NEURAL MECHANISMS OF HIGH-RISK, APPETITIVE DECISIONS IN ALCOHOL DEPENDENT WOMEN

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A defining feature of alcohol dependence (AD) is continuing to drink despite the risk of severe negative consequences. Currently, it is not known if the pattern of disordered activation in AD is more compatible with an over-sensitive reward system, a deficit in control systems or a combination of both to produce the high risk-taking behavior observed in alcohol dependents. Here, fMRI was used to examine neural mechanisms that drive high-risk behavior in alcohol dependent women (ADs). A novel ecological task was developed to assess high- and low-risk decisions to drink alcohol, have sex, eat food, and buy items in ADs and control women. In this dissertation, neural correlates of high-risk decisions to drink (Study 1), neural correlates of high-risk decisions to have sex (Study 2), and functional connectivity (fC) during high-risk decisions to drink using psychophysiological interactions (Study 3) are examined. Across these studies, the focus was on 1.) determining if a specific pattern of activation or fC drives high-risk behavior in ADs, and 2.) determining if neural patterns of activation or fC are specific to high-risk decisions to drink or if they generalize to other appetitive decisions in ADs. The results showed that for high-risk decisions to drink, ADs were significantly more likely to drink high-risk beverages compared to controls, and a specific pattern of activation was associated with high-risk decisions to drink compared to other appetitive decisions, in ADs compared to controls. ADs also had significantly reduced fC compared to controls during high-risk decisions to drink. However, for sexual decisions, there were no behavioral differences between ADs and controls, yet a

significant difference in neural activation was observed. Overall, the results suggest that disordered activation and fC in ADs observed during this task may be due to a problem with switching between different neural networks.

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All portions of this dissertation were greatly influenced by collaborators and other researchers. In particular, Chapters 2-4 have been either published or will be submitted for publication in peer-reviewed journals with the following authorships:

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CHAPTER 1

GENRERAL INTRODUCTION

1.1. Alcohol Dependence and Women

In the United States, alcohol is the most prevalent and socially acceptable drug of use and abuse. In 2012, 87.6 percent of people 18 and over in the United States reported that they drank alcohol at least once in their lifetime, with 56.3 percent having had alcohol in the last month (National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2014a). An estimated 17 million Americans are classified as having an alcohol use disorder (AUD), a term that includes alcohol dependence, alcohol abuse, and hazardous drinking that does not reach the level of alcohol dependence ([NIAAA], 2014a). In the United States, alcohol is the 3rd leading preventable cause of death, while globally it is the 5th leading risk factor for premature death and disability ([NIAAA], 2014a). Despite increased research and health initiatives, treatment outcomes for those with alcohol dependence have not improved in more than 50 years (Sutherland et al., 2012). These statistics emphasize the importance of understanding the neural mechanisms that drive decisions-to-drink alcohol in those with alcohol dependence.

Alcohol dependence is characterized by several criteria, including craving, loss of control, physical dependence, and tolerance (4th ed.; *DSM-IV*; American Psychiatric Association, 1994). Craving describes a strong urge, need, or desire to drink alcohol. Loss of control is the inability to stop drinking despite the risk of severe negative consequences. Physical dependence includes withdrawal symptoms such as negative emotional states, sweating, shakiness, and nausea after stopping drinking. Tolerance is

defined as the need to drink an increased amount of alcohol to achieve the same effect ([NIAAA], 2014b). In this dissertation, I focus on the loss of control experienced by women with alcohol dependence by using functional magnetic resonance imaging (fMRI) to examine the neural correlates of high-risk appetitive decisions.

Traditionally, research on alcohol dependence has focused only on men or has included mixed groups of male and female participants. However, current research emphasizes the need to examine both groups (Mann et al., 2006; Lee et al., 2009; Momenan et al., 2012). In particular, alcohol dependent (AD) women carry a higher risk for serious negative health consequences compared to men. Women's brains, hearts, and livers are more vulnerable to alcohol's detrimental effects (Centers for Disease Control and Prevention [CDC], 2012). The rate of binge drinking is also increasing for women, whereas rates of binge drinking have not changed for men (Centers for Disease Control and Prevention [CDC], 2013). Additionally, women's hormonal cycles may interact with alcohol use patterns, making it important to control for these effects in studies. These physiological differences may amount to differences observed in neural activity associated with decisions-to-drink alcohol between men and women, making it important to research the effects of alcohol dependence on both groups separately and comparatively.

Women also have increased sexual health risks associated with heavy drinking, such as contracting a sexually transmitted infection, unplanned pregnancy, and experiencing sexual assault (Leigh, 1999; O'Hare, 1998; Centers for Disease Control and Prevention [CDC], 2012). While sexual assault is one of the largest issues facing women

today, I am only investigating scenarios involving consensual sexual situations. Specifically, I am focusing on consensual sexual decisions as another type of appetitive decision, but more importantly as another type of decision where the negative consequences could be quite severe (i.e., deciding to have sex without a condom). Overall, in this dissertation I investigate the neural mechanisms of appetitive decision-making in women and how these mechanisms are disrupted by alcohol dependence.

1.2. Alcohol and Dopamine

The release of large quantities of dopamine is the major reinforcing property for all drugs of abuse (Koob & Volkow, 2010; Robinson & Berridge, 2008). This dopamine release is associated with the hedonic aspect of drug use. Alcohol exerts its rewarding effects primarily by modulating levels of dopamine release in the nucleus accumbens (NAcc) (Koob & Volkow, 2010). Dopamine release occurs indirectly as alcohol activates endogenous opioid peptides that in turn lead to the activation of dopaminergic neurons (Di Chiara, 1997). Like with food, dopamine is released upon ingestion of alcohol through gustatory pathways. However, with alcohol, dopamine is released again through its direct action on the brain. This results in two bursts of dopamine release in the NAcc with alcohol consumption. With repeated use, dopamine is no longer released at the start drinking but is instead released when alcohol-associated cues are encountered as a way to predict the presence of alcohol (Robinson & Berridge, 2008). This acts as a mechanism to motivate alcohol use by producing subjective feelings of craving and motor actions related to procuring alcohol.

Over a greater amount of time, heavy alcohol use leads to a decrease in the expression of dopamine D2 receptors that is associated with decreased dopaminergic activity for natural reinforcers, e.g. food and sex, and a relative hyperactive dopamine response to alcohol and alcohol associated cues (Volkow et al., 2004). This is in agreement with the "incentive sensitization" theory of addiction introduced by Robinson and Berridge (1993) stating that drugs of abuse work by making the brain hypersensitive to the drug and to drug-associated cues. Dysfunction in the expression of dopamine receptors sets off a cascade of whole-brain neural changes that ultimately results in a pathological consumption of alcohol where the user is unable to stop drinking despite severe negative consequences.

1.3. Cue Reactivity

1.3.1. Alcohol

The cue reactivity paradigm has been used to test the incentive sensitization theory by assessing differences in neural activation for alcohol and control cues. Functional magnetic resonance imaging (fMRI) studies have found a relationship between alcohol dependence and increased activation for drug-related cues in regions implicated in reward processing (Ihssen et al., 2011; Heinz et al., 2009) and a relationship between cue-induced reward activation and the level of attention directed at drug-related cues (Vollstadt-Klein et al., 2012). In a recent meta-analysis, Schacht and colleagues (2013) investigated regions most commonly activated in fMRI and PET studies during cue reactivity tasks using alcohol visual, olfactory, and taste cues in

those with alcohol use disorders (AUDs) and in healthy controls. This meta-analysis included data from both male and female participants; however, the overwhelming majority of participants were adult males. Among those with AUDs, alcohol compared to control cues elicited greater activation in the caudate head/body, globus pallidus, anterior cingulate, insula, medial frontal gyrus, posterior cingulate, middle temporal gyrus, precuneus, thalamus, fusiform gyrus, inferior occipital gyrus, parahippocampal gyrus, and middle frontal gyrus (Schacht et al., 2013). When comparing those with AUDs to control participants, only the posterior cingulate, superior temporal gyrus, and precuneus exhibited greater activation to alcohol cues. Some of the results of this meta-analysis are to be expected based off of predictions from the incentive sensitization theory of addiction, i.e., greater activation in dopamine-rich regions (caudate and globus pallidus) to alcohol compared to control cues. However, all of the regions reported for AUDs greater than controls, and most of the regions reported for AUDs-only are those associated with the default-mode network (DMN). These include the precuneus, posterior cingulate, ventral anterior cingulate, medial frontal gyrus, middle temporal gyrus, and hippocampus (Laird et al., 2009; Fox et al., 2005).

The DMN has been mostly associated with ”resting-state”, meaning that activation in this network is observed when participants are instructed to ”rest” or ”let your mind wander” while in the MRI scanner (Greicius et al., 2003). Additionally, the DMN is strongly anti-correlated with activation in the Central Executive Network (CEN) (Fox et al., 2005), the brain regions implicated reliably in central executive function. The core regions of the CEN are the dorsolateral prefrontal cortex (dlPFC)

and the lateral posterior parietal cortex (lPPC). Other regions of the CEN include the ventrolateral PFC (vlPFC), frontal operculum, and frontal eye fields (FEF) (Seeley et al., 2007; Menon, 2011). This finding has given the impression that the DMN is a "task-negative" network that is not involved in cognitive or effortful processing. Recent research, though, is beginning to provide evidence that the DMN is involved in much more than "resting" and is critical for self-referential thinking, prospective thinking, and goal-directed mental simulations (Andrews-Hanna et al., 2014; Spreng, 2012).

The insula and anterior cingulate were also regions that showed hyperactivation to alcohol cues in ADs (Heinz et al., 2009; Schacht et al, 2013). Together, the anterior insula and anterior cingulate are the core regions of the Salience Network (SN), which is involved in detecting and orienting to highly salient internal or external stimuli (Menon & Uddin, 2010; Menon, 2011). Greater activation of the anterior insula and anterior cingulate for alcohol cues suggests that ADs find alcohol cues to be more salient compared to control cues, and accompanied activation in reward regions may help to amplify the saliency signal.

The anterior insula has also been strongly implicated in drug craving (Naqvi et al., 2007, 2014). Naqvi and colleagues (2007), in a retrospective study, demonstrated that patients who were smokers and subsequently acquired insular damage (mostly from stroke) were much more likely to abruptly quit smoking compared to patients with lesion damage elsewhere who had also quit smoking. Patients with insular damage who quit smoking were able to do so immediately and without relapse compared to patients with damage to other brain regions. This phenomenon may have

been observed because of the insula's well-documented role in interoception (for a review see Craig, 2009). The insula is a multimodal region, situated in the limbic system such that inputs/information regarding the external and internal environment may be integrated in order to guide further processing or action planning by recruiting the appropriate networks based on homeostatic needs (Paulus & Stewart, 2013; Naqvi et al., 2014). This evidence indicates that the insula may be a substrate of craving in that it can represent the need to adjust homeostatic values and can guide behavior towards ingesting alcohol as the desired or optimal way of achieving homeostasis.

In sum, alcohol cue reactivity studies provide support for the incentive sensitization theory (Robinson and Berridge, 1993), showing that dopamine-rich regions activate more to alcohol cues than to control cues in ADs. They also show that alcohol cues are highly salient, which may have implications for making high-risk decisions-to-drink. Additionally, regions of the DMN are highly involved in alcohol cue reactivity studies as evidenced by a meta-analysis using data from 28 studies examining regions that are active to alcohol cues across varying modalities in those with AUDs and in AUDs greater than control participants (Schacht et al., 2013). As the function of the DMN during task states is still unclear, this research advocates that the role of the DMN in cue reactivity studies be further investigated.

1.3.2. Male Faces and Sexual Cues

Sexual behavior involves the same neurocircuitry underlying the motivation to seek food and drugs (Georgiadis & Kringelbach, 2012). Aharon and colleagues (2001), using

fMRI, demonstrated that passively viewing attractive faces elicited activation in reward regions and especially in the NAcc. The anterior and posterior insula, anterior cingulate, and motor areas are also highly involved in sexual arousal. The posterior insula is highly active to genital stimulation for both males and females, whereas the anterior insula is more involved with assessing the motivational level or craving for further stimulation (Stoléru et al., 2012). In women, activation in the anterior cingulate cortex (ACC) correlates positively with a subjective "sex likelihood" measure, but only in high-risk sexual situations (Rupp et al., 2009). The ACC is highly involved in risk prediction during monetary decisions (Brown & Braver, 2007) and that the ACC is also responsive to sexual risk further demonstrates the overlapping neural circuits involved in the evaluation of motivational stimuli. Sexual cues also activate motor cortex under arousal, which is thought to be involved with "sexual motor imagery" (Mouras et al., 2003). Together, these studies show that the neurocircuitry underlying sexual arousal and sexual cues are the same as those supporting motivation for food and drugs. Understanding that the same neurocircuitry is involved in different types of appetitive decisions (i.e., food, sex, drugs) provides a good framework for investigating how decisions for one type of appetitive stimulus can become unbalanced by using other appetitive cues as control stimuli.

1.4. Risky Decision-Making

A hallmark of alcohol dependence is continuing to drink despite the risk of negative consequences. Risky decision-making tasks like temporal discounting and the

Iowa Gambling Task (IGT) have been used to test for neural and behavioral markers that may be highly related to the "loss of control" experienced by ADs. As the cue reactivity studies reviewed above illustrate, an over-reactive reward response may be the primary reason why ADs perform poorly on these tasks. It may be that ADs are unable to disengage with the rewarding stimulus in order to make a choice that would be more beneficial in the long run. On the other hand, heavy alcohol use associated with alcohol dependence may have compromised the CEN to such an extent that alterations to this network are primarily responsible for poor performance. Indeed, there is a large body of research demonstrating that ADs have deficits in central executive function, suggesting that hypersensitive reward processing may not be the only issue associated with alcohol dependence (Crews & Boettiger, 2009). Central executive function describes the ability to store and manipulate information over time in accordance with behavioral goals (Kimberg et al., 1997). ADs perform significantly worse across many measures of central executive function compared to controls, including short-term memory, executive working memory, intelligence, and conditional associative learning (Sullivan, et al., 2002; Finn et al., 2009; Finn, 2002; Crews & Boettiger, 2009). Deficits in executive control are also related to greater impulsivity; ADs are typically more impulsive than controls (Bobova et al., 2009; Gunn & Finn, 2013), with greater impulsivity associated with greater drinking problems (Finn, 2002; Gunn & Finn, 2013).

Clearly, as shown in tasks like temporal discounting and IGT that tap reward response and central executive function, both have significant roles in risky decision-

making in ADs. On temporal discounting tasks, ADs have been shown to discount the future significantly more than controls, signaling that ADs prefer smaller immediate rewards compared to larger delayed rewards (Bickel et al., 2007, 2014). This finding is consistent across different types of appetitive stimuli including money, alcohol, and sex (Bickel et al., 2007; Jarmolowicz et al., 2013). On the IGT, ADs make more disadvantageous decisions than controls, reflecting choices that favor immediate larger rewards at the cost of long-term losses (Fein et al., 2004; Kim et al., 2011; Mazas et al., 2000). The neural mechanisms associated with performance on the IGT and temporal discounting tasks have been studied in healthy controls (Li, et al., 2010; Liu & Feng, 2012), but to my knowledge have not compared ADs to healthy controls. It is clear that ADs have behavioral deficits related to these tasks, but it is not known whether these deficits are primarily related to hypersensitive reward processing, possibly due to a disorder of the SN, or deficits in executive function due to a disorder of the CEN.

1.5. Importance of Ecological Decisions

While it is well documented that ADs make suboptimal decisions on tasks like the IGT and temporal discounting, these deficits may be exaggerated when faced with decisions specifically about alcohol (Bogg & Finn, 2009). Alcohol as a stimulus, clearly engages neurocircuitry associated with reward that to a greater extent than other appetitive stimuli in ADs. This hyperactivation may change network dynamics during decisions regarding alcohol such that any risk associated with the drink is not properly evaluated, providing significant implications for high-risk decisions like drinking and

driving. To my knowledge, the neural mechanisms of ecological decisions-to-drink have never been tested in ADs or healthy controls. This represents a major gap in the literature because compared to studies that target general deficits such as attention and working memory, results from ecological studies may be more easily translated into specific interventions.

1.6. Objectives

In the following chapters, I will investigate the neural mechanisms associated with high- and low-risk decisions to drink alcohol, have sex, eat food, and buy household/stationary items in alcohol dependent and control women using fMRI. Each participant completed the fMRI experiment twice, once during the follicular phase and once during the luteal phase of her menstrual cycle to control for effects of phase on decision-making. In each chapter I address different questions regarding this data set where the focus is either on high-risk decisions to drink or high-risk decisions to have sex, both using food and household/stationary items as appetitive and neutral control stimuli, respectively.

In Chapter 2, I will investigate the neural mechanisms of high-risk decisions-to-drink in alcohol dependent and control women. In Chapter 3, I will investigate the neural mechanisms of high-risk decisions to have sex in alcohol dependent and control women. In Chapter 4, I will test for differences in functional connectivity using psychophysiological interactions (PPIs) during high-risk decisions-to-drink between alcohol dependent and control women. In Chapter 5, I will discuss the significance of

my findings, new insights into how a loss of control is achieved in alcohol dependence, and future directions.

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CHAPTER 2

NEURAL MECHANISMS OF HIGH-RISK DECISIONS-TO-DRINK IN ALCOHOL DEPENDENT WOMEN

2.1. Introduction

A hallmark of alcohol dependence is continually drinking in situations that are associated with a high risk of serious negative consequences. Negative outcomes related to high-risk drinking in our society occur at an alarming frequency (such as car accidents related to driving under the influence or sexually transmitted infections related to unprotected sex) and the rate of binge drinking is increasing (Centers for Disease Control and Prevention [CDC], 2013). This reality underlines the importance of understanding the factors behind decisions to drink in low- and high-risk situations. Importantly, understanding the neural mechanisms involved in decisions-to-drink may provide crucial insights into understanding alcohol dependence that would be unattainable without such neural measures. In turn, these insights may lead to novel applications targeted at decreasing drinking in situations where the risk of negative consequences is high. Studies investigating the neural correlates of alcohol dependence have focused on a dual-process account of addiction where addictive behavior is considered to be the outcome of two independent neural systems – a reward-driven, bottom-up, approach system vs. a cognitive control-driven, top-down, avoidance system (Volkow et al., 2013; Cousijn et al., 2012; Bickel et al., 2007; Goldstein & Volkow, 2002; Kalivas & Volkow, 2005).

A large body of research demonstrates that reward systems become hypersensitive in alcohol dependence. Specifically, heavy drinking is associated with increased sensitivity of dopamine reward circuitry to alcohol and cues predicting alcohol use (Robinson & Berridge, 2008). Functional magnetic resonance imaging (fMRI) studies have found a relationship between alcohol dependence and increased activation with drug-related cues in regions implicated in reward processing (Ihssen et al., 2011; Heinz et al., 2009) and a relationship between cue-induced reward activation and the level of attention directed at drug related cues (Vollstadt-Klein et al., 2012). In a review article, Heinz et al. (2009) outlined core brain regions that were activated across most alcohol cue reactivity studies that used fMRI. These regions include: the anterior cingulate cortex (ACC), medial prefrontal cortex (PFC), orbitofrontal cortex (OFC), amygdala, and ventral and dorsal striatum. In addition, the anterior insula has been strongly implicated in drug craving (Naqvi & Bechara, 2010). Many of these regions belong to the Salience Network (SN), which is primarily involved in detecting and orienting to salient or rewarding stimuli (Menon & Uddin, 2010; Menon, 2011). The core regions of the SN are the anterior insular cortex (AIC) and dorsal ACC (dACC). Other regions in the SN include the pre-supplementary motor area (pre-SMA), dorsal and ventral striatum, substantia nigra, OFC (BA47), and frontal pole (BA10) (Seeley et al., 2007). Taken together, this previous work suggests that brain regions that are more strongly cue-reactive in relation to alcohol dependence are involved with detecting and orienting to highly motivating stimuli, that is, involved with processing stimulus

salience. This would include stimuli associated with high reward, and for people with alcohol dependence (ADs), would include alcohol cues.

