

We did not see any significant effects of dopamine depletion on AB captured by the dot probe task. However, visual inspection of the data after dopamine depletion revealed interesting patterns. In the moderate drinkers, most individuals look to have increased the attentional bias to alcohol related stimuli when depleted however, dopamine depletion appears to decrease attention bias in heavy binge drinkers. Moreover, upon close inspection of these findings it appears that individuals in both groups that exhibited either the most bias towards or away from alcohol related cues on the control behavior has the inverse behavior when depleted. Specifically, in moderate drinkers that showed the greatest amount of bias away from alcohol during the control condition also showed the greatest amount of alcohol AB when depleted. In heavy drinkers, those individuals that showed any alcohol related AB on the control condition, also exhibited the greatest amount of bias away from the alcohol related cues when depleted (Figure 4-1c-d). Again these results do not reach a level of significance for beverage effect nor is there an interaction between group and beverage but they may suggest that we were underpowered to detect a true effect of beverage. Furthermore, these findings support investigating whether the differences in functional connectivity under control conditions predicts individual differences in AB as it appears that there may indeed be some individual differences in the groups interacting with acute dopamine depletion.

Depletion Effects on Extended Attentional Hold

Utilizing the attentional blink task to explore the effects of acute dopamine depletion on extended attentional revealed no significant effect of dopamine depletion. Alcohol AB appears unaffected by acute depletion and behavior between the groups is comparable. AB captured by this task reflects a different form of AB than that which is captured by the dot probe task so it is not surprising that the same trends or

effects are not seen in this task. The development and maintenance of extended attentional may reflect different neural mechanisms or again as we saw in Chapter 2, the lower levels of binge drinking seen in our sample along with lower levels of adolescent binge exposure may not result in robust AB findings using this task.

Depletion Effect on Reward Conditioning

We assessed the effects of acute dopamine depletion and group on reward conditioning and found no significant findings. There were no group or beverage effects and no interaction between group and beverage. One of the caveats to this study was a protocol change after the beginning of data collection. Several participants did not have a within subjects design for this task and as such there are fewer individuals in this analysis making it grossly underpowered to detect difference. Future studies should put forth effort to fully explore the effects of dopamine depletion on reward conditioning by collecting a full data.

Depletion Effects on Functional Connectivity

We also did not detect a significant difference in functional connectivity in our frontolimbic network after depletion. While there were group effect trends, there were no beverage effect trends. Our lack of findings may reflect several factors. Again, our study sample was fairly small and we may have been unpowered to detect overall effects of beverage. In addition, our heavy drinking group exhibited lower levels of adolescent binge drinking than in our previous sample which may suggest that fewer alterations or changes occurred to the neural system that drive alcohol AB.

Group and Depletion Effects on Frontolimbic Functional Connectivity

We did not observe significant group by beverage interaction effects but similarly to our analysis of group, we also observed interesting trends. There were group × depletion interactions trends between the mOFC and both the executive striatum and the FIC. The group × depletion interaction trend of the mOFC and executive striatum suggests that acute dopamine depletion decreased functional connectivity of these regions in HD, while it tends to increase connectivity of these regions in the MD group. Moreover the

group × depletion interaction trend of the mOFC and FIC suggests that acute dopamine depletion increases the functional connectivity of the mOFC and FIC in HD, while it tends to decrease connectivity of these regions in MD. The FIC is also a hub of the salience network is widely characterized as playing a role in emotional and attention processing. It is suggests that the FIC in conjunction with other regions of the salience network help facilitate access to attention and working memory resources when a salient event is detected and regulate reactivity to salient stimuli (Menon 2011; Menon and Uddin 2010). Potential changes in functional connectivity in HD between the mOFC, a region shown to involved in attentional control as well as craving in addiction and the FIC, as a result of dopamine depletion may suggest underlying differences in attention and salience processing in these individuals that effects AB.

Individual Differences in Dopamine Depletion Effects on Functional Connectivity

Dopamine depletion did not appear to cause overall changes in functional connectivity between our frontolimbic ROIs or on behavior however, we observed trends in connectivity measures and interesting individual changes in behavior on the dot probe task. Thus, we evaluated individual differences in whether dopamine depletion effects on AB correlated with depletion effects on functional connectivity.

Our analysis revealed two significant findings. The extent to which acute dopamine depletion increased AB toward alcohol cues in the dot probe task was associated with the magnitude of increase in functional connectivity between the VTA and the executive striatum. Similarly, the extent to which dopamine depletion increased AB toward alcohol cues in the attentional blink task was associated with the magnitude of increase in function connectivity between the VTA and dlPFC; interestingly this effect was driven solely by the moderate drinkers.