There is also a large body of research demonstrating that ADs have deficits in central executive function, suggesting that hypersensitive reward processing may not be the only issue associated with alcohol dependence. Central executive function describes the ability to store and manipulate information over time, in accordance with behavioral goals (Kimberg et al., 1997). ADs perform significantly worse across many measures of central executive function compared to controls, including short-term memory, executive working memory, intelligence, and conditional associative learning (Sullivan, et al., 2002; Finn et al., 2009; Finn, 2002; Crews & Boettiger, 2009). Deficits in executive control are also related to greater impulsivity and ADs are typically more impulsive than controls (Bobova et al., 2009; Gunn & Finn, 2013), with greater impulsivity also being associated with greater drinking problems (Finn, 2002; Gunn & Finn, 2013). The brain regions implicated reliably in central executive function have been termed the Central Executive Network (CEN). The core regions of the CEN are the dorsolateral prefrontal cortex (dlPFC) and the lateral posterior parietal cortex (lPPC). Other regions of the CEN include the: ventrolateral PFC (vlPFC), frontal operculum (BA44), and frontal eye fields (FEF) (BA8/9) (Seeley et al., 2007; Menon, 2011).

Together, these two bodies of research suggest that both a hypersensitive reward system and deficits in central executive function may contribute to the inflated rate of high-risk decisions-to-drink associated with alcohol dependence. Thus, tasks that tap

general reward processing and executive control (e.g., temporal discounting tasks and the Iowa Gambling Task (IGT)) may be able to dissociate the exact role of these opposing systems in alcohol dependence. On temporal discounting tasks, ADs have been shown to discount the future significantly more than controls, suggesting that ADs prefer smaller immediate rewards compared to larger delayed rewards relative to controls (Bickel et al., 2007). ADs also have poorer performance on the IGT compared to controls. On the IGT, ADs make more disadvantageous decisions, which reflect choices that favor immediate larger rewards at the cost of long-term losses (Fein et al., 2004; Kim et al., 2011; Mazas et al., 2000). The neural mechanisms associated with performance on the IGT and temporal discounting tasks have been studied in healthy controls (Li, et al., 2010; Liu & Feng, 2012), but to our knowledge, have not compared ADs to controls. It is clear that ADs have behavioral deficits related to these tasks, but it is not known whether these deficits are primarily related to hypersensitive reward processing, possibly due to a disorder of the SN, or deficits in executive function, and hence due to a disorder of the CEN.

An important concern about studying reward and control in ADs with typical generic decision-making tasks – tasks that reward points or money -- is that they are not ecologically valid insofar as their relevance for actual decisions to *drink* is unclear (Bogg & Finn, 2009). An assumption of using generic decision-making tasks is that they serve as trait-like measures of decision-making biases, associated with broad reward sensitivities and/or control problems, and that such tasks would predict decision-making problems across a wide range of appetitive behaviors, including drinking.

However, dual-process models of self-regulation (Weirs et al., 2010) emphasize that impulse control problems are usually very specific to certain behaviors and contexts, with alcohol consumption being a prime example. Weirs and colleagues (2010) note that general measures of trait impulsivity, and by implication, generic decision-making task measures, do not predict specific impulsive behaviors as well as more specific measures of impulsive processes.

With this in mind, the current study was designed to specifically investigate decisions to drink in young women with AD. The intent was to examine decision-making biases of ADs as well as the brain activation correlates of those decisions. This was done using a task that included hypothetical contexts regarding alcohol, food (appetitive control), or household/stationary items (neutral control) that non-independently varied the level of risk and potential reward. In addition, each participant was scanned twice to control for potential hormonal effects due to menstrual cycle phase, and as part of the larger project, participants also made decisions about low- and high-risk sexual scenarios. Sexual decisions were not examined in the current study (see *Methods* for rationale). In a study using a similar drinking decision task (without the use of appetitive and neutral control stimuli), ADs reported that they would drink more than controls in hypothetical contexts that combined increased risk of negative consequences and high reward probabilities (Bogg & Finn, 2009). We hypothesized that AD women will chose to drink significantly more high-risk alcoholic beverages compared to control women. We also hypothesized that AD women would show differential patterns of neural activation for alcohol stimuli compared to

appetitive and control stimuli and compared to controls. Specifically, we hypothesized that AD women would show hyperactivation in reward regions for alcohol compared to control stimuli and compared to controls. We also hypothesized that AD women would show less activation in central executive regions for high-risk alcohol compared to high-risk control stimuli and compared to controls. Importantly, because one of the most compelling problems for ADs is continuing to drink in high-risk situations, the main focus of the study was on patterns of brain activation produced during the high-risk decisions-to-drink scenarios.

2.2. Methods

Participants.

Recruitment. Participants were recruited using Indiana University list serves and by placing flyers around the Indiana University campus and in local bars. They were also recruited from a large sample of AD women in the Bloomington, IN area whom Dr. Finn recruited for another NIAAA funded project and who met the group criteria for this study. Participants from Dr. Finn's project were contacted directly if they indicated that they would like to be contacted for other studies. Three types of flyers were used to recruit participants. The first type of flyer/email was neutral in regard to the level of drinking and was designed to attract responses from controls and alcohol abusers/dependents (Wanted: Women currently interested in participating in an fMRI research study). The second type of flyer/email was designed to recruit control women with low levels of drinking (Wanted: Light drinking women currently interested in participating in an fMRI research study). The third type of flyer was used to recruit

women who are self-identified as heavy drinkers (Wanted: Heavy drinking women interested in participating in an fMRI research study). In all cases, responses were requested from women who were 18 to 28 years of age, were not currently under treatment or taking medication for mental disorders, including depression and anxiety, who had regular 28-32 day menstrual cycles, and who were not using hormonal contraceptives.

Telephone screening interview. All participants calling in response to flyers/emails or who were contacted through Dr. Finn's project underwent an initial eligibility screen that began with a general description of the study, followed by questions that assessed whether they met the basic requirement of the study (described under study exclusion criteria). Next, we asked a series of questions to determine whether they met the criteria for our control or alcohol dependence group (described under group inclusion/exclusion criteria), followed by questions to rule out psychosis or traumatic brain injuries (TBIs). Finally, we asked a series of MRI safety questions to determine whether or not they would be eligible to participate in the fMRI portion of this experiment. Potential participants were told that they would come into the lab for a diagnostic interview and that only those who met the diagnostic criteria would be allowed to continue in the study. They were also told that they would need to refrain from drinking alcohol or using any illicit psychoactive drugs for a period of at least 24 hours before each test session. In addition, they were told that they would need to not engage in any sexual activity with a partner for 24 hours prior to each test session and not eat within four hours of testing.

Study exclusion criteria. Participants were excluded from this study for the following reasons: (1) they were not female, (2) they were not between the ages of 18 and 28, (3) they were currently undergoing treatment for depression or anxiety, (4) they were not heterosexual, (5) they did not experience regular 28-32 day menstrual cycles, (6) they were pregnant, (7) they used hormonal contraceptives within the last 3 months, (8) they currently used any drugs except for occasional marijuana use, (9) they had any contraindications for MRI, (10) they were currently seeking treatment for alcohol abuse, (11) they reported symptoms of psychosis or TBI , (12) they had never had a full drink of alcohol, and/or (13) they were currently abstaining from alcohol use.

Group inclusion/exclusion criteria. Control women had the following inclusion criteria: (1) no recreational drug use in the last three months, (2) no history of drug use besides marijuana in their lifetime, (3) have used marijuana less than 25 times in their lifetime, (4) are social drinkers, (5) report no history of drug or alcohol abuse or dependence and not meeting DSM-IV (4th ed.; *DSM-IV*; American Psychiatric Association, 1994) criteria for current or past alcohol abuse or dependence. Alcohol and drug use were measured by using a reduced version of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994). Alcohol dependent women had the following inclusion criteria: (1) meeting the *DSM-IV* criteria for AD (2) not currently using opiates, sedatives, or be stimulant-dependent, (3) past use of psychoactive drugs and past or present marijuana is allowed due to high rates of co-occurrence between alcohol and drug dependence (Finn et al., 2009), and/or (4) not marijuana dependent.

Test session exclusion criteria. Test session included the following exclusion criteria: (1) did not refrain from drinking alcohol and/or using any illicit psychoactive drug for a period of at least 24 hours before testing, (2) did not refrain from sexual activity with a partner for 24 hours prior to the test session, (3) did not refrain from eating within 4 hours before the test session. At each test session, participants submitted to a breath alcohol test using an AlcoSensor IV (Intoximeter, Inc., St. Louis, MO) and a urine drug screen, and answered questions that determined whether they had participated in any sexual activity with a partner with the past 24 hours or ate food within the past 4 hours. If participants' breath alcohol concentration was greater than .0%, or there were any positives on their urine drug screen, or they did not meet our other test session requirements, they were asked to reschedule the test session.

Sample Characteristics. A total of 72 participants were recruited for this study after completing the phone interview. Of the 72 participants, 28 (10 AD and 18 controls) were excluded after the initial phone interview session. Of those participants, 2 ADs and 5 controls did not qualify for the study after completing the interview, and the remainder did not followed up with scheduling the fMRI sessions. Of the remaining 44 participants (25 controls, 19 ADs), 6 controls and 4 ADs completed only one of the two required fMRI sessions. Of the 34 participants (19 controls, 15 ADs) that completed both fMRI sessions, 2 controls had motion that was too excessive for inclusion in our analyses, and data was corrupted for 1 control. Thus, a total of 31 participants (16 controls, 15 ADs) completed the interview and 2 fMRI sessions, constituting our sample for all reported analyses. The ethnicity of our sample was 71% Caucasian, 13% African

American, 10% Hispanic, and 6% Asian. The majority of our sample had at least some college education (87%), indicating that college educated persons are over-represented in this sample (see Table 2.1.).

Assessment materials

Recent alcohol and other substance use. In an interview, participants were asked if they regularly consumed alcohol or other drugs on each day of the week, and if yes, how much they usually consumed. Alcohol use was quantified as the sum of the usual amount of alcohol consumed for each day of the week, and the number of days per week where drinking usually occurred within the past 3 months. Drug use was quantified as the number of times used ever in their lifetime.

Diagnostic interview. The Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholtz et al., 1994), which uses criteria from the *DSM-IV* (American Psychiatric Association, 1994), was used to determine whether participants satisfied diagnostic criteria for AD, marijuana dependence, and drug dependence. Problem counts for alcohol and marijuana were also calculated from the SSAGA.

Questionnaires. Questionnaires were given to participants to complete directly after the diagnostic interview. Questionnaires were given regarding (1) demographics, (2) general health, (3) menstrual cycle, (4) eating patterns (Three Factor Eating Questionnaire, TFEQ), and (5) mood (Positive and Negative Affect Schedule; Beck Depression Inventory II (BDI-II)) (Table 2.1.). Specifically, participants provided recent dates and typical lengths of their menstrual cycles, as well as previous or current use of hormonal contraceptives, in addition to information about past or current psychiatric

treatment, including use of psychotropic medications. The TFEQ (Stunkard & Messick, 1985) contains three subscales, we used the first subscale, Cognitive Restraint, which is a 21-item index of conscious control of eating. The Positive and Negative Affect Schedule (PNAS, Watson et al., 1988) is a 10-item mood questionnaire widely used and validated as a measurement of positive and negative mood. The Beck Depression Inventory II (Beck et al., 1996) is a 21-item depression questionnaire also widely used and validated as a measurement of depression. Participants also completed other questionnaires related to the larger project that were not a part of the current study.

Appetitive and neutral cues. There were four categories of cues, alcoholic beverages, food, and household/stationary items, plus faces, which were not the focus of this article and were not included in any of the current analyses. Faces were not included in the current analyses because there is no prior literature examining the neural correlates of sexual decision-making in AD women. The hypotheses to be tested for sexual decisions are completely separate from the hypotheses tested in the current study.

Forty-five pictures from each category were normed with measures of arousal, valence, and desirability. Arousal and valence were acquired using the same procedures as for the International Affective Picture System (IAPS; Lang et al., 1997). Desirability was acquired using a similar nine-point scale as arousal, but participants were instructed to rate the desirability or attractiveness of the cue. A set of negative valence IAPS pictures was included only in the norming procedure to ensure that participants used the full range of rating values for the three measures. The a priori hypothesis was that alcohol, food, and face stimuli would be treated as appetitive cues

and would be rated with positive valence and above average arousal and desirability, whereas items would be considered neutral and would be rated with low arousal and desirability and neutral valence. Thirty-six pictures were chosen from the forty-five in each category based on the mean ratings using selection criteria meant to further bias the a priori categorization into appetitive and neutral sets and to attempt to equate the various appetitive cue categories on measures of arousal, desirability, and valence. Selection criteria were prioritized as follows: 1) the valence of each alcohol and food cue was at least 4; 2) the mean valence of alcohol cues and the mean valence of food cues were as similar as possible; 3) the mean desirability of each alcohol and food cue was at least 4; 4) the mean desirability of alcohol cues and the mean desirability of food cues were as similar as possible; 5) the mean desirability and arousal of item cues was as close to 1 as possible; 6) the mean valence of item cues as close to 4 as possible. The mean (SD) desirability ratings of the resulting pictures sets were: alcohol 5.2 (0.87), food 5.3 (0.55), item 2.8 (0.44). The mean (SD) valence ratings were: alcohol 5.7 (0.81), food 5.9 (0.52), item 4.2 (0.34). The mean (SD) arousal ratings were: alcohol 5.2 (0.81), food 5.6 (0.31), item 1.9 (0.31). The face cues (not included in the current analyses), had mean desirability of 4.0 (0.49), arousal of 4.6 (0.45), and valence of 5.2 (0.44).

During the fMRI procedure, each appetitive or neutral cue was presented simultaneously with text providing the participant with information for gauging the potential risk of negative consequences associated with the cue in the picture (Figure 2.1.). This "risk" information was used to create both a low- and a high-risk context for each picture. There were two parts to the "risk" information, either the word "Yes" or

"No", and also a single number. Both were presented to the right side of the picture with the yes/no above the number. The risk information conveyed the different contexts depending on the type of cue: for alcohol cues, whether or not the participant had a designated driver and how many alcohol units (1 unit = alcohol content in 1 shot, 1 glass of wine, or 1 beer depending on whether the alcohol cue depicted a cocktail, glass of wine, or beer) the drink contained (low, 1±1 [mean ±SD]; high, 6±1); for food cues, whether or not the food establishment passed its latest health and safety inspection and the caloric content (low, 200±10; high, 800±10); for item cues, whether or not the store had a return policy and the cost in dollars (low, 2±1; high, 20±1); and for face cues (not included in the current analyses), whether or not the male usually uses condoms and the number of sexual partners (low, 2±1; high, 8±1). Specific number values were selected randomly on each trial, with a minimum value of 0 and no maximum value. The two pieces of "risk" information were non-independently varied such that all low-risk situations contained "yes" and low-risk numbers and all high-risk situations contained "no" and high-risk numbers (Figure 2.1.).

The high-risk context was clearly considered more risky in previous similar work (Rupp et al., 2009), but it is also likely that it was considered somewhat more rewarding. Although the major difference between high- and low-risk contexts was the chance of a negative outcome, another mediating difference was reward (see discussion). Likewise, although the appetitive stimulus types were selected to be equally appealing and desirable, it is likely that the perceived risk of negative outcomes associated with the decisions (sex, drinking, eating) even in the low-risk condition were

somewhat different across types. Even with these limitations of the stimulus sets and tasks, the behavioral data (see results) show that manipulation of "risk" information had a strong effect on endorsement, suggesting that all subjects deemed the high-risk context more risky.

Procedure

After the first interview session, where participants reported recent alcohol and drug use, underwent a diagnostic interview, and answered questionnaires, as described above, participants were scheduled for two fMRI sessions. As part of the larger project, each participant was scanned specifically at the follicular and luteal phases of their menstrual cycles with the order of the two sessions for each participant determined by which of the two phases was most imminent. Determination of menstrual phase for test scheduling was done using a counting method and verified by later hormone assay from urine samples. Testing for the ovulatory phase session occurred between days 10-14 after the women report menstruation began and testing for the luteal phase occurred days 19-23 following menstruation.

The procedure was conducted with a script programed in Matlab 7.6 and the Psychophysics Toolbox (https://www.mathworks.com; http://www.psychtoolbox.org; Brainard, 1997; Pelli, 1997) on a Apple MacPro laptop. Before each fMRI session, participants reported their recent alcohol and drug use for the last week and provided a small urine sample (20 mL) for later hormone assay. This urine sample was also used for a drug screen and pregnancy test. The urine samples remained in the refrigerator for the remainder of the session at which point they were

transferred to deep freeze storage (-20 degrees Celsius). Samples were sent to the University of Wisconsin's National Primate Research Center Assay lab for estradiol, testosterone, and progesterone measurement to verify phase of menstrual cycle at the time of testing and whether naturally cycling women had ovulatory cycles (Israel et al., 1972), in addition to obtaining absolute measures of hormone levels. Following the urine sample, if the drug screen and pregnancy tests were negative, participants were introduced to the task that they were asked to perform in the fMRI scanner and given the opportunity to practice it on a laptop.

Imaging took place at the Indiana University Imaging Research Facility. Participants were safety screened and completed a practice run of the task outside of the scanner. The practice run was a shortened version of the actual data collection runs and used pictures from all of the same cue categories, but the pictures were not the same ones used during scanning. After participants understood the task, they were comfortably positioned in an fMRI scanner (3T Siemens TRIO). Functional scanning of 280 total trials was broken up into five ~7 minute runs, to allow participants breaks. The protocol for each run was based on a rapid event-related design with 56 trials all separated by variable-length inter-trial intervals. Each interval was either 2, 4, or 6 s long and the different length intervals were used in a ratio of 4:2:1, respectively. On each trial, a stimulus from one of the four cue categories was pseudorandomly chosen without replacement, such that 14 cues from each category were presented during each run, 7 with low-risk information and 7 with high-risk information. The cue was presented simultaneously with the risk information for 4 s. Participants appraised the

combination of cue and risk information and rated their likelihood to drink alcohol, eat food, or buy the item (or have sex with the person/face) on a four-point scale where 1=very unlikely, 2=unlikely, 3=likely, 4=very likely. Across the five runs, this protocol produced 35 trials for each of the eight combinations of cue category (4) and risk condition (2). In the current article, only three cue categories were analyzed (alcohol, food, and items).

Imaging parameters

Imaging was carried out using a Siemens Magnetom Trio 3-T, whole-body MRI and collected on a 32-channel phased-array head coil. Each fMRI session took about an hour, during which the following scans were acquired: (1) three-plane scout used for choosing slice planes for the remaining scans (10 s), (2) Gradient-echo T2* echo-planar imaging (EPI) scans for blood oxygen-level dependent (BOLD)-based functional neuroimaging (duration ~7 min, five scans/session, ~35 min total functional scanning), and (3) T1 3-D turbo-flash structural scan of the entire brain at high resolution (1-mm isotropic voxels) (~5 min). The functional pulse sequence had the following EPI parameters: echo time (TE)=30 ms, flip angle=70°, field of view=240x240 mm, matrix 96x96, in-plane resolution=2.5 mm slice thickness=3.5 mm, gap thickness=0 mm. A typical volume was 32 EPI slices acquired at a time of 62.5 ms per slice for a total volume acquisition time 2 s [repetition time (TR)=2]. Slices were acquired approximately parallel to the anterior commissure/posterior commissure (AC-PC) plane to efficiently cover the entire brain. High-resolution T1-weighted anatomical volumes were acquired using Turbo-flash 3-D (TI=900 ms, TE=2.67 ms, TR=1800 ms,

flip angle=9°) with 160 sagittal slices with a thickness of 1 mm and a field of view of 224x256 (voxel size=1x1x1 mm).

Data analysis

Imaging data were analyzed using FSL v4.1.9 (FMRIB Software Library; online at http://www.fmrib.ox.ac.uk/fsl, August 2012). GLM-based analysis in FSL was carried out with the fMRI Expert Analysis Tool (FEAT) (Jenkinson et al., 2012; Woolrich et al., 2009). Functional scans were co-registered to the MNI template (MNI-152 average brain). Functional scans were preprocessed using MCFLIRT for motion correction, the brain extraction tool (BET) for skull stripping, with a spatial smoothing FWHM window of 5mm, and a high-pass temporal filter (Smith et al., 2004). The first-level analysis used custom predictors based on the timing protocol of each of the eight combinations of cue category and risk information, convolved with a two-gamma hemodynamic response function. Outputs from the first-level analysis were contrasts among various cue and risk conditions. The second-level analysis combined first-level outputs from separate runs for each level of the menstrual cycle phase factor for each participant. Outputs from the second-level analysis were contrasts representing each phase, both phases combined, and the difference between phases. The third-level analysis combined second-level outputs across participants within each group (controls and ADs). In addition, reaction time was included as a covariate for each participant (Grinband et al., 2008). The reaction time covariate was calculated separately for each first-level contrast by applying the same contrast to the mean reaction time across conditions. Before entry into the model, reaction time covariates were demeaned. Outputs from the third-level

analysis were contrasts representing each group, both groups combined, and the difference between groups. The higher-level analyses were performed using a mixed-effects model (FLAME 1). The multiple testing problem was addressed by using a voxel-wise $z > 2.3$ threshold, which was then corrected at the cluster level with alpha=0.05 using random field theory (Worsley, 2001).

2.3. Results

Behavior.

Likelihood of Endorsement. Likelihood of endorsement was calculated as a dependent variable from the participants' responses during the scanning session by taking the average of their responses for each stimulus type. A repeated-measures ANOVA with endorsement rate as the dependent variable, stimulus and risk as within-subjects factors, and group as a between-subjects factor showed highly significant effects. There were main effects of stimulus ($F_{(2,58)}$=13.531, p=0.000), risk ($F_{(2,29)}$=122.380, p=0.000), and group ($F_{(1,29)}$=4.347, p=0.046); two-way interactions of stimulus type by risk ($F_{(2,58)}$=4.287, p=0.018), stimulus type by group ($F_{(2,58)}$=7.042, p=0.002), and risk by group ($F_{(2,58)}$=20.334, p=0.000); and a three-way interaction of stimulus type by risk by group ($F_{(2,58)}$=3.994, p=0.024). Importantly, the main effect of risk shows that our risk manipulation was successful for both groups, across all stimulus categories where all participants significantly reduced their endorsement of all high-risk stimuli compared to their endorsement of all low-risk stimuli.

The significant 3-way interaction of group x stimulus type x risk was interpreted before any of the other effects were considered. Post-hoc pairwise tests were performed

using Tukey's HSD. As expected ADs endorsed high-risk alcohol stimuli significantly more than controls ($q_{(2,58)}$=4.46), but the difference with low-risk alcohol stimuli was only marginal ($q_{(2,58)}$=1.73). Both ADs and controls significantly reduced their drinking in the high-risk alcohol condition compared to the low-risk alcohol condition ($q_{(2,58)}$=4.58 and $q_{(2,58)}$=7.30, respectively), demonstrating that manipulating risk information had the desired impact on both ADs and controls. ADs endorsed high-risk alcohol decisions less than low-risk alcohol decisions, but more than controls (Figure 2.1.). ADs and controls did not differ on endorsement of high- and low-risk food ($q_{(2,58)}$=0.16 and $q_{(2,58)}$=0.60, respectively) or high- and low-risk household items ($q_{(2,58)}$=0.38 and $q_{(2,58)}$=0.35, respectively) (Figure 2.2.).

Reaction Time. A repeated-measures ANOVA with reaction time as the dependent variable, stimulus and risk as within-subjects factors, and group as a between-subjects factor showed significant effects. There was a main effect of risk ($F_{(2,29)}$=4.325, p=0.047) where participants took a significantly longer amount of time to respond to high- compared to low-risk stimuli; two-way interaction of stimulus type by risk ($F_{(2,58)}$=20.334, p=0.000); and a three-way interaction of stimulus type by risk by group ($F_{(2,58)}$=6.552, p=0.003).

The significant 3-way interaction of group x stimulus type x risk was interpreted before any of the other effects were considered. Post-hoc pairwise tests were performed using Tukey's HSD. ADs took a significantly longer amount of time to make high-risk alcohol decisions compared with low-risk alcohol decisions ($q_{(2,58)}$=3.84). There was also a marginally significant difference between ADs and controls for the difference in

reaction time between low- and high-risk alcohol ($q_{(2,58)}$=2.81). Here, ADs tended to take a longer amount of time compared to controls to make a decision in the high-risk alcohol compared to low-risk alcohol conditions (Figure 2.3.).

The significant 2-way interaction of stimulus type x risk was driven by participants taking a longer amount of time to make high- compared to low- risk alcohol decisions compared to item stimuli where participants took a longer amount of time to make low- compared to high- risk decisions. The only significant post-hoc comparison was in comparing the difference between high- and low- risk alcohol decisions to the difference between high- and low- risk item decisions ($q_{(2,58)}$=3.45).

fMRI. BOLD fMRI data were analyzed in a 3 x 2 x 2 x 2 full-factorial, whole-brain GLM analysis with stimulus cue (alcohol, food, item), risk (high, low), and phase (follicular, luteal) as within-subject factors and group (controls, ADs) as a between-subject factor. Procedurally, menstrual cycle phase was included as a factor due to hypotheses about its influence on face/sex decisions. Because face/sex decisions were not analyzed for this article, there was no specific hypothesis made about the influence of phase on stimulus cue activation. For completeness, phase was included as a factor in the overall analysis. However, for alcohol decisions, phase did not interact with risk, nor did it interact with group. As such, the results below are reported collapsed across phase (i.e., two sessions worth of data per participant).

Decisions-to-Drink: Low-risk. Before describing the higher-order effects, we first describe the lower-order effects, in particular those for low-risk decisions, to establish a baseline from which the higher-order effects deviate. The low-risk maps (Figure 2.4.)

were generated by comparing alcohol decisions to food and item decisions in the low-risk condition (i.e., 2 x ($ALC^{Low\text{-}risk}$) – ($FOOD^{Low\text{-}risk}$ + $ITEM^{Low\text{-}risk}$)) for each group separately, and also for the two-way stimulus by group interaction. No clusters were found that showed a significant interaction, suggesting that patterns of activation across the whole brain in ADs and controls were similar for low-risk situations. This was confirmed by examining the separate groups maps. The pattern in both groups was mainly associated with greater activation of the "default-mode network" (DMN) for alcohol decisions, including the precuneus BA7/31, posterior cingulate BA31, ventral anterior cingulate BA32, medial PFC BA9/10/11, right inferior parietal lobule BA40, and middle temporal gyrus BA39. Both groups also activated extensive regions of visual cortex, including the lateral occipital cortex (LOC) BA19 and fusiform gyrus (FG) BA 37. Activation of the hippocampus, nucleus accumbens and right caudate head and tail was also observed in both controls and ADs. Both groups significantly deactivated (i.e., produced less activation with alcohol decisions compared to food and item decisions) the medial occipital cortex, specifically the lingual gyrus, cuneus, and intracalcarine cortex (BA18, BA17) (Table 2.2.)

Decisions-to-Drink: High-risk. The high-risk maps (Figure 2.5.) were generated the same way as the low-risk maps, except comparing all high-risk conditions (i.e., (2 × $ALC^{High\text{-}risk}$) – ($FOOD^{High\text{-}risk}$ + $ITEM^{High\text{-}risk}$)). The results for high-risk decisions were quite different from low-risk decisions. Here, ADs showed significantly greater activation for alcohol decisions compared to food and item decisions than controls in regions of the SN, including the substantia nigra, dorsal striatum, bilateral anterior

insula, and pre-SMA (Figure 2.5.a,b). ADs also showed significantly greater activation for alcohol decisions compared to food and item decisions than controls in regions of the CEN, including the mid-ventral lateral PFC (mid-vlPFC), which includes the inferior frontal sulcus (IFS) BA9, the inferior frontal gyrus (IFG) BA46/45/44, and the frontal operculum/insula, which will be referred to here as the fronto-insular cortex (FIC) (BA47/13) (Figure 2.5.a). In addition to greater activation in regions of the SN and CEN, ADs also showed significantly greater activation for alcohol decisions in the LOC (BA19), FG (BA37), and cerebellum (crus 1, bilateral) (Figure 2.5.b) (Table 2.5.). There were no regions where controls showed significantly greater activation for alcohol decisions than other decisions relative to ADs.

Separate group maps for high-risk alcohol decisions (Figure 2.5.) were examined to determine what patterns of activation/deactivation were driving the interaction for different clusters. The map for controls only (top rows of Figure 2.5.a,b) represents the "normative" pattern of activation for the high-risk alcohol decisions. It is worthwhile noting that this normative control pattern for high-risk decisions was very similar to the control pattern for low-risk decisions; controls showed greater activation for alcohol decisions than other decisions in regions associated with the DMN (posterior cingulate and vmPFC) (Table 2.3.). However, unlike with low-risk decisions, for high-risk decisions controls also "deactivated" (i.e., produced less activation with alcohol decisions than other decisions) core regions of the SN, including posterior and anterior portions of the insula, the dACC, and pre-SMA. In addition, controls showed significant deactivation of the medial occipital cortex (Table 2.3.).

Because controls showed "deactivation" in some regions that also showed a significant stimulus by group interaction, it is possible that the interaction in those regions was driven by controls' deactivation for alcohol decisions relative to other decisions, rather than ADs' greater activation with alcohol decisions relative to other decisions. The AD-only map for high-risk alcohol decisions (Figure 2.5.a,b), showed significant activation for ADs in bilateral anterior insula, but not the pre-SMA. This suggests that the greater activation for alcohol decisions compared to other decisions in the pre-SMA for ADs over controls (i.e., the stimulus x group interaction) was driven by controls' "deactivation" (Figure 2.5.a) rather than ADs' "activation". However, in the anterior insula, the same two-way interaction appears to be a combined effect of ADs' greater activation with alcohol decisions over other decisions and controls' greater "deactivation" with alcohol decisions relative to other decisions. The AD-only map also showed another significant pattern of activation was not revealed in the group x stimulus interaction, namely greater activation with alcohol decisions than other decisions in core regions of the DMN (posterior cingulate and vmPFC) (Figure 2.5.a) (Table 2.4.). These were the same regions that controls activated -- and the *only* regions that controls activated -- for high-risk alcohol decisions. It is worthwhile noting that, unlike controls, ADs showed no regions of significant "deactivation" for alcohol decisions relative to food or item decisions.

To summarize the results of low- and high-risk decisions analyzed separately, controls activated the same network (DMN) for high- and low-risk alcohol decisions, but for high-risk alcohol decisions they also deactivated regions of the SN. ADs

activated the same regions as controls for low-risk decisions, however, for high-risk decisions, ADs not only activated regions of the DMN, they also activated regions of the SN and CEN, and also activated visual regions, including the LOC and FG, and cerebellar regions. Controls showed "deactivation" with alcohol decisions relative to other decisions in the SMA for high-risk decisions, whereas ADs showed no significant "deactivation".

Decisions-to-Drink: High-risk > Low-risk. The effects within low-risk and high-risk are important to examine, however, perhaps the most important effect is the relative difference of high-risk and low-risk alcohol decisions (compared to other decisions) between ADs and controls. Thus lastly, we tested to see if there were any brain regions that were associated with a stimulus x risk condition x group interaction (i.e., $(ALC^{High\text{-}risk} - ALC^{Low\text{-}risk}) - ((FOOD^{High\text{-}risk} - FOOD^{Low\text{-}risk}) + (ITEM^{High\text{-}risk} - ITEM^{Low\text{-}risk}))$. Consistent with a comparison of low- and high-risk maps, the regions showing the greatest difference of high-risk and low-risk between ADs and controls included the right anterior insula (BA13), right FIC (BA44/13), right IFS (BA6), inferior temporal gyrus, ventral occipitotemporal aspect (BA37), fusiform gyrus (BA37), lateral occipital cortex (BA19), caudal inferior parietal sulcus (cIPS, BA 31) and cerebellum (vermis and bilateral crus I) (Figure 6) (Table 2.7.). In all of these clusters, the three-way interaction was driven by a greater difference in activation between alcohol decisions and food and item decisions that was greater for high-risk than low-risk situations, and that was greater for ADs than controls.

To further explain these results of the three-way interaction, we examined the two-way interactions between stimulus and risk for each group, by performing the same contrast ((ALC$^{\text{High-risk}}$ vs. ALC$^{\text{Low-risk}}$) – ((FOOD$^{\text{High-risk}}$ vs. FOOD$^{\text{Low-risk}}$) + (ITEM$^{\text{High-risk}}$ vs. ITEM$^{\text{Low-risk}}$)) in each group separately. This contrast showed no significant clusters of activation or "deactivation" for controls. However, there was a significant stimulus x risk interaction for ADs in all of the regions that showed the significant three-way interaction described above (stimulus x risk x group). In addition to those regions, ADs also showed a significant stimulus x risk interaction in the supramarginal gyrus (BA40), middle frontal gyrus (BA8), IFG (BA46), frontopolar (BA10), orbital frontal cortex (BA11), precentral gyrus (BA4), postcentral gyrus (BA3), middle temporal gyrus (BA22), dACC (BA24), paracingulate gyrus (BA32), and lingual gyrus (BA18) (Table 2.6.).

In sum, consistent across all regions, the three-way stimulus x risk x group interaction was driven by ADs' over-activation during high-risk alcohol decisions compared to high- and low-risk decisions with both appetitive and neutral control stimuli and compared to controls. The three-way interaction was seen in regions that are components of the SN (right anterior insula) and CEN (right IFG), as well as visual processing regions, and the cerebellum.

2.4. Discussion

The critical question addressed in this study is whether high-risk decisions-to-drink alcohol in ADs is more associated with a hypersensitive reward response or deficits in prefrontal cortical cognitive control circuits. The results suggest that a main

factor driving excessive drinking behavior in ADs is heightened reward sensitivity compared to controls in high-risk scenarios that is specific to alcohol decisions. ADs showed greater activation for alcohol decisions than other decisions in regions of the Salience Network (SN), including the substantia nigra and anterior insula. Regions of the prefrontal cortex implicated in cognitive control were also involved in AD's high-risk decisions-to-drink, but not in the manner hypothesized. Importantly, ADs showed *greater* activation in regions of the Central Executive Network (CEN), including the IFS/IFG and FIC. Based on previous reports of the function of the CEN, this finding suggests that ADs were exerting *more* effort at cognitive control than control participants, perhaps in an attempt to override their reward hypersensitivity. One of the clearest findings was that control participants recruited very similar networks for low- and high-risk decisions, whereas ADs recruited the same network as controls for low-risk decisions (DMN), but recruited different networks than controls for high-risk decisions (SN, CEN, and DMN). We suggest that part of the problem with high-risk decisions-to-drink in ADs is related to poor regulation of – or more specifically difficulty switching between – different brain networks and that the key site of this impairment may be the anterior insula.

Anatomical (Stevens et al., 2011) and functional (Sridharan et al., 2008; Menon & Uddin, 2010) evidence suggests that the anterior insula is a network "hub" and that it plays a causal role (Sridharan et al., 2008) in switching between the Central Executive and Default-Mode networks, which are normally negatively correlated (Fox et al., 2005). Our results show that for high-risk decisions-to-drink, controls "deactivated" the SN,

including the anterior insula, pre-SMA, and dACC, and activated the DMN. On the other hand, ADs activated regions from the DMN, CEN, and SN (including the anterior insula). First, the fact that controls "deactivated" the anterior insula for alcohol decisions relative to other decisions and ADs *activated* the same region, suggests a crucial role for the anterior insula in explaining the differences in decision making between groups. Second, like healthy controls in previous studies, the controls in this study did not recruit both the DMN and CEN simultaneously. This is in stark contrast to ADs who activated the CEN and DMN together. Together, these findings suggest that the problem with alcohol decisions in ADs may not be a deficit in either the DMN or CEN per se, but instead may be a deficit in the regulation of those networks. We speculate the site of the deficit may be the anterior insula and that the specific problem may involve effective switching between recruitment of the DMN and CEN.

Other regions associated more with high- compared to low-risk decisions-to-drink in ADs included the high-order visual regions LOC and FG. Because the same stimulus cues were used for high- and low-risk conditions and for ADs and controls, it is difficult to explain activation in these regions as an artifact of stimulus characteristics. Serences (2007), has shown that activation in visual regions as early as V1 is influenced by learned reward histories with objects. The LOC and FG are also highly sensitive to affective or motivational arousal associated with stimulus cues (Lang et al., 1998; Schupp et al., 2003; Hendler et al., 2001). It is possible that activation in the LOC and FG in our data is associated with the motivational reward aspect of the alcohol cues. For this to be the case, we would need to assume that the risk information provided in the

high-risk condition not only increased the perceived risk of the decision, but also increased the perceived reward. This premise, and how it limits the interpretation of the findings, is discussed further below. There is also research showing that the dorsal visual system has direct anatomical projections to the anterior insula (Uddin et al., 2010). It is plausible that the activation observed in the LOC and FG is a part of the salience detection network for high-risk decisions-to-drink in AD. It is also possible that the LOC and FG receive recurrent feedback from regions of the SN and/or CEN, and that activation in these regions in ADs reflects an inability to control visual engagement with a salient or rewarding stimulus.

Although not hypothesized, there was robust and widespread activation of the cerebellum that was associated more with high- compared to low-risk decisions-to-drink in ADs. Other research has suggested that activation of the cerebellum is associated with automatic motor responses for addictive cues, such as alcohol for people with alcohol dependence (Yalachkov et al., 2010). There is also evidence that the vermis of the cerebellum plays a significant role in the storage and recall of automatic, emotional memories conditioned by drug cues (Miquel et al., 2009). Additionally, the vermis has connections to the ventral tegmental area (VTA) and substantia nigra. In our results we observed that ADs activated the substantia nigra during high-risk decisions-to-drink, and we also observed activation in the ventral thalamus, dorsal striatum, and sensorimotor cortex. These regions are all part of the "sensorimotor network" described by Yin and Knowlton (2006) that is the major network underlying habit formation. Thus, ADs choosing to endorse high-risk alcohol may also be in part

due to the initiation of automatic approach motor responses upon seeing alcohol cues, and changes to the cerebellum related to AD may be an important contributor to this hypothesized mechanism.

Previous work also shows that the cerebellum contributes to activation in the CEN, SN, and DMN (Habas et al., 2009), all of the networks that were active in ADs during high-risk decisions-to-drink. Habas et al. (2009) found that crus I and II of both cerebellar hemispheres were especially involved in contributing to activation in the left and right CENs. In our results, we not only observed activation of the cerebellar vermis but also activation in crus I, specifically during high-risk decisions-to-drink in ADs. Activation of both the vermis and crus I may be a contributing factor to ADs activation of the CEN, SN, and DMN during high-risk alcohol decisions. Alternatively, it may be that fronto-cerebellar circuits represent a secondary "route" – and perhaps a less adaptive route -- for decision making that is recruited by ADs in high-risk situations, but not by controls, again possibly due to problems with switching between recruitment of different decision making networks.

Thus far, we have discussed regions of activation specific to high-risk decisions-to-drink for ADs greater than controls that are associated more with cue saliency, however, we also observed activation in the right FIC (BA 44/13) and mid-vlPFC (IFS, BA9), which are regions mainly associated with the CEN. A large body of research has suggested that the right inferior frontal gyrus (mid-vlPFC), has a specialized role in inhibiting motor responses (Aron et al., 2004). However, other research has found that the mid-vlPFC is also active in situations where increased attentional control is needed

regardless of the motor response associated with the task (Hampshire et al., 2010; Dodds et al, 2011). For example, Dodds et al. (2011) showed that the FIC and mid-vlPFC (referred to in their paper as right inferior frontal cortex) increase in responsiveness when there was an increase in cognitive demand, regardless of whether or not the motor response was to be inhibited. Hampshire et al. (2010) showed a relation between activation in the mid-vlPFC and attentional demands in the absence of a motor response, even though activation in the mid-vlPFC was maximized if a motor response was required. Furthermore, in a recent mata-analysis, Nee et al. (2013) found that the IFS, insula, and frontal operculum are active during tasks where it is necessary to filter out memories or information that are not aligned with the goal or aim of the task (intrusion resistance). Taken together, these previous studies suggest that activation in the FIC and the mid-vlPFC is driven by efforts at cognitive control, whether or not that control is effective at inhibiting a response. Our behavioral data show that ADs were unable to inhibit their responses relative to controls with high-risk decisions-to-drink. However, activation in the FIC and mid-vlPFC may still be due to the increased effort expended on attentional control needed by ADs to decide whether or not to drink in high-risk contexts. This activation may be further exaggerated due to heightened levels of input from overactive reward regions or from automatic sensorimotor processes.