These findings support our hypothesis that dopaminergic function and frontolimbic neural circuitry plays a role in facilitating AB. However, we were surprised to see that acute dopamine depletion actually increased both forms of AB and that increases were positively correlated with increases in functional connectivity of key frontolimbic regions. Moreover, the relationship between the change in VTA and dlPFC connectivity and change in AB captured by the attentional blink task being driven by moderate

drinkers was particularly surprising.

The changes in functional connectivity between the VTA and the executive region of the striatum is not surprising given the role of the striatum in response to drug related cues (Grusser et al. 2004; Volkow and Morales 2015; Volkow et al. 2006). The executive region of the striatum has been shown to facilitate executive function, goal directed behavior and cognition. Additionally, this striatal region plays a role in goal directed behavior and evaluating action selection (de Wit et al. 2012; Tanaka et al. 2008; Tanaka et al. 2004) which may be mediated by dopaminergic function in this region. The dlPFC has been found to be particularly vulnerable to substance use and plays a critical role in addiction, specifically in response to drug related cues (Goldstein and Volkow 2011). Moreover, AB measured in the attention blink task of another study was found to decrease following anodal TMS to the left DLPFC in normal participants with large baseline AB (London and Slagter 2015). This study's findings are of particular interest because they suggest that individual differences in neural circuitry predict changes in AB. It is likely that larger baseline AB reflected significant differences in neural circuitry that could be manipulated with TMS, whereas those neural changes were not present in those without large baseline AB. One neural mechanism that is relevant to this finding is the role of dopamine. We hypothesized that depletion would decrease functional connectivity and AB. Previous studies have shown that acutely depleting dopamine will decrease reward related brain activations (Bjork et al. 2014; da Silva Alves et al. 2011; Frank et al. 2016) and even improves attentional control as assessed by Stroop performance (Scholes et al. 2007). These studies in combination with the wealth of information suggests that dopamine levels and function changes as a result of addiction (Asensio et al. 2010; Freeman et al. 2015; Goldstein and Volkow 2002; Vengeliene et al. 2008; Volkow and Morales 2015; Volkow et al. 2010; Volkow et al. 2006; Volkow et al. 2007) make interpretation of this finding particularly convoluted. Although our participants were not treatment seeking individuals with clinical diagnoses of AUDs, their patterns of heavy, binge drinking may make them susceptible to these changes in dopamine function as well.

Although, significant evidence suggests that the relationship between dopamine depletion and

changes in attentional bias should be fairly straightforward, prefrontal dopamine tone often affects behavior in an inverted U shaped fashion (Freeman et al. 2015; Smith et al. 2013; Vijayraghavan et al. 2007). This inverted U results in differential optimal levels of dopamine functions. Individuals with too little or too much PFC dopamine exhibit different behavioral patterns to similar tasks. Research has shown dopamine levels change as a result of clinical disorders such addiction, but that there exist genetic differences in PFC dopamine levels as a function of a genetic polymorphism in the catechol O-methyltransferase (COMT) enzyme, which is an enzyme predominantly thought to exert its cognitive effect through PFC dopamine transmission (Craddock et al. 2006; Kelm and Boettiger 2013; Smith and Boettiger 2012; Smith et al. 2013; Wu et al. 2012). Considering these potential individual differences in baseline dopamine levels and function, the effects of acute dopamine depletion become unclear. For example, did acutely depleting dopamine shift individuals outside of their optimal dopamine functioning resulting in AB? One way this can be addressed is to assess the role of the genetic biomarker for PFC dopamine, COMT and use it as a predictor of change in functional connectivity and AB. Moreover, directly assessing changes in dopamine levels by measuring plasma levels and concentrations of dopamine extracted from blood and using the magnitude of change in plasma levels to predict functional connectivity and behavioral changes would shed light on the role of dopamine in frontolimbic functional connectivity and AB. Both of our findings of changes in connectivity of frontolimbic regions and different forms of AB suggest that dopaminergic function or tone may play a global role in facilitating functional connectivity and cognitive behaviors, such that multiple forms of AB are effected and that individual differences in baseline dopamine function will result in different neural and behavioral responses.

General Limitations and Future Directions

As outlined in Chapters 2, 3, and 4 there were several limitation in this research. One of the most glaring limitations of our imaging study in Chapter 4 is the small sample size Our sample was actually comparable and larger than some studies using an acute dopamine depletion method but our goal was, in

part, to look at group differences in behavior (Bjork et al. 2014; Carbonell et al. 2014; da Silva Alves et al. 2013; da Silva Alves et al. 2011; Venugopalan et al. 2011). While our study may have been sufficiently powered to assess the effects of the dopamine manipulation it may have lacked the power to capture group differences in a highly variable population such as hazardous drinkers.