Other regions that were activated more for high-risk alcohol decisions compared to food and item decisions were regions of the DMN. Both ADs and controls activated mainly regions of the DMN during low-risk decisions. The DMN has been primarily

associated with the "resting-state" or "task-negative" network. However, researchers are now demonstrating that tasks involving self-referential mental simulations (e.g., imagining yourself in particular scenarios) and prospective, goal-directed mental stimulations (Menon, 2011; Gerlach et al., 2011) primarily activate regions of the DMN. These previous results and our own results support the idea that the DMN is not solely a "resting-state" or "task-negative" network (Spreng, 2012). For high-risk decisions-to-drink, controls only activated core regions of the DMN (post. cingulate and vmPFC) and deactivated core regions of the SN (AI and dACC), illustrating the potential importance of the DMN in prospective, risky decision-making.

One limitation of this study is that it was likely that the high-risk context not only increased the perceived risk of negative outcomes, but also increased the perceived level of reward, compared to the low-risk context. For example, endorsing a drink with 6 units compared to 2 units increases the chances of a negative outcome, but it may also increase the potential 'high'; the increase in caloric food content may be an indicator that the food will taste better, and the increase in item cost may be an indicator that the item is of better quality. This leads to the possibility that high-risk consequences and high-risk rewards may have been perceived differently by controls and ADs. Realistically, 6 units of alcohol in one drink may differentially affect controls compared to ADs, who usually have developed a tolerance to alcohol. In fact, controls may consider the high-risk alcohol condition aversive (~6 units per drink), making it easier for controls to deactivate approach regions in the high-risk alcohol condition compared to ADs. On the other hand, ADs may consider the low-risk alcohol condition not very

desirable (~2 units per drink). The high-risk alcohol condition may have produced more conflict or uncertainty for ADs compared to controls and compared to food and item decisions, eliciting stronger responses from both reward and control networks. In future work, the level of conflict or uncertainty could be controlled for, either at the group level or at the subject level. However, for this study, the goal was to produce low- and high-risk conditions that would influence the endorsement of cues by both groups. In that sense, the manipulation of "risk" was successful, because both groups endorsed all high-risk situations significantly less than low-risk situations. Nevertheless, in future work, it would be desirable to disentangle conceptions of risk (and reward) information conveyed by the text and the reward (and risk) information conveyed by stimulus cue and attempt to equate their perceived value across groups or across subjects.

Another limitation is that we only tested AD and control women. As such, our results may only be generalizable to women. In the future, male participants should be tested to determine if the effects we have found in the current study also exist in AD men compared to controls.

In conclusion, our results suggest that ADs' decision-making is most impaired in situations where there is a rewarding alcohol cue and an indication of a high risk of negative consequences, as these high-risk decisions produce the strongest differences in recruitment of brain networks between ADs and controls. It is worthwhile noting that high-risk alcohol decisions were the only situations that produced these dramatic differences; impairment did not generalize to other appetitive or neutral decisions or to any of the low-risk conditions, including low-risk alcohol decisions. For low-risk

alcohol decisions, ADs and controls did not significantly differ in their patterns of neural activation, and both groups activated regions highly consistent with the core regions of the DMN (Laird et al., 2009). ADs and controls also activated the DMN during high-risk decisions-to-drink, but in addition ADs also activated regions of the SN and CEN. The simultaneous activation of these networks during high-risk decisions-to-drink in ADs may underlie a state of conflict or uncertainty where automatic or past histories of actions in these contexts primarily drive behavior. It may also be the case that the impairment in ADs is primarily one of switching between recruitment of different networks involved in decision making and that the site of the switching impairment may be the anterior insula. Our findings underscore the importance of further investigating the role of the right anterior insula in network switching, the role of visual and cerebellar regions in salience detection and automatic behavioral responses, the role of the FIC and mid-vlPFC in attentional control and intrusion resistance, and how all of these regions are particularly affected in alcohol dependence.

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Table 2.1.
Participant Demographics, SSAGA Problem Counts, Substance Use, Mood Ratings, and Eating Patterns

	Control (*n* = 16)	Alcohol Dependent (n = 15)	Sig.
Age (years)	20.25 (1.57)	21.20 (2.08)	n.s.[a]
Education (*n*)			
High school graduate	1	3	
Some college	13	9	
College graduate	2	3	
Ethnicity (n)			n.s.[b]
Caucasian	12	10	
African American	2	2	
Hispanic	2	1	
Asian	0	2	
SSAGA problem counts			
Alcohol problems	0.94 (1.34)	7.87 (3.07)	< .001[a]
Marijuana problems	0.00 (0.00)	1.67 (3.37)	n.s.[a]
Recent substance use			
Alcohol frequency (days/week)	1.50 (1.21)	4.20 (1.15)	< .001[a]
Alcohol quantity (drinks/week)	4.47 (4.62)	36.57 (18.10)	< .001[a]
Mood			
PANAS negative affect	12.19 (3.31)	13.50 (4.83)	n.s.[a]
PANAS positive affect	24.44 (7.74)	25.08 (6.97)	n.s.[a]
BDI	7.94 (9.59)	6.67 (5.88)	n.s.[a]
Eating			
TEFQ factor 1 (dietary restraint)	19.13 (3.50)	19.20 (3.12)	n.s.[a]
TEFQ factor 2 (disinhibition)	20.69 (2.57)	19.00 (3.30)	n.s.[a]
TEFQ factor 3 (perceived hunger)	17.63 (2.31)	16.00 (2.36)	n.s.[a]

Note. SSAGA = Semi-structured Assessment for the Genetics of Alcoholism; PANAS = Positive and Negative Affect Schedule; BDI = Beck Depression Inventory; TEFQ = Three Factor Eating Questionnaire.
[a] *t*-test. [b] Chi-square test.

Table 2.2. List of Low-risk ROIs for ADs and Controls

"Activation for Low-Risk Alcohol Decisions"
($2xAlc_{Low}$) > ($Food_{Low}$+$Item_{Low}$)

	Controls and ADs (N=31)					
Network Association	Region	BA	z-score	x	y	z
DMN	Medial prefrontal cortex					
	inferior aspect, R	11	5.95	0	48	-20
	inferior aspect, R	10	5.60	2	48	-14
	inferior aspect, L	10	5.58	-4	52	-10
	superior aspect, R	9	4.23	5	56	18
	ventral anterior cingulate	32	5.73	0	50	-10
	Posterior cingulate, R	31	2.91	4	-39	33
	Precuneus, R	7	4.00	4	-62	38
	Inferior parietal lobule, R	40	2.73	50	-43	31
	Middle temporal gyrus					
	temporoccipital aspect, R	39	3.49	53	-55	14
	temporoccipital aspect, L	39	3.23	-46	-58	15
Other	*anterior aspect, L*	21	5.76	-60	-12	-14
	anterior aspect, L	21	5.62	-56	-14	-16
	anterior aspect, R	21	3.78	60	-12	-14
	anterior aspect, R	21	3.40	56	-14	-16
	Hippocampus, R		2.70	30	-14	-21
	Hippocampus, L		3.84	-29	-14	-21
SN	Nucleus accumbens, R		2.90	10	18	-6
	Nucleus accumbens, L		2.50	-10	16	-6
	Caudate head, R		2.64	13	23	-2
	Caudate tail, R		3.16	18	-14	24
Visual Processing	Fusiform gyrus					
	temporal aspect, R	37	3.50	34	-46	-13
	temporal aspect, L	37	3.42	-30	-47	-16
	occipital, inferior aspect, R	19	3.77	20	-86	-18
	occipital, inferior aspect, L	19	3.39	-20	-86	-18
	occipital, superior aspect, R	18	3.71	28	-78	0
	Lateral occipital cortex					
	superior aspect, R	18	3.28	30	-88	4
	inferior aspect, R	18	3.25	28	-84	-4
	inferior aspect, R	18	4.09	38	-82	-6
	inferior aspect, L	18	3.35	-39	-84	-7
	inferior aspect, R	19	3.68	48	-76	-4

"Deactivation for Low-Risk Alcohol Decisions"
($Food_{Low}$+$Item_{Low}$) > ($2xAlc_{Low}$)

	Controls and ADs (N=31)					
Network Association	Region	BA	z-score	x	y	z
Visual Processing	Cuneus, R	17	4.47	16	-88	10
	Intracalcarine cortex, L	17	4.49	-6	-86	0
	Intracalcarine cortex, R	17	4.09	10	-88	12
	Lingual gyrus, R	18	4.09	14	-88	2
	Lingual gyrus, L	18	4.03	-6	-84	-8
	Lingual gyrus, L	18	4.27	-10	-84	-8

Table 2.3. List of High-risk ROIs for Controls-only

"Activation for High-Risk Alcohol Decisions"
$(2xAlc_{High}) > (Food_{High}+Item_{High})$

Controls (N=16)

Network Association	Region	BA	z-score	x	y	z
DMN	Medial prefrontal cortex					
	superior aspect, R	9	3.96	2	56	18
	inferior aspect, R	32	3.05	2	50	-14
	paracingulate gyrus, L	32	3.33	-2	48	4
	paracingulate sulcus, R	9	2.93	12	48	14
	Precuneus					
	inferior aspect	23	4.98	0	-62	26
	inferior aspect, R	29	3.91	6	-52	12
	Posterior cingulate					
	gyrus, R	23	4.26	4	-52	22
	sulcus, R	23	4.21	8	-54	20
	sulcus	23	3.94	0	-46	22

"Deactivation for High-Risk Alcohol Decisions"
$(Food_{High}+Item_{High}) > (2xAlc_{High})$

Controls (N=16)

Network Association	Region	BA	z-score	x	y	z
SN	Pre-supplementary motor area					
	superior aspect, L	6	4.40	-6	-4	70
	superior aspect, R	6	4.08	-4	-2	60
	inferior aspect, L	6	3.48	8	-12	68
	Precentral sulcus, L	6	3.37	-6	-24	52
	Precentral sulcus, R	6	3.23	2	-22	56
	Anterior Cingulate					
	superior, doral aspect, L	24	2.34	-3	2	42
	inferior, doral aspect, L	32	2.95	-6	14	34
	Insular cortex					
	anterior, superior aspect, L	13	3.90	-40	16	-6
	anterior, inferior aspect, L	13	3.75	-36	20	-6
	anterior, insular-frontal sulcus, L	13	3.19	-40	20	2
	posterior, inferior aspect, L	13	3.19	-40	-6	-6
	posterior, middle aspect, L	13	3.06	-40	-4	0
	posterior, superior aspect, R	13	3.96	38	-10	12
	posterior, inferior aspect, R	13	3.81	44	-2	-4
	posterior, middle aspect, R	13	3.64	40	-12	6
	posterior, insular-parietal sulcus, R	13	3.30	36	-24	18
	posterior, insular-temporal sulcus, R	13	3.14	34	-18	-6
Visual Processing	Intracalcarine cortex					
	posterior aspect, L	18	3.51	-8	-86	4
	anterior aspect, L	18	3.40	-12	-70	4
	middle aspect, L	18	3.28	-12	-86	-4
	Lingual gyrus					
	posterior aspect, L	18	3.50	-12	-62	-4
	anterior aspect, L	18	3.18	-12	-56	-10

Table 2.4. List of High-risk ROIs for ADs-only

"Activation for High-Risk Alcohol Decisions"

$(2xAlc_{High}) > (Food_{High}+Item_{High})$

ADs (N=15)

Network Association	Region	BA	z-score	x	y	z
SN	Anterior Insula					
	superior aspect, L	13	3.07	-36	19	0
	inferior aspect, L	13	3.05	-38	17	-7
	superior aspect, R	13	2.41	37	20	0
	inferior aspect, R	13	2.43	39	18	-7
	Dorsal Striatum					
	caudate, L		2.75	-13	10	6
	caudate, R		2.88	12	10	12
	caudate, R		3.14	12	4	16
	Orbital Frontal Cortex					
	medial aspect, L	11	3.89	-20	32	-22
	medial aspect, R	11	2.87	-20	32	-22
	lateral aspect, L	47	2.98	-40	25	-18
	lateral aspect, L	47	2.59	35	21	-16
	Frontopolar					
	inferior, lateral aspect, L	10	3.54	-44	44	-5
	inferior, lateral aspect, R	10	3.22	44	44	-5
	superior aspect, L	10	4.25	-23	56	18
	superior aspect, R	10	2.60	25	56	15
CEN	mid-vlPFC					
	fronto-insular cortex, R	47	3.62	-48	20	-7
	fronto-insular cortex, L	47	2.93	48	20	-7
	inferior frontal sulcus, L	9	3.88	-47	20	23
	inferior frontal sulcus, R	9	3.23	-47	20	23
	inferior frontal gyrus, L	46	2.95	-47	30	13
	inferior frontal gyrus, R	46	3.20	50	30	14
	inferior frontal gyrus, R	45	3.29	52	22	8
	inferior frontal gyrus, L	45	2.60	-52	22	8
	dorsal PFC					
	superior frontal gyrus, R	8	3.00	3	24	53
	superior *frontal* gyrus, L	6	3.29	-3	28	57
	superior *frontal* gyrus, R	6	3.13	4	25	57
	middle frontal gyrus, R	6	2.88	37	13	53
	middle frontal gyrus, L	6	3.71	-47	7	45
	middle frontal gyrus, L	6	2.60	-40	4	55
DMN	Middle Temporal Cortex					
	gyrus, temporoccipotal aspect, R	22	3.37	65	-39	4
	gyrus, temporoccipotal aspect, L	22	2.89	-63	-39	1
	sulcus, posterior aspect, R	21	4.33	47	-34	-2
	gyrus, anterior aspect, L	21	3.28	-60	-10	-14
Visual Processing	Lateral Occipital Cortex					
	inferior aspect, R	19	4.36	38	-83	-10
	inferior aspect, L	19	3.82	-38	-83	-10
	Occipital Fusiform Gyrus, L	18	3.30	-26	-92	-10
	Occipital Fusiform Gyrus, R	18	2.90	26	-92	-10
	Fusiform Gyrus, L	37	3.86	-30	-66	-13
	Fusiform Gyrus, R	37	3.50	27	-63	-14
Cerebellar processing	Cerebellum					
	crus 1, R		4.70	33	-64	-28
	crus 1, L		5.04	-37	-66	-28
Other	Thalamus, L		3.04	-13	-19	10

Continued, “Activation for High-Risk Alcohol Decisions”, ADs (N=15)

Network Association	Region	BA	z-score	x	y	z
Other	Thalamus, R		3.05	8	-16	12
	Subcallosal Cortex	25	3.55	-8	24	-22
	Parahippocampal Gyrus	35	3.07	29	-28	-18
	Inferior Temporal Gyrus					
	posterior aspect, L	20	3.20	-62	-26	-24
	inferior aspect, R	13	2.43	39	18	-7

Table 2.5. List of High-risk ROIs for ADs > Controls

"Activation for High-Risk Alcohol Decisions"
$(2xAlc_{High}) > (Food_{High}+Item_{High})$

	ADs > Controls (N=31)					
Network Association	Region	BA	z-score	x	y	z
SN	Anterior Insula					
	superior aspect, L	13	3.40	-35	19	0
	inferior aspect, L	13	3.85	-35	18	-7
	superior aspect, R	13	3.12	34	22	0
	inferior aspect, R	13	2.68	42	16	-7
	Substantia nigra		2.89	-6	-15	-14
	Dorsal Striatum					
	caudate, L		3.71	-13	10	6
	putamen, L		2.71	-19	10	2
	globus pallidus, L		2.50	-15	0	2
	Pre-supplementary Motor Area					
	superior aspect, L	6	4.11	-6	-6	70
	inferior aspect, L	6	2.68	-3	1	56
	superior aspect, R	6	3.04	6	4	69
	superior aspect, R	6	3.04	6	-12	69
	Orbital Frontal Cortex					
	medial aspect, L	11	3.91	-20	32	-22
	medial aspect, R	11	2.85	20	32	-22
	lateral aspect, L	47	3.15	-30	32	-18
	lateral aspect, R	47	2.76	38	30	-18
	Frontopolar					
	inferior aspect, L	10	2.97	-45	45	-8
	inferior aspect, R	10	2.59	30	60	-5
	superior aspect, L	10	3.04	-23	56	21
CEN	mid-vlPFC					
	fronto-insular cortex , R	47	3.82	-48	20	-7
	fronto-insular cortex , L	47	3.01	48	20	-7
	inferior frontal sulcus , L	9	2.90	-47	20	23
	inferior frontal gyrus , L	46	2.74	-48	33	8
	inferior frontal gyrus , R	44	2.78	57	16	2
	inferior frontal gyrus , R	45	2.39	52	22	8
	Superior Frontal Gyrus					
	dorsal aspect, L	6	2.72	-3	25	57
	dorsal aspect, R	6	2.59	4	25	56
DMN	Middle Temporal Gyrus					
	lateral, temporoccipotal aspect, R	22	3.77	66	-40	4
	middle, temporoccipotal aspect, R	22	2.58	56	-40	4
	lateral, posterior aspect, R	21	2.94	61	-20	-8
Visual processing	Lateral Occipital Cortex					
	inferior aspect, R	19	4.72	48	-66	-10
	inferior aspect, L	19	2.75	-37	-84	-15
	Fusiform Gyrus, L	37	3.39	-30	-66	-13
	Fusiform Gyrus, R	37	3.31	34	-66	-15
Cerebellar processing	Cerebellum					
	crus 1, R		3.60	33	-64	-28
	crus 1, L		3.19	-37	-66	-28
Other	Thalamus, L		2.48	-12	-20	10
	Red nucleus, L		2.93	-6	-20	-4
	Subcallosal Cortex	25	3.29	-7	23	-21

Table 2.6. List of High-risk > Low-risk ROIs for ADs-only

"Activation for High-Risk Alcohol Decisions Greater than Low-Risk Alcohol Decisions"
$(Alc_{High} - Alc_{Low}) > ((Food_{High} – Food_{Low}) + (Item_{High} - Item_{Low}))$

	ADs (N=15)					
Network Association	Region	BA	z-score	x	y	z
Cerebellar Processing	Cerebellum					
	crus I, R		4.47	28	-67	-30
	crus I, L		4.25	-38	-64	-26
	crus I, L		4.60	-36	-68	-24
	crus I, L		3.39	-8	-80	-26
	crus I, L		4.34	-38	-68	-24
	vermis, R		2.37	4	-72	-26
SN	Frontopolar					
	inferior aspect, L	10	4.17	-30	54	6
	lateral, inferior aspect, L	10	3.27	-44	48	-6
	Orbital Frontal Cortex, R	11	3.43	25	33	-18
	Anterior Insula, R	13	2.58	41	18	-4
	Anterior Cingulate Cortex, L	24	2.73	-7	23	31
	Paracingulate Gyrus, R	32	4.00	-6	24	36
CEN	dorsal PFC					
	superior frontal gyrus, L	6	3.92	-20	22	60
	mid-vlPFC					
	fronto-insular cortex, R	13	3.14	46	16	-2
	fronto-insular cortex, R	13	3.19	46	14	6
	fronto-insular cortex, R	13	2.41	46	12	10
	fronto-insular cortex, R	44	2.88	46	8	2
	inferior frontal sulcus, R	6	2.61	44	10	18
	inferior frontal gyrus, L	46	2.59	-48	24	20
	middle frontal gyrus, L	8	2.91	-48	17	38
	middle frontal gyrus, L	6	2.79	-48	10	44
Visual Processing	Lateral Occipital Cortex					
	inferior aspect, R	19	3.13	44	-75	-16
	inferior aspect, L	19	3.04	-42	-76	-16
	Fusiform gyrus					
	occipital, inferior aspect, R	19	3.14	29	-81	-14
	occipital, inferior aspect, L	37	3.30	-33	-74	-16
	temporal, inferior aspect, R	37	2.82	42	-54	-18
	Lingual Gyrus	18	2.84	-5	-77	-6
DMN	Parietal					
	supramarginal gyrus, R	40	2.72	51	-38	55
	superior parietal lobule, L	40	3.02	-44	-39	55
	superior parietal lobule, L	7	3.21	-35	-65	50
	superior parietal lobule, R	7	3.29	39	-63	52
	superior parietal sulcus, R	7	2.80	31	-59	44
	Middle Temporal Gyrus, R	22	2.81	59	-34	-3
Other	Inferior temporal Gyrus, L	37	3.29	-52	-48	-19
	Precentral Gyrus, L	4	3.11	-35	-15	63
	Precentral Gyrus, L	6	2.44	-28	-12	64
	Postcentral Gyrus, L	3	2.77	-35	-28	63

Table 2.7. List of High-risk > Low-risk ROIs for ADs > Controls

"Activation for High-Risk Alcohol Decisions Greater than Low-Risk Alcohol Decisions"
$(Alc_{High} - Alc_{Low}) > ((Food_{High} – Food_{Low}) + (Item_{High} - Item_{Low}))$

ADs > Controls (N=31)

Network Association	Region	BA	z-score	x	y	z
Cerebellar Processing	Cerebellum					
	crus I, R		3.85	28	-67	-30
	crus I, L		3.95	-38	-64	-26
	crus I, L		3.89	-36	-68	-24
	crus I, L		3.80	-8	-80	-26
	crus I, L		3.78	-46	-68	-24
	vermis, R		3.35	4	-72	-26
CEN	mid-vlPFC					
	fronto-insular cortex, R	13	3.50	46	16	-2
	fronto-insular cortex, R	13	3.40	46	14	6
	fronto-insular cortex, R	13	3.29	46	12	10
	fronto-insular cortex, R	44	3.19	46	8	2
	inferior frontal sulcus, R	6	3.02	44	10	18
SN	Anterior Insula		2.86	42	14	18
	inferior aspect, R	13	2.44	40	18	-7
	superior aspect, R	13	2.80	36	20	-2
Visual Processing	Lateral Occipital Cortex					
	inferior aspect, R	19	3.13	44	-75	-16
	inferior aspect, L	19	2.82	-42	-76	-16
	Fusiform Gyrus					
	occipital, inferior aspect, R	19	2.53	29	-81	-14
	temporal, inferior aspect, R	37	3.20	42	-58	-16
	temporal, inferior aspect, L	37	2.85	-47	-62	-16
	temporal, inferior aspect, R	37	2.87	46	-46	-14
	temporal, inferior aspect, L	37	2.79	-53	-46	-18
Other	Caudal Inferior Parietal Sulcus, R	31	2.91	26	-80	21
	Inferior Temporal Gyrus, L	37	3.77	-52	-52	-20

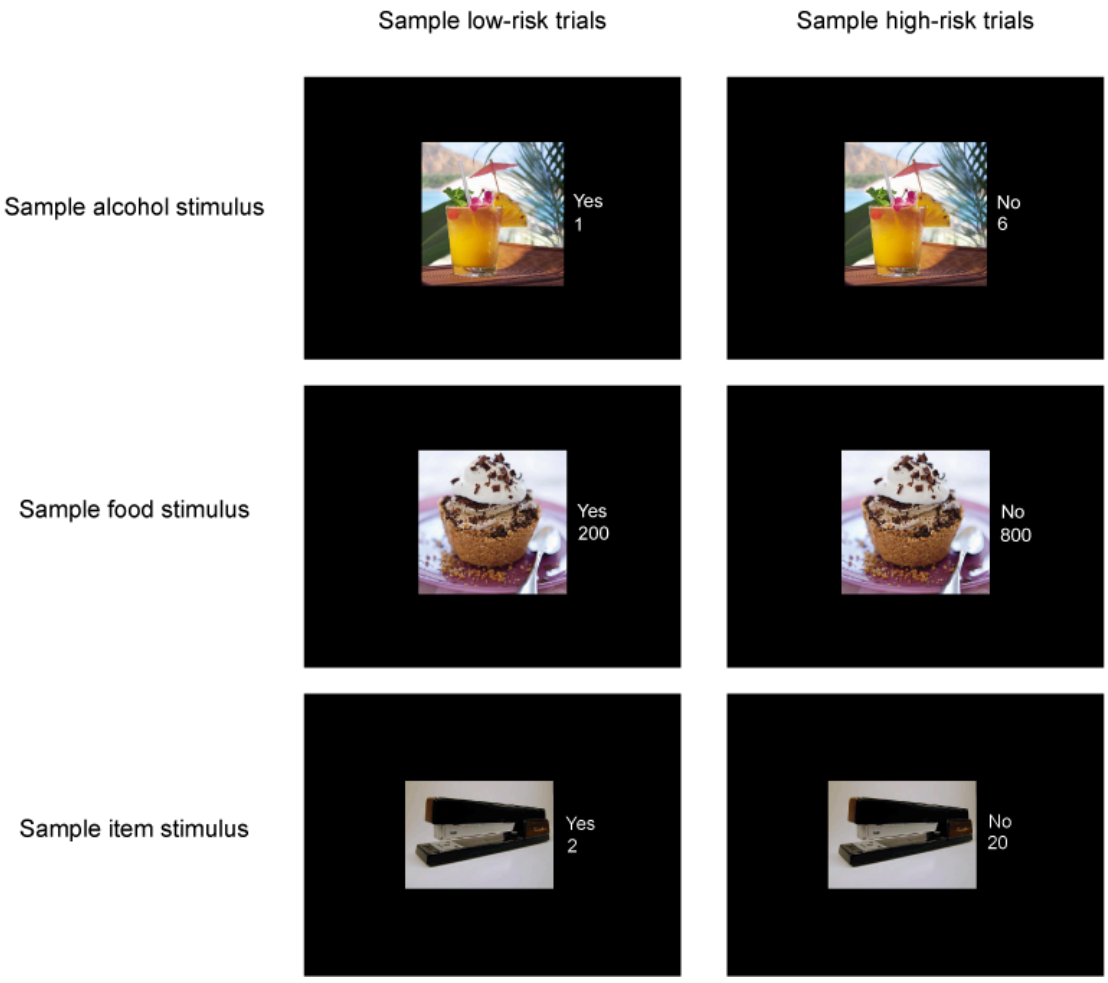

Figure 2.1. Examples of stimulus cues and risk information. Sample pictures of alcohol, food, and household/office items presented with high- or low-risk information to create high- and low-risk decisions. The same pictures were used across high- and low-risk conditions. See methods section for the meaning of the numeral and the yes/no risk information.

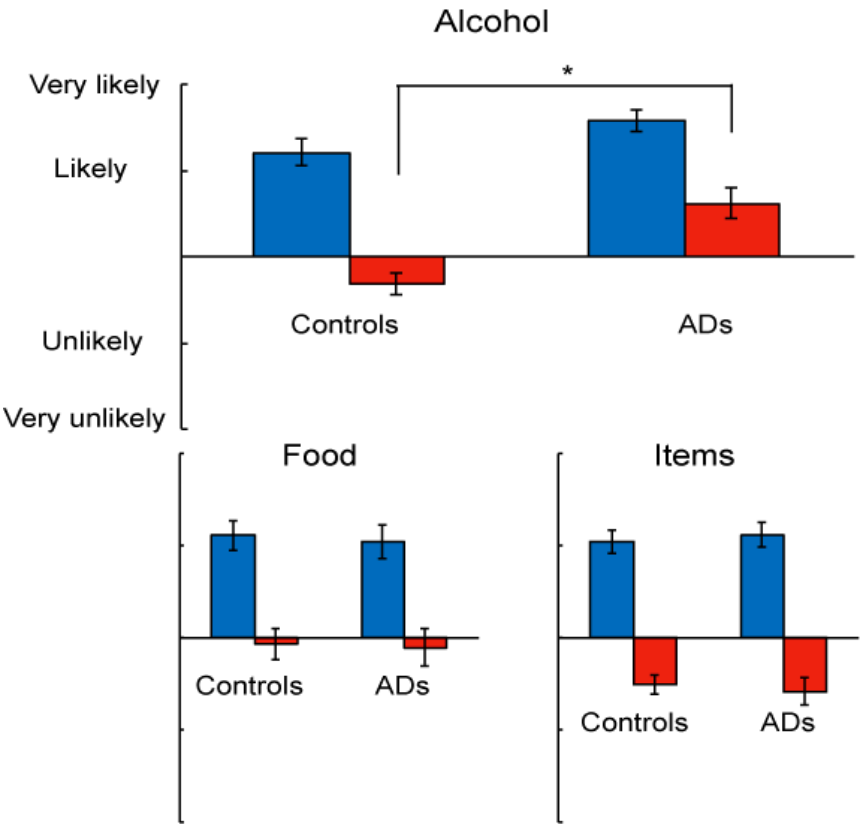

Figure 2.2. Mean endorsement rating as a function of stimulus cue, risk condition, and group. Red bars: high-risk; blue bars: low-risk. * indicates a significant difference using Tukey's HSD.

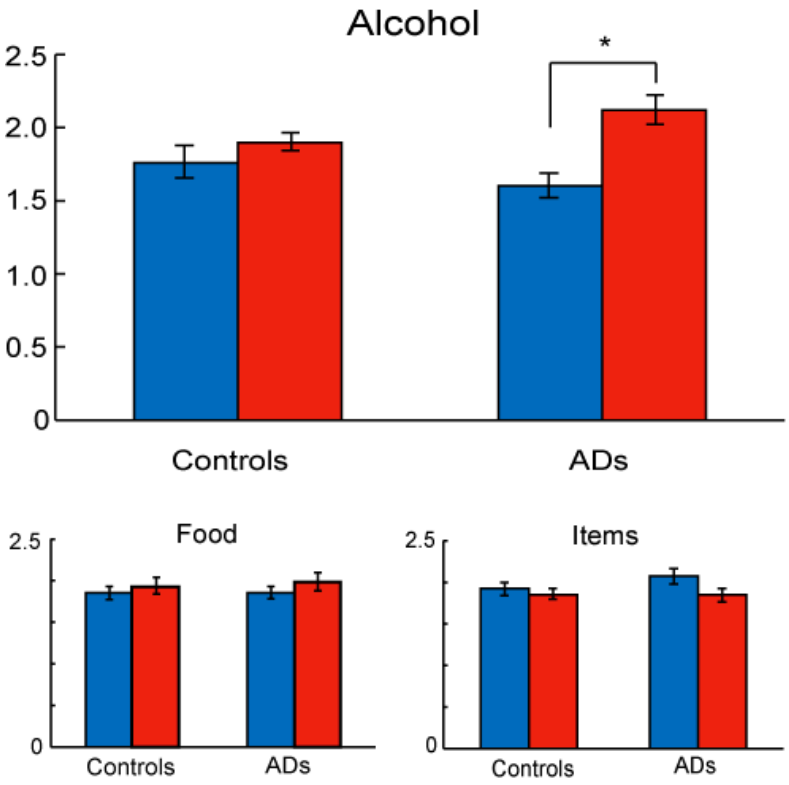

Figure 2.3. Mean reaction time as a function of stimulus cue, risk condition, and group. Red bars: high-risk; blue bars: low-risk. * indicates a significant difference using Tukey's HSD.

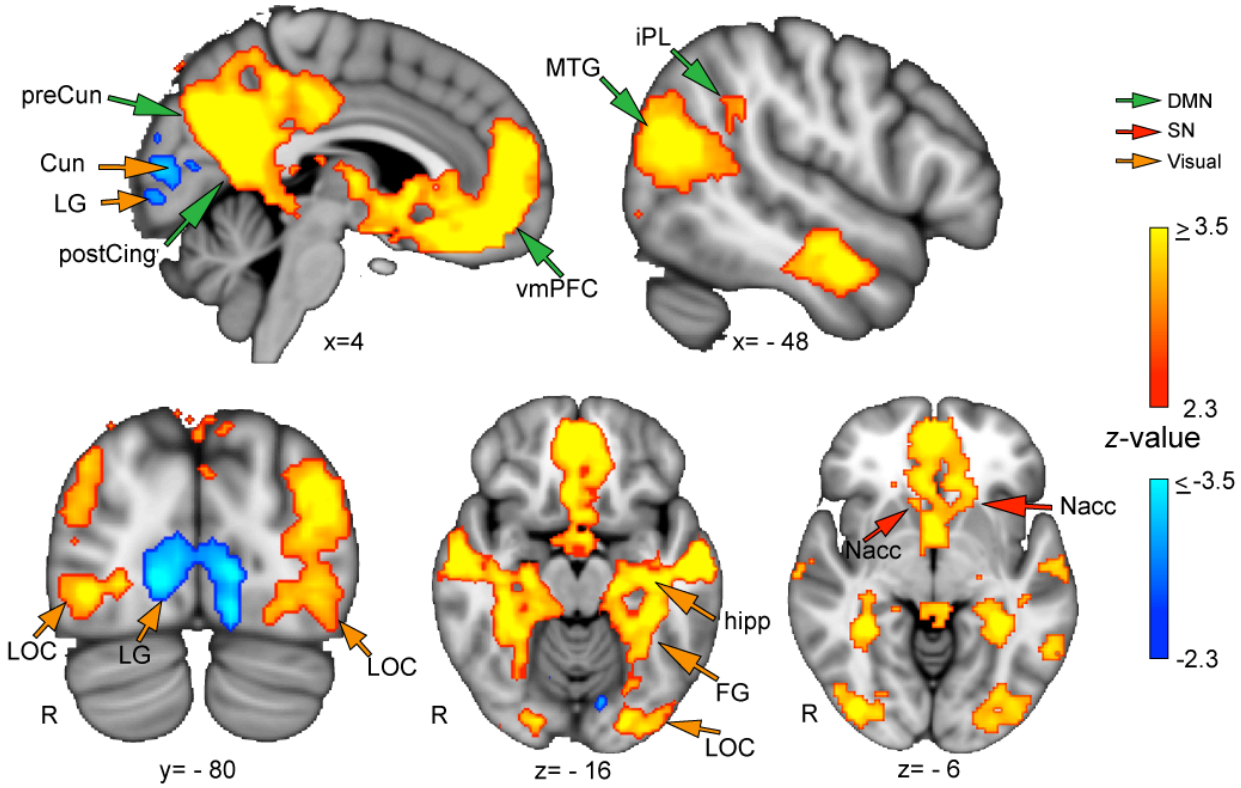

Figure 2.4. Statistical maps for low-risk decisions to drink alcohol in controls and ADs. [(2xAlc_Lo)>(Food_Lo+ItemLo)]. Green arrows mark regions associated with the default mode network (DMN); red arrows: salience network (SN); orange arrows: visual processing. Abbreviations: preCun, precuneus; Cun, cuneus; LG, lingual gyrus; postCing, posterior cingulate; vmPFC, ventromedial prefrontal cortex; MTG, middle temporal gyrus; iPL, inferior parietal lobule; LOC, lateral occipital cortex; FG, fusiform gyrus; hipp, hippocampus; Nacc, nucleus accumbens.

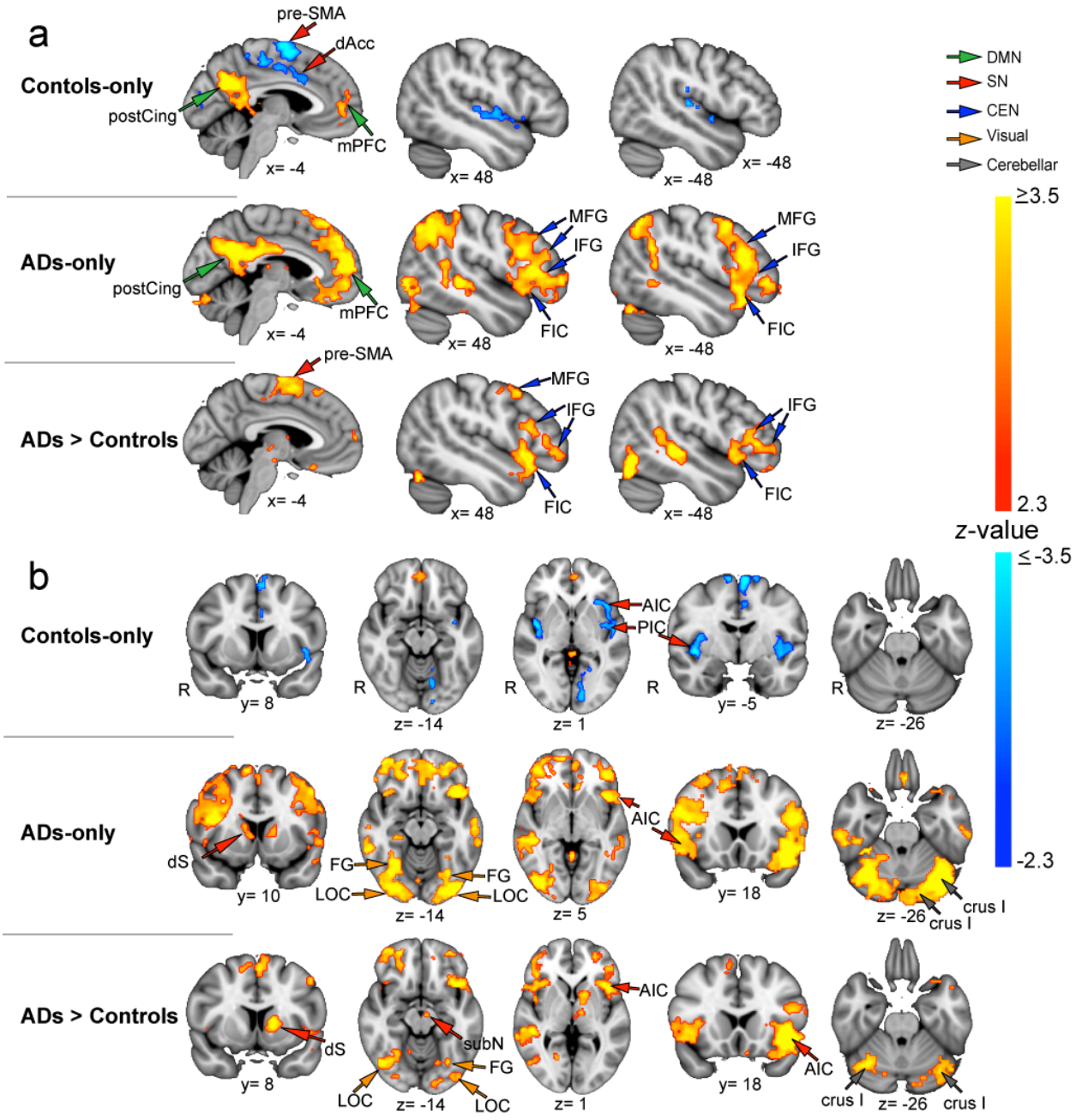

Figure 2.5. Statistical maps for high-risk decisions to drink alcohol. [(2 × $ALC^{High\text{-}risk}$) – ($FOOD^{High\text{-}risk}$ + $ITEM^{High\text{-}risk}$)]. Sagittal slices are shown in (a). Axial and coronal slices are shown in (b). Green arrows mark regions associated with the DMN; red arrows: SN; blue arrows: central executive network (CEN); orange arrows: visual processing; gray arrows: cerebellar processing. Abbreviations: postCing, posterior cingulate; pre-SMA,

pre-supplementary motor area; dACC, dorsal anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; FIC, fronto-insular cortex; AIC, anterior insular cortex; PIC, posterior insular cortex; FG, fusiform gyrus; LOC, lateral occipital cortex; dS, dorsal striatum; subN, substantia nigra;

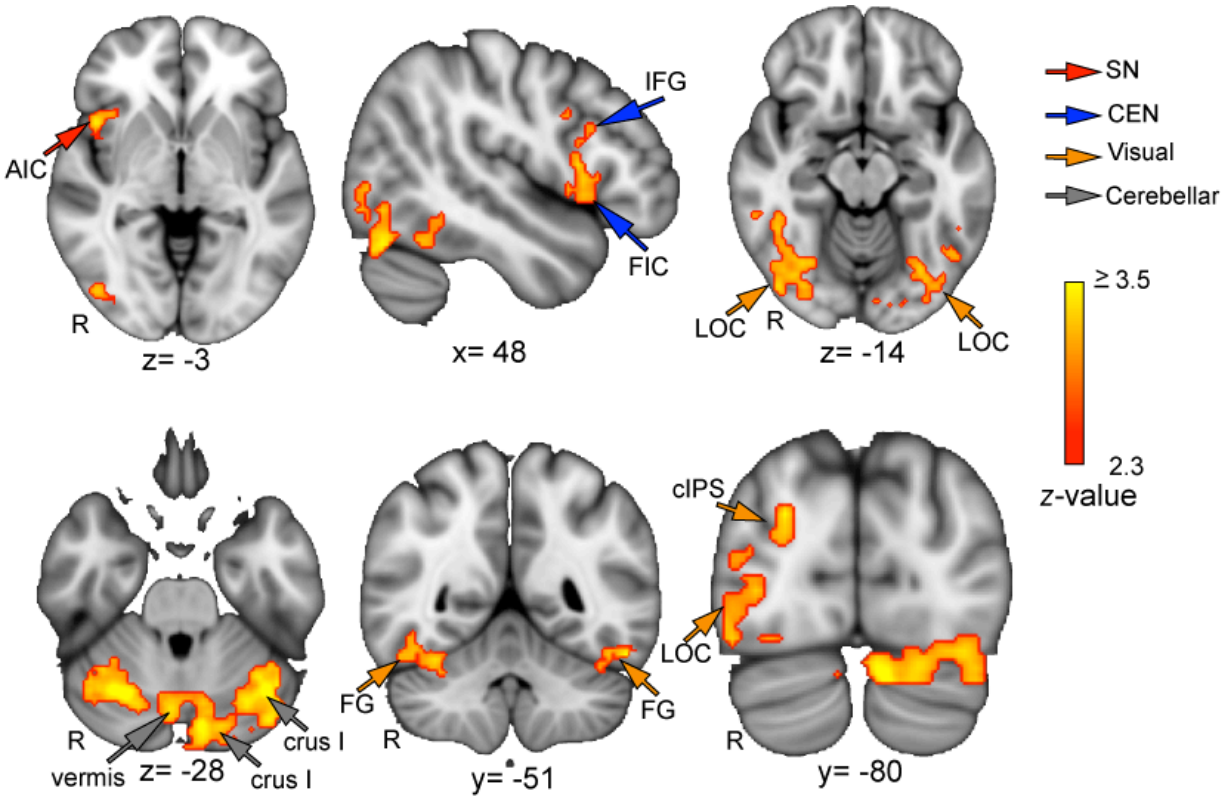

Figure 2.6. Statistical maps for high-risk > low-risk decisions to drink alcohol in ADs > Controls. [($ALC^{High\text{-}risk}$ vs. $ALC^{Low\text{-}risk}$) – (($FOOD^{High\text{-}risk}$ vs. $FOOD^{Low\text{-}risk}$) + ($ITEM^{High\text{-}risk}$ vs. $ITEM^{Low\text{-}risk}$)]. Red arrows mark regions associated with the SN; blue arrows: CEN; orange arrows: visual processing; gray arrows: cerebellar processing. Abbreviations: AIC, anterior insular cortex; FIC, fronto-insular cortex; IFG, inferior frontal gyrus; LOC, lateral occipital cortex; FG, fusiform gyrus; cIPS, caudal inferior parietal sulcus.