Another limitation of this study is the lack of variability in adolescent binge drinking. Preclinical research on adolescent binge drinking has provided significant evidence of the deleterious effects of binge like drinking exposure on neural development (Boutros et al. 2014; Crews et al. 2016; Liu and Crews 2015; Vetreno and Crews 2015; Vetreno et al. 2016). Our groups did not differ significantly adolescent binge on drinking measures before the age of 18 in Chapter 4 and as a result it is possible that our heavy binge drinking group did not have enough exposure to result in the neural changes that lead to differences in functional connectivity and dopamine modulation of AB. In Chapters 2 and 3, we saw strong relationships with the frequency of binge drinking in adolescence and AB and reward conditioning which suggests it indeed plays a role in the phenomenon of AB and generalized reward conditioning.

Future studies may benefit from performing additional, more complex neuroimaging analysis. The study involved an 8 minute resting state functional connectivity scan, which provides sufficient data to perform dynamic functional connectivity analysis. This analysis would look at changes in functional connectivity across the 8 minutes of scanning using smaller windows of time, ie.1.5min bins. It is possible that the depletion method causes more variability in network connectivity or makes networks more unstable. Another analysis that may provide insight into the neural circuit of interest is using a whole brain analysis method. This method can be utilized to identify regions or networks that are most sensitive to the effects of dopamine depletion and show group differences in activity or connectivity. Starting our investigations by looking at the whole brain and assessing only those changes that are related to our measures will increase our power to detect significant findings. It is apparent from the trends we saw in increased functional connectivity of salience network regions and regions of the central executive network that there are likely relevant findings in our dataset that will contribute to the growing body of

knowledge on the neural mechanisms of AB.

Conclusions

The studies in this dissertation attempted to investigate multiple forms of AB and its underlying neural mechanisms in a subclinical group of heavy, binge and light to moderate social drinkers. While there were several limitations in this studies that may have affected our ability to capture significant findings, as a whole these studies contribute to several areas of addiction research.

Significant findings in the area of reward conditioning suggest that adolescent binge exposure appears to heighten Pavlovian reward conditioning in females. Our data adds to mounting evidence that adolescence is a time of vulnerability to the effects of alcohol, leading to persistent neural and behavioral sequelae. We demonstrated that adolescent binge frequency before the age of 18 predicted propensities for reward conditioning in females, demonstrating the need to consider gender in assessment of reward conditioning.

Our findings of the positive correlations between the change in alcohol AB and change in functional connectivity of the VTA and DLPFC and VTA and executive striatum after acute dopamine depletion provide evidence of the role of dopamine in this neural pathway and demonstrate that this neural circuit may potentially be useful as a biomarker for this form of AB. These results provide support for previous findings in the literature that identify the role of the DLPFC in AB (Choi et al. 2012; London and Slagter 2015) and suggest that VTA to DLPFC neural connectivity may be altered as a result of heavy binge drinking.

The research in this dissertation suggest that AB complex and sensitivity cognitive phenomenon often seen across addicted and alcohol using populations. However, inconsistent findings in the literature and even within this dissertation make characterizing and determining its clinical relevance difficult. AB appears to a very sensitive cognitive phenomenon that is influenced by a number of factors such as addiction or binge drinking severity, addiction states and status (craving, withdrawal, treatment or non-treatment seeking), alcohol use history, mood and personality traits. All of these factors involve levels of individual variability that may change throughout the course of addiction and are often associated with

hazardous drinking behavior. Attempting to better understand this phenomenon presents many challenges and leaves many questions about AB and its underlying neural mechanisms unanswered. A number of studies have assessed the clinical relevance of AB (Christiansen et al. 2015b; Field et al. 2014). Attentional training aims to train individuals to avoid or approach drug related or problematic cues using visual probe task, reflecting selective attention capture. Several studies been able to reduce AB in the groups trained to avoid drug related cues (Attwood et al. 2008; Field and Eastwood 2005; Schoenmakers et al. 2010). These studies suggest that modifying selective attentional capture may be a viable treatment for addiction related bias however several studies have failed to replicate its findings, although this may be attributed to differences in study methodology (Field et al. 2009a; Schoenmakers et al. 2007). While these studies and others that suggest AB predicts aspects of active drug use and treatment success, and as such can be utilized as a potential biomarker for addiction or treatment we must continue to try to understand how it develops and which systems mediate this phenomenon.

Taken together, this dissertation adds to the fields of addiction research and cognitive neuroscience by contributing to our understanding of alcohol related attentional bias, generalized reward conditioning and the role of dopamine and frontolimbic neurocircuitry in these behavioral phenomenon.

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