CHAPTER 3

NEURAL CORRELATES OF RISKY SEXUAL DECISIONS IN ALCOHOL DEPENDENT WOMEN

3.1. Introduction

Alcohol dependence is strongly associated with serious negative consequences. In particular, alcohol dependent (AD) women carry a higher risk for serious negative health consequences compared to men. Women's brains, hearts, and livers are more vulnerable to alcohol's detrimental effects compared to men (Centers for Disease Control and Prevention [CDC], 2012). In addition, women have increased sexual health risks associated with heavy drinking, such as contracting a sexually transmitted infection, unplanned pregnancy, and experiencing sexual assault (Leigh, 1999; O'Hare, 1998; Centers for Disease Control and Prevention [CDC], 2012). While the effects of alcohol consumption on sexual behavior have been extensively studied in women and men (Carrol & Carrol, 1995; Castilla et al., 1999; Crowe & George, 1989; George et al., 2009; Jones et al., 2003; Abbey et al., 2005), little research has examined the neural mechanisms that drive sexual decisions in either men or women (Rupp et al., 2009). Mostly, the previous literature has focused on the neural mechanisms associated with the approach/reward features of sexual arousal (see Stoléru et al., 2012 for a review), which is only one component of sexual decision-making. This represents a critical gap in the literature, because both approach/reward and avoidance/inhibition systems contribute significantly to sexual decision-making (Janssen & Bancroft, 2007). Understanding how neural circuits that control approach and avoidance behaviors

interact to influence sexual decision-making could greatly help in creating strategies or treatments aimed at reducing sexual health risks in AD women.

Heavy alcohol use consistent with that observed in AD produces changes in both approach and avoidance neural systems. Specifically, heavy drinking is associated with changes in the mesolimbic dopamine system, such that this system becomes hypersensitive to alcohol and to cues predicting alcohol use (Robinson & Berridge, 2008). Additionally, AD is also associated with deficits in central executive function (Sullivan, et al., 2002; Finn et al., 2009; Finn, 2002; Crews & Boettiger, 2009). Recently, Arcurio and colleagues (2013) using fMRI, showed that for AD women, high-risk decisions-to-drink alcohol was associated with hyperactivation in both reward and cognitive control networks. However, it is unclear whether or not these results generalize to sexual decisions.

For AD and control women, alcohol intoxication has been shown to be associated with making risky sexual decisions that could lead to negative sexual outcomes (Leigh, 1999; O'Hare, 1998; Rehm, et al., 2012). Acute alcohol consumption has been shown to decrease the perception of sexual risk and increase the perception of potential benefits (Cooper, 2002; Hull & Slone, 2004; White et al., 2009). One explanation for this finding is that consuming alcohol creates an "alcohol myopia" where processing of temporally close (present) salient information (sexual arousal) is enhanced relative to temporally distance (future) consequences (risks of having sex) (Steele & Josephs, 1990). Indeed recent research using laboratory controlled alcohol consumption has supported alcohol myopia, in that intoxication had a direct effect on sexual risk-taking in heavy-episodic-

drinking young women during a sexual scenario (George et al., 2014). In persons with AD, it is unknown whether sexual risk-taking is related to chronic changes in approach or avoidance systems (or both) associated with AD or influenced by the acute effects of alcohol intoxication. Recently, Jarmolowicz and colleagues (2013) tested both AD individuals and controls on a delay sexual discounting task and found that ADs discounted safe sex at significantly higher rates compared to controls. Both ADs and controls were tested while sober, providing evidence that there may be an underlying neural factor related to riskier sexual decision-making in ADs.

In healthy women, Rupp and colleagues (2009) tested the hypothesis that sexual decision-making recruits brain regions also involved in economic decision-making tasks, such as delayed discounting tasks. Rupp et al. (2009) found that activation in the dorsal anterior cingulate cortex (dACC) played a significant role in high- versus low-risk sexual decisions. Specifically, the dACC was deactivated when women were making high- compared to low-risk sexual decisions, and dACC activation was positively correlated with subjective ratings of sexual activity likelihood. The dACC has been shown to be involved in weighing the costs and benefits of social and economic decisions, showing that the dACC may be a region that is generally involved in the valuation of many different types of stimuli, including sexual stimuli (Quilodran et al., 2008; Cohen et al., 2005; Rupp et al., 2009).

Based on prior research (Rupp et al., 2009; Jarmolowicz et al., 2013; Arcurio et al., 2013), we hypothesized that a sexual decision-making task using fMRI will reveal group differences between AD women and controls that will significantly contribute to our

understanding of heavy alcohol use and increased risk of negative sexual consequences in women. To date, no study has examined the neural correlates of sexual decision-making in AD women, thus we took a largely exploratory approach to investigating group differences with particular attention to regions involved in reward or sexual arousal. We used the same sexual decisions task as Rupp and colleagues (2009) with the addition of appetitive (food) and neutral (household/stationary items) control stimuli to test for differences in behavior and neural activation between ADs and controls for sexual decisions.

3.2. Methods

Participants.

Participants in this study were recruited as part of a larger study. Details of recruitment and the telephone-screening interview can be found in Arcurio et al. (2013).

Study exclusion criteria. Participants were excluded from this study for the following reasons: (1) they were not female, (2) they were not between the ages of 18 and 28, (3) they were currently undergoing treatment for depression or anxiety, (4) they were not heterosexual, (5) they did not experience regular 28-32 day menstrual cycles, (6) they were pregnant, (7) they used hormonal contraceptives within the last 3 months, (8) they currently used any drugs except for occasional marijuana use, (9) they had any contraindications for MRI, (10) they were currently seeking treatment for alcohol abuse, (11) they reported symptoms of psychosis or TBI , (12) they had never had a full drink of alcohol, and/or (13) they were currently abstaining from alcohol use.

Group inclusion/exclusion criteria. Control women had the following additional? inclusion criteria: (1) no recreational drug use in the last three months, (2) no history of drug use besides marijuana in their lifetime, (3) have used marijuana less than 25 times in their lifetime, (4) are social drinkers, (5) report no history of drug or alcohol abuse or dependence and not meeting DSM-IV (4th ed.; *DSM-IV*; American Psychiatric Association, 1994) criteria for current or past alcohol abuse or dependence. Alcohol and drug use were measured by using a reduced version of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994). Alcohol dependent women had the following inclusion criteria: (1) meeting the *DSM-IV* criteria for AD (2) not currently using opiates, sedatives, or be stimulant-dependent, (3) past use of psychoactive drugs and past or present marijuana is allowed due to high rates of co-occurrence between alcohol and drug dependence (Finn et al., 2009), and/or (4) not marijuana dependent.

Test session exclusion criteria. Test session included the following exclusion criteria: (1) did not refrain from drinking alcohol and/or using any illicit psychoactive drug for a period of at least 24 hours before testing, (2) did not refrain from sexual activity with a partner for 24 hours prior to the test session, (3) did not refrain from eating within 4 hours before the test session. At each test session, participants submitted to a breath alcohol test using an AlcoSensor IV (Intoximeter, Inc., St. Louis, MO) and a urine drug screen, and answered questions that determined whether they had participated in any sexual activity with a partner with the past 24 hours or ate food within the past 4 hours. If participants' breath alcohol concentration was greater than

.0%, or there were any positives on their urine drug screen, or they did not meet our other test session requirements, they were asked to reschedule the test session.

Sample Characteristics. A total of 31 participants (16 controls, 15 ADs) completed the interview and 2 fMRI sessions, constituting our sample for all reported analyses. Participant demographics are described in Table 1.

Assessment materials

Recent alcohol and other substance use. In an interview, participants were asked if they regularly consumed alcohol or other drugs on each day of the week, and if yes, how much they usually consumed. Alcohol use was quantified as the sum of the usual amount of alcohol consumed for each day of the week, and the number of days per week where drinking usually occurred within the past 3 months. Drug use was quantified as the number of times used ever in their lifetime.

Diagnostic interview. The Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholtz et al., 1994), which uses criteria from the *DSM-IV* (American Psychiatric Association, 1994), was used to determine whether participants satisfied diagnostic criteria for AD, marijuana dependence, and drug dependence. Problem counts for alcohol and marijuana were also calculated from the SSAGA.

Mood, sexuality, and risk-taking. Mood was assessed using the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988; $\alpha = .77$) and the Beck Depression Inventory-II (BDI; Beck, Steer, & Brown, 1996; $\alpha = .88$). Recent sexual behavior was assessed using a brief questionnaire which asked about current sexual relationship(s), lifetime number of sexual partners, and condom use. Participants'

experiences with and attitudes toward uncommitted sexual relations were measured using the 7-item Sociosexual Orientation Inventory (SOI; Simpson & Gangestad, 1991; α = .82). Overall sexual functioning was assessed using the 22-item Brief Index of Sexual Functioning for Women (BISFW; Taylor, Rosen, & Leiblum, 1994; α = .87) with the scoring system developed by Mazer and colleagues (2000). Individual differences in the propensity for sexual inhibition and excitation were measured using the 45-item Sexual Inhibition Scale/Sexual Excitation Scale (SIS/SES; Janssen, Vorst, Finn, & Bancroft, 2002), which consists of three subscales: Excitation (SES; α = .84), Inhibition Due to the Threat of Performance Failure (SIS1; α = .75), and Inhibition Due to Threat of Performance Consequences (SIS2; α = .70). Participants' histories of unwanted sexual experiences due to verbal or physical coercion, or when under the influence of alcohol or drugs, were assessed with the 13 item Sexual Experiences Survey (Koss et al., 1987; α = .77). Last, a general propensity toward risky behavior was assessed using the Evaluation of Risks Scale (EVAR; Killgore et al., 2006; α = .70).

Mean (*SD*) scores for the control and AD groups on the mood, sexuality, and risk-taking measures are provided in Table 1. Women in the AD group reported more lifetime sexual partners and more unprotected sexual encounters (number of partners without condoms) over the past year than did control women. In addition, AD women scored higher than control women on the SOI, indicating a greater tendency to engage in short-term sexual encounters. There were no significant group differences on the PANAS, BDI, BISF-W, SIS/SES, Sexual Experiences Survey, or EVAR.

Imaging materials and procedure

Stimuli. There were four categories of cues: male faces, food, and household/stationary items (plus alcoholic beverages, which were not the focus of this article and were not included in any of the current analyses). Forty-five pictures from each category were normed with measures of arousal, valence, and desirability, and were normed by a separate group of undergraduates at Indiana University who did not participate in this study. Arousal and valence were acquired using the same procedures as for the International Affective Picture System (IAPS; Lang et al., 1997). Desirability was acquired using a similar nine-point scale as arousal, but participants were instructed to rate the desirability or attractiveness of the cue. A set of negative valence IAPS pictures was included only in the norming procedure to ensure that participants used the full range of rating values for the three measures. The a priori hypothesis was that face stimuli, food, and alcohol would be treated as appetitive cues and would be rated with positive valence and above average arousal and desirability, whereas items would be considered neutral and would be rated with low arousal and desirability and neutral valence. Thirty-six pictures were chosen from the forty-five in each category based on the mean ratings using selection criteria meant to further bias the a priori categorization into appetitive and neutral sets and to attempt to equate the various appetitive cue categories on measures of arousal, desirability, and valence. Selection criteria were prioritized as follows: 1) the valence of each face and food cue was at least 4; 2) the mean valence of faces and the mean valence of food cues were as similar as possible; 3) the mean desirability of each face and food cue was at least 4; 4) the mean desirability of faces and the mean desirability of food cues were as similar as possible;

5) the mean desirability and arousal of item cues was as close to 1 as possible; 6) the mean valence of item cues as close to 4 as possible. The mean (SD) desirability ratings of the resulting pictures sets were: face 4.0 (0.49), food 5.3 (0.55), item 2.8 (0.44). The mean (SD) valence ratings were: face 4.6 (0.45), food 5.9 (0.52), item 4.2 (0.34). The mean (SD) arousal ratings were: face 5.2 (0.44), food 5.6 (0.31), item 1.9 (0.31). The alcohol cues (not included in the current analyses), had mean desirability of 5.2 (0.87), arousal of 5.7 (0.81), and valence of 5.2 (0.81).

During the fMRI procedure, each appetitive or neutral cue was presented simultaneously with text providing the participant with information for gauging the potential risk of negative consequences associated with the cue in the picture (Figure 1). This risk information was used to create both a low- and a high-risk context for each picture. There were two parts to the risk information, either the word "Yes" or "No", and also a single number. The low-risk context was always created with low-risk information, i.e., both parts of the risk information were low-risk, whereas the high-risk context was always created with high-risk information. Both were presented to the right side of the picture with the yes/no above the number. The risk information conveyed the different contexts depending on the type of cue: for face cues, whether or not the male usually uses condoms and the number of sexual partners (low, 2±1; high, 8±1); for food cues, whether or not the food establishment passed its latest health and safety inspection and the caloric content (low, 200±10; high, 800±10); for item cues, whether or not the store had a return policy and the cost in dollars (low, 2±1; high, 20±1); and for alcohol cues (not included in the current analyses), whether or not the

participant had a designated driver and how many alcohol units (1 unit = alcohol content in 1 shot, 1 glass of wine, or 1 beer depending on whether the alcohol cue depicted a cocktail, glass of wine, or beer) the drink contained (low, 1±1 [mean ±SD]; high, 6±1). Specific number values were selected randomly on each trial, with a minimum value of 0 and no maximum value.

Scanning session procedure. After the first interview session, where participants reported recent alcohol and drug use, underwent a diagnostic interview, and answered questionnaires, as described above, participants were scheduled for two fMRI sessions. As part of the larger project, each participant was scanned specifically at the follicular and luteal phases of their menstrual cycles with the order of the two sessions for each participant determined by which of the two phases was most imminent. Determination of menstrual phase for test scheduling was done using a counting method from first day of prior menses and verified by later hormone assay from urine samples. Testing for the ovulatory phase session occurred between days 10-14 after the women report menstruation began and testing for the luteal phase occurred days 19-23 following menstruation.

The procedure was conducted with a script programmed in Matlab 7.6 and the Psychophysics Toolbox (https://www.mathworks.com; http://www.psychtoolbox.org; Brainard, 1997; Pelli, 1997) on a Apple MacPro laptop. Before each fMRI session, participants reported their recent alcohol and drug use for the last week and provided a small urine sample (20 mL) for later hormone assay. This urine sample was also used for a drug screen and pregnancy test. The urine samples

remained in the refrigerator for the remainder of the session at which point they were transferred to deep freeze storage (-20 degrees Celsius). Samples were sent to the University of Wisconsin's National Primate Research Center Assay lab for estradiol, testosterone, and progesterone measurement to verify phase of menstrual cycle at the time of testing and whether naturally cycling women had ovulatory cycles (Israel et al., 1972), in addition to obtaining absolute measures of hormone levels. Following the urine sample, if the drug screen and pregnancy tests were negative, participants were introduced to the task that they were asked to perform in the fMRI scanner and given the opportunity to practice it on a laptop.

Imaging took place at the Indiana University Imaging Research Facility. Participants were safety screened and completed a practice run of the task outside of the scanner. The practice run was a shortened version of the actual data collection runs and used pictures from all of the same cue categories, but the pictures were not the same ones used during scanning. After participants understood the task, they were comfortably positioned in an fMRI scanner (3T Siemens TRIO). Functional scanning of 280 total trials was broken up into five ~7 minute runs, to allow participants breaks. The protocol for each run was based on a rapid event-related design with 56 trials all separated by variable-length inter-trial intervals. Each interval was either 2, 4, or 6 s long and the different length intervals were used in a ratio of 4:2:1, respectively. On each trial, a stimulus from one of the four cue categories was pseudorandomly chosen without replacement, such that 14 cues from each category were presented during each run, 7 with low-risk information and 7 with high-risk information. The cue was

presented simultaneously with the risk information for 4 s. During this time, participants appraised the combination of cue and risk information and rated their likelihood to have sex, eat food, or buy the item (or drink alcohol) on a four-point scale where 1=very unlikely, 2=unlikely, 3=likely, 4=very likely. Across the five runs, this protocol produced 35 trials for each of the eight combinations of cue category (4) and risk condition (2). In the current article, only three cue categories were analyzed (faces, food, and items).

Imaging parameters. Imaging was carried out using a Siemens Magnetom Trio 3-T, whole-body MRI and collected on a 32-channel phased-array head coil. Each fMRI session took about an hour, during which the following scans were acquired: (1) three-plane scout used for choosing slice planes for the remaining scans (10 s), (2) Gradient-echo T2* echo-planar imaging (EPI) scans for blood oxygen-level dependent (BOLD)-based functional neuroimaging (duration ~7 min, five scans/session, ~35 min total functional scanning), and (3) T1 3-D turbo-flash structural scan of the entire brain at high resolution (1-mm isotropic voxels) (~5 min). The functional pulse sequence had the following EPI parameters: echo time (TE)=30 ms, flip angle=70°, field of view=240x240 mm, matrix 96x96, in-plane resolution=2.5 mm slice thickness=3.5 mm, gap thickness=0 mm. A typical volume was 32 EPI slices acquired at a time of 62.5 ms per slice for a total volume acquisition time 2 s [repetition time (TR)=2]. Slices were acquired approximately parallel to the anterior commissure/posterior commissure (AC-PC) plane to efficiently cover the entire brain. High-resolution T1-weighted anatomical volumes were acquired using Turbo-flash 3-D (TI=900 ms, TE=2.67 ms, TR=1800 ms,

flip angle=9°) with 160 sagittal slices with a thickness of 1 mm and a field of view of 224x256 (voxel size=1x1x1 mm).

Imaging analysis. Imaging data were analyzed using FSL v4.1.9 (FMRIB Software Library; online at http://www.fmrib.ox.ac.uk/fsl, August 2012). GLM-based analysis in FSL was carried out with the fMRI Expert Analysis Tool (FEAT) (Jenkinson et al., 2012; Woolrich et al., 2009). Functional scans were co-registered to the MNI template (MNI-152 average brain). Functional scans were preprocessed using MCFLIRT for motion correction, the brain extraction tool (BET) for skull stripping, with a spatial smoothing FWHM window of 5mm, and a high-pass temporal filter (Smith et al., 2004). The first-level analysis used custom predictors based on the timing protocol of each of the eight combinations of cue category and risk information, convolved with a two-gamma hemodynamic response function. Outputs from the first-level analysis were contrasts among various cue and risk conditions. The second-level analysis combined first-level outputs from separate runs for each level of the menstrual cycle phase factor for each participant. Outputs from the second-level analysis were contrasts representing each phase, both phases combined, and the difference between phases. The third-level analysis combined second-level outputs across participants within each group (controls and ADs). In addition, reaction time was included as a covariate for each participant (Grinband et al., 2008). The reaction time covariate was calculated separately for each first-level contrast by applying the same contrast to the mean reaction time across conditions. Before entry into the model, reaction time covariates were demeaned. Outputs from the third-level analysis were contrasts representing each group, both

groups combined, and the difference between groups. The higher-level analyses were performed using a mixed-effects model (FLAME 1). The multiple testing problem was addressed by using a voxel-wise z > 2.3 threshold, which was then corrected at the cluster level with alpha=0.05 using random field theory (Worsley, 2001).

3.3. Results

Behavior.

Endorsement ratings. Mean endorsement ratings for each combination of stimulus type and risk category presented during the scanning session are shown in Table 2.2. A Group (2: AD, Control) x Stimulus Type (3: male faces, food, items) x Risk (2: low, high) repeated-measures ANOVA (RMANOVA) revealed a significant Stimulus Type x Risk interaction, $F(2, 58) = 6.19$, $p = .004$. Posthoc comparisons (Tukey's HSD) revealed that, for low risk stimuli, endorsement rates were lower for male faces relative to food ($q = 7.86$, $p < .05$) or items ($q = 6.47$, $p < .05$). For high-risk stimuli, endorsement ratings were lower for male faces than for food ($q = 7.01$, $p < .05$), and endorsement ratings for food were higher than those for items ($q = 7.01$, $p < .05$). No other pairwise comparisons were significant (qs < 1.39, n.s.).

Reaction times (RTs). Mean RTs for each combination of stimulus type and risk category are presented for each group in Table 2.2. The Group x Stimulus Type x Risk RMANOVA revealed a significant Stimulus Type x Risk interaction, $F(2, 58) = 8.59$, $p = .001$. For low-risk stimuli, posthoc comparisons indicated that participants responded faster to food stimuli than to male faces ($q = 3.86$, $p < .05$) and marginally faster to food

than to items (q = 3.30, p < .10). For high-risk stimuli, RTs to faces were faster than those to food (q = 4.23, p < .05). Furthermore, RTs were faster for high-risk male faces versus low-risk faces (q = 5.68, p < .05), and marginally faster for high-risk items versus low-risk items (q = 3.27, p < .10). No other pairwise comparisons approached significance (qs < 2.40, n.s.).

fMRI

BOLD fMRI data were analyzed in a 3 x 2 x 2 x 2 full-factorial, whole-brain GLM analysis with stimulus cue (male faces, food, item), risk (high, low), and phase (follicular, luteal) as within-subject factors and group (controls, ADs) as a between-subject factor. Menstrual cycle phase did not interact with risk, nor did it interact with group. As such, the results below are reported collapsed across phase (i.e., two sessions worth of data per participant).

Sexual Decisions: Sex > Appetitive & Neutral Controls. First, we compared sexual to appetitive and neutral control decisions to determine if there were any brain regions associated with a stimulus x group interaction (i.e., 2 x ($SEX^{High\text{-}risk}$ + $SEX^{Low\text{-}risk}$) > (($FOOD^{High\text{-}risk}$ + $FOOD^{Low\text{-}risk}$ + $ITEM^{High\text{-}risk}$ + $ITEM^{Low\text{-}risk}$). We found a significant interaction of stimulus x group where ADs showed significantly greater activation for sexual decisions compared to both appetitive and neutral decisions than controls. Here, ADs showed significantly greater activation in the dorsal ACC (BA 24), pre-SMA (BA 6), postcentral gyrus (BA2/3/43), precentral gyrus (BA 4/43), parietal operculum (BA 40), inferior parietal lobule (BA 40/39), anterior insula (BA 13), posterior insula (BA 13), superior temporal gyrus (BA 41/22), middle frontal gyrus (BA 8), and frontopolar (BA

10) (Table 3.3) (Figures 3.1, 3.2). Controls did not significantly activate any regions for sexual compared to appetitive and neutral decisions relative to ADs. In sum, ADs showed patterns of hyperactivation for sexual decisions compared to appetitive and neutral control decisions and compared to control women. Hyperactivation in ADs was found in the ACC, prefrontal, motor, and insular regions.

Separate group maps for sexual decisions versus food and item decisions were examined to determine what patterns of activation or "deactivation" were driving the interaction for different clusters. The map for controls only (Figures 3.1, 3.2) represents the "normative" pattern of activation for sexual decisions. For sexual decisions, controls activated the midbrain, hypothalamus, hippocampus, amygdala, globus pallidus, putamen, caudate, thalamus, middle temporal gyrus (BA 21), lingual gyrus (BA 18), lateral occipital gyrus (BA 19), lateral OFC (BA 47), IFG (BA 44/45), medial prefrontal cortex including subcallosal cortex (BA 25), ACC (BA 32/24), paracingulate gyrus (BA 9), medial frontal gyrus (BA 9), superior frontal gyrus (BA 8), posterior cingulate (BA 23/30), precuneus (BA 31/7), fusiform gyrus (BA 37) (Table 4). Controls also significantly "deactivated" – less activation with sexual than food and item decisions -- the dACC (BA 24), pre-SMA (BA 6), postcentral gyrus (BA2/3/43), precentral gyrus (BA 4/43), parietal operculum (BA 40), superior parietal lobule (BA 7), inferior parietal lobule (BA 40), anterior insula (BA 13), posterior insula (BA 13), superior temporal gyrus (BA 41/22), occipital fusiform gyrus (BA 37), temporal fusiform gyrus (BA 37), inferior temporal gyrus (BA 20), superior occipital gyrus (BA 19), middle occipital gyrus (BA 19), portions the cerebellum (Table 3.4) (Figures 3.1, 3.2).

In sum, controls activated regions previously shown to be involved in sexual behavior including reward regions, amygdala, and hypothalamus, areas involved in risky decisions including the lateral OFC and medial prefrontal cortex, and those involved in cognitive control including the IFG, MFG, and SFG. Controls deactivated the dACC and regions previously shown to be activated in female sexual arousal and general approach behavior, including the pre-SMA, insular, and motor regions.

The map for ADs had a similar pattern of activation compared to controls, but the pattern of "deactivation" differed markedly. For sexual relative to other decisions, ADs significantly deactivated only the temporal fusiform gyrus (BA 37), inferior temporal gyrus (BA 37), cuneus (BA 19), and precuneus (BA 19) (Table 5). ADs activated all of the regions controls activated and, in addition, activated frontopolar (BA 10) and middle frontal gyrus (BA 8) (Table 5) (Figures 1, 2). In sum, the pattern of activation across ADs and controls was very similar except for the additional recruitment of portions of the MFG and frontopolar cortex in ADs. However, the pattern of deactivation between groups was very different where controls deactivated regions associated with sexual arousal and general approach behavior, whereas ADs did not "activate" or "deactivate" these regions.

Sexual Decisions: High-risk > Low-risk. Lastly, we examined the influence of high- vs low-risk contexts on decisions regarding the sex, food, and items and the different groups to determine if there were any brain regions associated with a stimulus x risk condition x group interaction (i.e., ($SEX^{High\text{-}risk}$ - $SEX^{Low\text{-}risk}$) > (($FOOD^{High\text{-}risk}$ - $FOOD^{Low\text{-}risk}$) + ($ITEM^{High\text{-}risk}$ - $ITEM^{Low\text{-}risk}$)). No clusters were found that showed a significant

interaction, suggesting that patterns of activation across the whole brain in ADs and controls were similar for high-risk > low-risk sexual decisions. Next, we combined AD and control groups to determine if there were any brain regions, across both AD and control groups, associated with a stimulus x risk interaction. Here, we found a significant interaction where both groups showed significant deactivation for high-risk compared to low-risk sexual decisions. Both groups deactivated the pons, substania nigra, putamen, thalamus, anterior insula, dACC (BA24/32), paracingulate gyrus, superior frontal gyrus (BA6), middle frontal gyrus (BA6/9), precentral gyrus (BA6), inferior frontal gyrus (BA46), frontal operculum (BA47), frontal pole (BA10), orbital frontal cortex (BA47), and inferior parietal lobule (BA40) (Table 3.6). There were no regions where both groups showed significant activation for high-risk compared to low-risk sexual decisions.

3.4. Discussion

This is the first study to examine the neural correlates of comparative risk in sexual decision-making among alcohol dependent women. While there were no behavioral differences between AD and control women for sex, food, or item decisions, we did observe significant differences in neural activation between AD and control women for sexual decisions greater than food and item decisions. To briefly summarize these results, most notably, controls deactivated the dACC and regions previously found to be involved in female sexual arousal (posterior insula, pre-SMA, motor cortex), (Stoléru et al., 2012) whereas AD women showed no significant patterns of activation or

deactivation in these regions. Instead, ADs showed significant activation in two frontal regions (frontopolar and MFG) that were not a part of the sexual decision-making network in controls.

For sexual compared to food and item decisions, controls activated regions previously shown to be involved in sexual behavior including reward regions, amygdala, and hypothalamus (Stoléru et al., 2012), those involved in risky decisions including the lateral OFC and medial prefrontal cortex (Krain et al., 2006), and those involved in inhibition and cognitive control including the IFG, MFG, and SFG (Aron et al., 2004; Ridderinkhof et al., 2004). Controls deactivated the dACC and regions previously shown to be involved in female sexual arousal and general approach behavior, including the pre-SMA, insular, and motor regions. In sum, controls activated regions associated with sexual behavior and regions associated with inhibition, while deactivating regions associated with approach behaviors. This pattern of activation and deactivation is what we use as a "baseline" to compare patterns of activation and deactivation in ADs for sexual compared to food and item decisions.

ADs activated all of the regions controls activated for sexual compared to food and item decisions and, in addition, activated frontopolar (BA 10) and middle frontal gyrus (BA 8). The pattern of *activation* across ADs and controls was very similar except for the additional recruitment of portions of the MFG and frontopolar cortex in ADs. However, the pattern of deactivation between groups varied markedly. Controls deactivated regions associated with sexual arousal and general approach behavior, whereas ADs did not activate or deactivate these regions. Instead, ADs significantly

deactivated only the temporal fusiform gyrus (BA 37), inferior temporal gyrus (BA 37), cuneus (BA 19), and precuneus (BA 19). Given that ADs did not deactivate the pre-SMA, insula, or motor regions like controls, it is likely ADs recruited additional frontal regions (frontopolar and MFG) to regulate their behavior.

With regard to the roles of frontopolar cortex and MFG in relation to inhibition or cognitive control, recruitment of frontopolar cortex (BA10) in ADs may be associated with inhibition of sexual arousal. Beauregard et al. (2001) showed erotic film clips to healthy men, and asked participants to respond "normally" or to "inhibit" their sexual arousal to the clip. During the inhibition condition, participants were asked to continue to look at the erotic film clips and to inhibit their response by imagining they were detached observers. The normally viewed erotic film clip produced significant activation in regions previously associated with sexual arousal in men (amygdala, anterior temporal pole, and hypothalamus). The inhibition condition produced significant activation in the right frontal pole and right ACC (BA32), and was associated with no activation (or deactivation) in regions activated during the normally viewed condition. The authors concluded that the frontal pole and ACC were involved in the regulation of regions involved in sexual arousal during the inhibition condition.

Recruitment of the lateral portion of MFG (BA8) may also be related to self-regulation. The MFG is a part of the dorsolateral prefrontal cortex (dlPFC), which has rich connections to premotor areas and widespread connections with many other brain regions making it ideal for regulating activity in many neural circuits (Ridderinkhof et al., 2004). Given that AD women did not differ from controls in their endorsement

during sexual decisions and given the association of frontopolar and MFG regions with cognitive control reported in previous research (Beauregard et al., 2001; Ridderinkhof et al., 2004), activation in frontopolar cortex and MFG in AD women are most likely related to efforts in inhibiting responses to sexual compared to other appetitive and neutral decisions.

Our results show that AD and control women significantly differed in their patterns of neural activation and "deactivation" for sexual decisions, even though there was no group difference in behavior. However, it is unclear why AD and control women recruited different circuits for sexual decisions. There are two main questions to consider: 1) why do ADs show reduced dACC, insula, pre-SMA, motor reactivity (i.e., no activation or deactivation in these regions) compared to controls and 2) what is the mechanism that triggers additional frontal activity during sexual decisions compared to other appetitive and neutral decisions and compared to controls? Next we explore alternative responses to the above questions.

One hypothesis accounting for the differences in neural activation and deactivation between controls and ADs is that each group is using a different self-regulation strategy to decide about behavior. Siep et al. (2012) conducted a study in healthy women investigating how suppression, reappraisal, and up-regulation techniques affected brain activation and craving elicited by food images. They found that using a suppression (view food in neutral way and inhibit thoughts or cravings for food) compared to cognitive reappraisal strategy (think about negative consequences of eating the food) produced significant deactivation of the mesocorticolimbic system

associated with food craving and was also associated with increased prefrontal activation (Siep et al., 2012). The results of our control group map for sexual compared to other appetitive and neutral decisions suggest that controls may use a suppression strategy in their sexual decisions compared to food and item decisions as evidenced by the significant deactivation of regions previously associated with sexual arousal, including the pre-SMA, insula, and motor cortices and significant activation of frontal regions. ADs do not show this pattern of deactivation and may therefore be using a different self-regulation strategy in their decision-making that relies on the recruitment of additional frontal regions and does not involve the suppression of regions involved in sexual arousal.

Another hypothesis is that controls and ADs are using the same self-regulation strategy, but that the normal pathway or network involved in this strategy is disrupted in ADs. In the control-only map, we observed significant activation of frontal regions (dlPFC, vmPFC, IFG) known to be involved in response inhibition and delayed discounting tasks (Aron et al., 2004; Bari & Robbins, 2013) and "deactivation" of regions involved in approach and sexual arousal networks. The activation observed in frontal regions of controls might be inhibiting regions involved in approach behavior and sexual arousal in an attempt to inhibit responding. In ADs, we see the same pattern of frontal activation as controls with the exception of ADs additionally recruiting the MFG and frontal pole. Activation of these frontal regions by ADs, in addition to the frontal regions controls activate, may be needed to suppress approach/sexual arousal regions because of changes brought on by excessive alcohol use. Excessive alcohol use has been

shown to produce changes in gray (Momenan et al., 2012) and white matter (Crews & Nixon, 2009) and network dynamics (Chanraud et al., 2011; Schmaal et al., 2013) between frontal regions and regions involved in approach behavior. Due to these changes in brain structure and function, additional activation of the MFG and frontal pole in ADs may be required to engage inhibition areas in decision-making during our task.

In addition to the group x stimulus interaction, we also examined the group x stimulus x risk interaction. Here, we did not find a group difference for high-risk greater than low-risk sexual decisions compared to high- greater than low- risk food and item decisions. The absence of a group difference in activation for high- greater than low- risk sexual decisions may be due to a floor effect in the high-risk sexual decisions for both groups. On average, both groups are responding "very unlikely" for the high-risk sexual decisions trials (see Table 2). The high-risk decisions may possess less uncertainty or conflict and may be easier for both groups to make as reflected in the decreased reaction time in high- compared to low- risk sexual decisions. For future investigations of low- and high- risk decisions, the level of risk and reward should be independently varied to create low- and high- risk scenarios that do not elicit floor or ceiling responses.

Given that ADs and controls differed significantly on several sexual measures including the number of sexual partners (lifetime), number of different sexual partners without condoms (past year), and SOI where ADs reported higher numbers for each of these measures, we expected to also find behavioral differences between ADs and

controls in endorsement rate for sexual decisions, but did not. One interpretation is that the group difference in reported sexual behavior could reflect ADs making risky sexual decisions primarily when consuming alcohol, but less risky decisions when sober, though this presumes that the behavioral differences in our samples emerge during alcohol consumption. Alcohol has been shown to have acute effects on the frontal cortex (for a review see: Bjork & Gilman, 2013) by reducing glucose consumption in frontal regions (Volkow et al., 2006). In addition, acute alcohol consumption has been shown to decrease frontal ERP components during response conflict (Stroop task), which was associated with a significant increase in error rate and response time (Curtin & Fairchild, 2003). Our results show that AD women may rely significantly more on frontal regions (frontal pole and MFG) when making sexual decisions compared to both food and item decisions and compared to controls. Given that acute alcohol consumption directly affects neural processing in the frontal cortex, AD women may be especially vulnerable when faced with sexual decisions while consuming alcohol.

Limitations. Across high- and low- risk conditions, sexual decisions had the lowest endorsement rate compared to food and item decisions, indicating that sexual decisions may inherently carry more risk compared to food and item decisions. For future experiments it may be fruitful to parametrically vary the potential reward and potential negative consequences for each stimulus type such that the endorsement rate is similar across the stimulus types for low- and high- risk decisions. This would allow for a more focused examination of how the stimulus influences neural activation across low- and high- risk conditions. In addition, with the increase in binge drinking among

the general population of women (Centers for Disease Control and Prevention [CDC], 2013), it is critical to test women who binge drink but do not qualify as AD. There is a link between binge drinking and making risky sexual choices, however, our results may only be specific to AD women. Finally, though drinkers the age of the women in this study are an important target population given the drinking and sexual risks that occur (Truman et al., 2013), the findings of the study should be seen as reflecting that age range; older samples may show different patterns and should be studied as well.

Conclusions. This is the first study to examine the neural correlates of risky sexual decision-making in alcohol dependent young women. While endorsement was the same between groups for sexual, food, and item decisions, we showed that AD women recruited additional frontal cortical regions (frontal pole and MFG) when making sexual decisions compared to both food and item decisions and compared to controls. Acute alcohol consumption has been shown to directly affect functioning of these regions, which may make AD women especially vulnerable when faced with sexual decisions while drinking alcohol. Our results suggest that a more differentiated understanding of central and behavioral self-regulation techniques that require less frontal activity to successfully regulate behavior (cognitive reappraisal vs. suppression, see Siep et al., 2012) may be an important intervention pathway to help decrease risky sexual engagements while drinking alcohol.

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Table 3.1.
Participant Demographics, SSAGA Problem Counts, Substance Use, and Mood Ratings

	Control (*n* = 16)	Alcohol Dependent (n = 15)	Sig.
Age (years)	20.25 (1.57)	21.20 (2.08)	n.s.[a]
Education (*n*)			
High school graduate	1	3	
Some college	13	9	n.s.[b]
College graduate	2	3	
SSAGA problem counts			
Alcohol problems	0.94 (1.34)	7.87 (3.07)	< .001[a]
Cannabis problems	0.00 (0.00)	1.67 (3.37)	n.s.[a]
Recent substance use			
Alcohol frequency (days/week)	1.50 (1.21)	4.20 (1.15)	< .001[a]
Alcohol quantity (drinks/week)	4.47 (4.62)	36.57 (18.10)	< .001[a]
Cannabis frequency (days/week)	0.00 (0.00)	1.60 (2.44)	.014[a]
Mood			
PANAS negative affect	12.19 (3.31)	13.50 (4.83)	n.s.[a]
PANAS positive affect	24.44 (7.74)	25.08 (6.97)	n.s.[a]
BDI	7.94 (9.59)	6.67 (5.88)	n.s.[a]
Sexuality			
n currently in a sexual relationship	5	9	n.s.[b]
No. of different sexual partners (lifetime)	1.81 (2.10)	5.67 (3.92)	.003[a]
No. of different sexual partners without condoms (past year)	0.25 (0.58)	1.07 (1.10)	.014[a]
SOI	40.38 (17.94)	61.87 (29.61)	.02[a]
BISF-W composite score	23.71 (14.45)	28.60 (15.11)	n.s.[a]
Sexual Experiences Survey	1.00 (2.00)	2.07 (1.98)	n.s.[a]
SES	49.69 (6.62)	49.00 (7.00)	n.s.[a]
SIS1 - Performance failure	39.19 (4.48)	40.00 (5.34)	n.s.[a]
SIS2 - Performance consequences	19.31 (3.77)	20.67 (4.88)	n.s.[a]
Risk-taking			
EVAR	12.73 (1.98)	14.03 (2.54)	n.s.[a]

Note. SSAGA = Semi-structured Assessment for the Genetics of Alcoholism; PANAS = Positive and Negative Affect Schedule; BDI = Beck Depression Inventory; SOI = Sociosexuality Orientation Inventory; SIS = Sexual Inhibition Scale; SES = Sexual Excitation Scale; EVAR= Evaluation of Risks Scale.
[a] *t*-test. [b] Chi-square test.

Behavioral Task Performance

	Control (n = 16)	Alcohol Dependent (n =15)	Sig.
Mean (SD) endorsement rates			
Male faces – low risk	2.71 (0.74)	2.61 (0.52)	n.s.[a]
Male faces – high risk	1.35 (0.44)	1.56 (0.45)	n.s.[a]
Food – low risk	3.11 (0.64)	3.23 (0.73)	n.s.[a]
Food – high risk	1.93 (0.68)	1.90 (0.79)	n.s.[a]
Household items – low risk	3.04 (0.50)	3.12 (0.52)	n.s.[a]
Household items – high risk	1.49 (0.42)	1.41 (0.57)	n.s.[a]
Mean (SD) response times (s)			
Male faces – low risk	1.93 (0.52)	2.11 (0.35)	n.s.[a]
Male faces – high risk	1.60 (0.33)	1.93 (0.43)	n.s.[a]
Food – low risk	1.85 (0.31)	1.85 (0.31)	n.s.[a]
Food – high risk	1.93 (0.39)	1.98 (0.44)	n.s.[a]
Household items – low risk	1.92 (0.33)	2.07 (0.37)	n.s.[a]
Household items – high risk	1.86 (0.26)	1.84 (0.30)	n.s.[a]

[a]ANOVA.

Table 3.3. List of Sexual Decisions ROIs for ADs > Controls

"Activation for Sexual Decisions"
$(2xSex_{Low}+Sex_{High}) > (Food_{Low}+Food_{High}+Item_{Low}+Item_{High})$
ADs > Controls (N=31)

Region	BA	z-score	x	y	z
Anterior cingulate cortex, dorsal	24	2.43	8	0	41
Pre-supplementary motor area	6	3.74	-2	-9	54
Post-central gyrus	2/3/43	3.66	-56	-21	43
Pre-central gyrus	4/43	3.82	-56	-6	34
Parietal operculum	40	2.78	-50	-35	24
Inferior parietal lobule	40/39	3.49	56	-43	48
Insula, anterior	13	3.53	-33	11	2
Insula, posterior	13	3.84	39	-13	10
Superior temporal gyrus	41/22	3.69	-59	-9	-1
Middle frontal gyrus	8	3.06	35	29	36
Frontopolar	10	3.76	44	47	-5

Table 3.4. List of Sexual Decisions ROIs for Controls-Only

"**Activation** for Sexual Decisions"
($2xSex_{Low}+Sex_{High}$) > ($Food_{Low}+Food_{High}+Item_{Low}+Item_{High}$)

Controls-Only (N=16)

Region	BA	z-score	x	y	z
Midbrain	--	3.49	2	-18	-22
Hypothalamus	--	4.03	-6	-5	-10
Hippocampus	--	4.52	30	-17	-15
Amygdala	--	5.96	21	-5	-19
Globus pallidus	--	2.78	13	3	-2
Putamen	--	3.06	27	11	-10
Caudate	--	2.80	-15	16	4
Thalamus	--	3.92	-5	-8	4
Middle temporal gyrus	21	4.78	62	-11	-21
Lingual gyrus	18	3.95	7	-81	-5
Lateral occipital gyrus	19	3.77	47	-76	-4
Orbital frontal cortex, lateral	47	4.05	41	25	-18
Inferior frontal gyrus	44/45	3.72	55	20	8
Medial prefrontal cortex					
Subcallosal cortex	25	3.48	3	6	-11
Anterior cingulate cortex	32/24	2.78	-2	35	1
Paracingulate gyrus	9	4.15	-3	36	30
Medial frontal gyrus	9	2.61	35	15	58
Superior frontal gyrus	8	3.09	11	46	47
Posterior cingulate	23/30	4.53	-2	-50	22
Precuneus	31/7	4.70	-2	-62	35
Fusiform gyrus	37	3.40	37	-50	-21

"**Deactivation** for Low-Risk Sexual Decisions"
($Food_{Low}+Food_{High}+Item_{Low}+Item_{High}$) > ($2xSex_{Low}+Sex_{High}$)

Controls-Only (N=16)

Region	BA	z-score	x	y	z
Anterior cingulate gyrus, dorsal	24	3.01	-4	5	34
Pre-supplementary motor area	6	4.48	-2	-4	50
Postcentral gyrus	2/3/43	3.43	-60	-6	15
Precentral gyrus	4/43	4.22	-60	0	13
Parietal opperculum	40	3.35	-48	-31	16
Superior parietal lobule	7	3.55	-31	-49	57
Inferior parietal lobule	40	4.52	-45	-41	53
Insula, anterior	13	3.25	35	8	5
Insula, posterior	13	3.79	40	-15	1
Superior temporal gyrus	41/22	3.46	-58	-1	-7
Occipital fusiform	37	2.90	-26	-73	-13
Temporal fusiform gyrus	37	3.19	-28	-53	-8
Inferior temporal gyrus	37	4.20	-48	-52	-14
Superior occipital gyrus	41/22	3.76	28	-87	34
Middle occipital gyrus	19	3,28	31	-93	18
Cerebellum	--	3.66	-22	-44	-24

Table 3.5. List of Sexual Decisions ROIs for ADs-Only

"Activation for Sexual Decisions"
$(2xSex_{Low}+Sex_{High}) > (Food_{Low}+Food_{High}+Item_{Low}+Item_{High})$

ADs-Only (N=15)

Region	BA	z-score	x	y	z
Midbrain	--	3.21	2	-18	-22
Hypothalamus	--	3.94	-6	-5	-10
Hippocampus	--	3.78	22	-17	-16
Amygdala	--	5.27	21	-5	-19
Globus pallidus	--	2.98	16	2	-2
Putamen	--	3.57	27	11	-10
Caudate	--	3.75	13	3	16
Thalamus	--	3.99	-5	-8	4
Middle temporal gyrus	21	3.82	62	-11	-21
Lingual gyrus	18	5.26	7	-81	-5
Orbital frontal cortex, lateral	47	2.80	38	25	-18
Inferior frontal gyrus	44/45	3.92	55	20	8
Medial prefrontal cortex					
Subcallosal cortex	25	3.05	0	9	-19
Anterior cingulate cortex	32/24	3.26	-2	35	1
Paracingulate gyrus	9	4.41	-3	36	30
Medial frontal gyrus	9	3.22	35	15	58
Superior frontal gyrus	8	2.92	11	46	47
Posterior cingulate	23/30	4.09	-2	-50	22
Precuneus	31/7	4.18	-2	-62	35
Fusiform gyrus	37	3.59	37	-50	-21
Frontopolar	10	3.07	37	53	-5
Middle frontal gyrus	8	3.06	34	24	39

"Deactivation for Low-Risk Sexual Decisions"
$(Food_{Low}+Food_{High}+Item_{Low}+Item_{High}) > (2xSex_{Low}+Sex_{High})$

ADs-Only (N=16)

Region	BA	z-score	x	y	z
Temporal fusiform gyrus	37	4.20	-28	-53	-8
Inferior temporal gyrus	37	3.77	-48	-52	-14
Cuneus	19	2.87	-15	-90	28
Precuneus	19	3.24	-27	-71	45

Table 3.6. List of High-Risk > Low-Risk ROIs for ADs and Controls

"**Deactivation** for High-Risk Sexual Decisions > Low-Risk Sexual Decisions"
$((Food_{High}- Food_{Low})+(Item_{High}- Item_{Low})) > (Sex_{High}-Sex_{Low})$
ADs and Controls (N=31)

Region	BA	z-score	x	y	z
Pons	--	2.42	-1	-19	-23
Substania nigra	--	2.52	-7	-17	-17
Putamen	--	2.41	27	8	-2
Thalamus	--	3.51	4	-10	-2
Insula, anterior	13	2.48	38	18	-2
Anterior cingulate cortex, dorsal	24/32	2.74	5	26	28
Paracingulate gyrus	6	3.64	5	16	46
Superior frontal gyrus	6	3.86	12	21	61
Middle frontal gyrus	6/9	2.95	30	11	52
Precentral gyrus	6	3.22	45	2	34
Inferior frontal gyrus	46	3.46	45	23	12
Frontal operculum	47	3.17	48	20	-8
Frontpolar	10	3.52	38	56	4
Orbital frontal cortex	47	2.79	45	20	-14
Inferior parietal lobule	40	3.50	45	-47	44

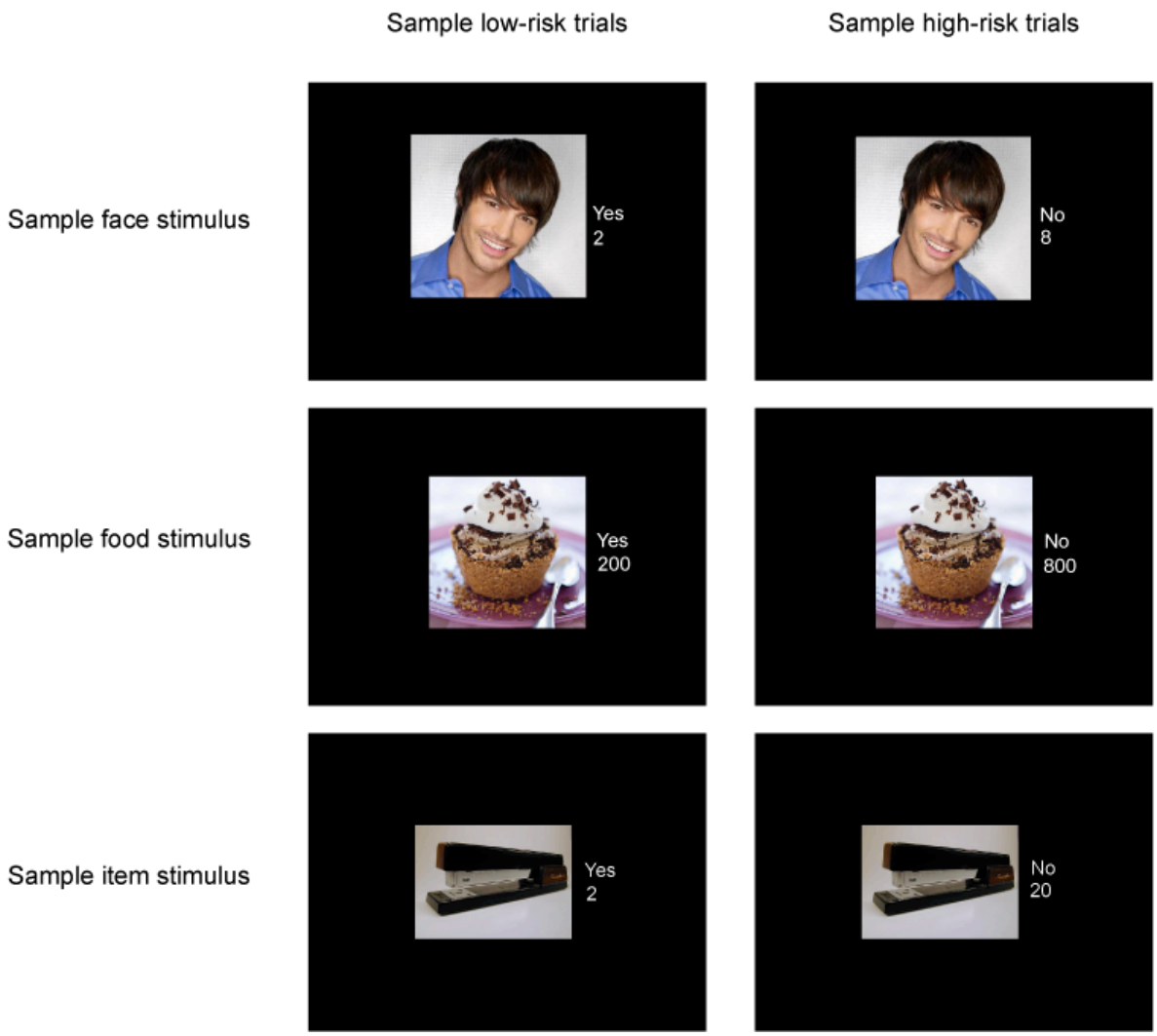

Figure 3.1. Sample stimuli.

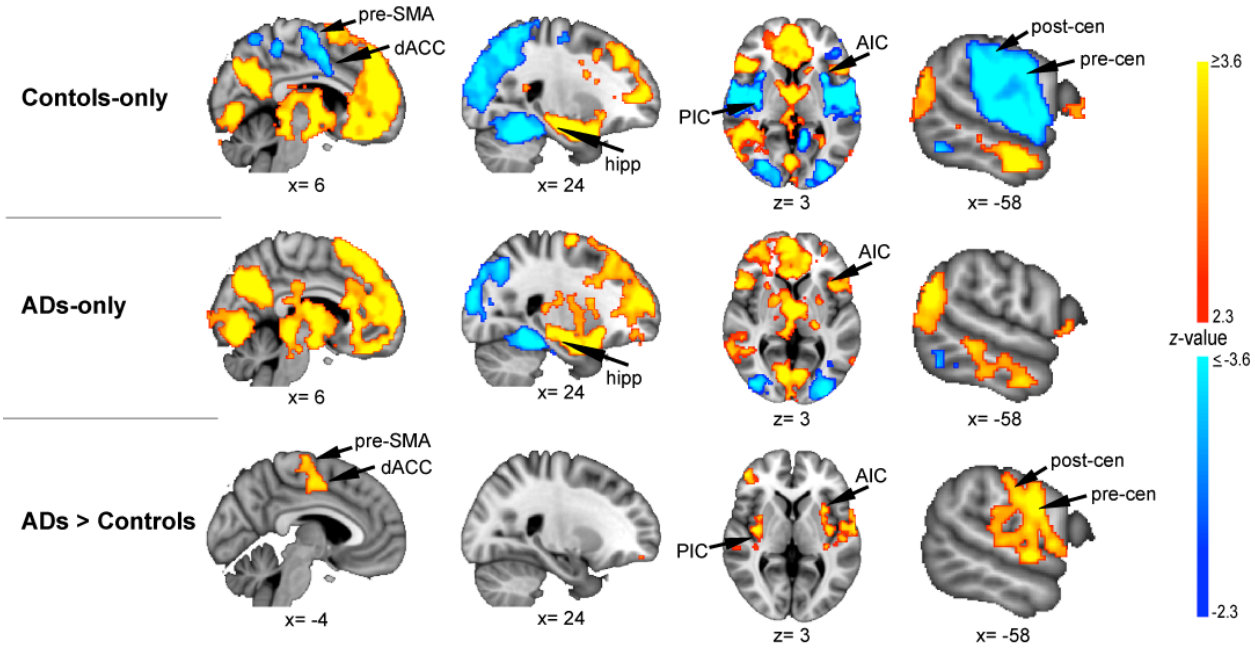

Figure 3.2. Statistical maps for sexual decisions. [(2xSex_{Low}+Sex_{High}) > ($Food_{Low}$+$Food_{High}$+$Item_{Low}$+$Item_{High}$)]. Abbreviations: pre-SMA, pre-supplementary motor area; dACC, dorsal anterior cingulate; hipp, hippocampus; PIC, posterior insular cortex; AIC, anterior insular cortex; post-cen, posterior central gyrus; pre-cen, pre-central gyrus.

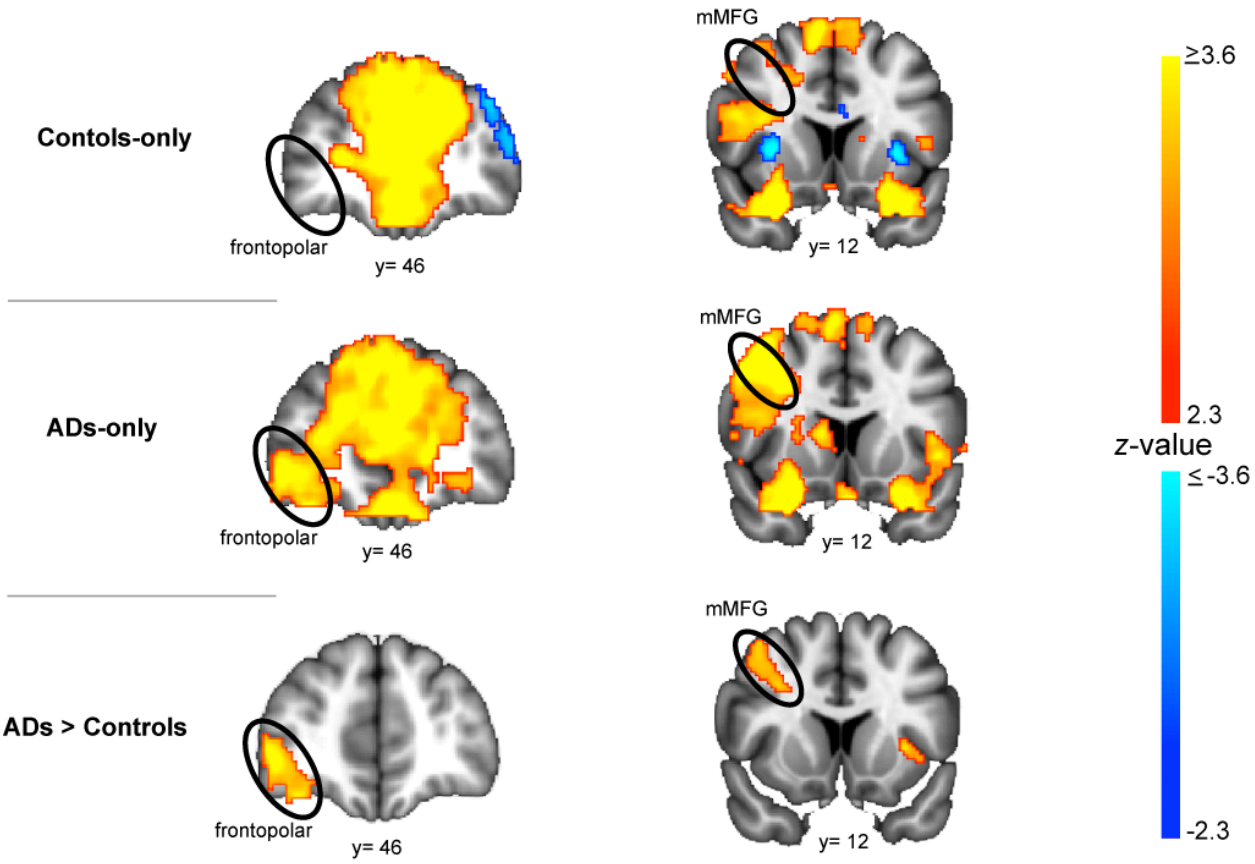

Figure 3.3. Statistical maps for sexual decisions. [(2xSex_{Low}+Sex_{High}) > ($Food_{Low}$+$Food_{High}$+$Item_{Low}$+$Item_{High}$)]. Abbreviations: mMFG, medial aspect of the middle frontal gyrus.

CHAPTER 4

RIGHT ANTERIOR INSULA FUNCTIONAL CONNECTIVITY DURING HIGH-RISK DECISIONS-TO-DRINK IN ALCOHOL DEPENDENT WOMEN

"I ordered a Jamison, and I stared at it for about 20 minutes. It was like knowing if you take a drink right now, you're going to lose your wife and your kid. You don't want to drink, you don't want to get drunk, and yet I knew I was going to drink. And I took that drink knowing those things. […] No right-minded man would go, 'I'm going to lose my wife and my kid, yeah give me another one!'"

– Billy Gardell, WTF podcast with Marc Maron

4.1. Introduction

Alcohol consumption is rewarding, but it carries the risk of future negative consequences. Information regarding risks and rewards associated with drinking alcohol need to be considered in order to maximize reward and minimize risk. A key feature of alcohol dependence is an inability to appropriately integrate information about alcohol's reward and risk as evidenced by the continuation of drinking despite severe negative consequences. This deficit is due in part by neural changes accompanying the heavy drinking associated with alcohol dependence. Heavy alcohol use produces changes in the mesolimbic dopaminergic system and in prefrontal executive control regions (Robinson & Berridge, 2008; Sullivan et al., 2002). In addition, it is a robust finding that those with alcohol dependence (ADs) perform worse than controls on tasks that require integrating information about reward and negative

outcomes. On temporal discounting tasks, ADs have been shown to discount the future significantly more than controls, suggesting that ADs prefer smaller immediate rewards compared to larger delayed rewards (Amlung et al., 2012; Bickel et al., 2007, 2014). ADs also have poorer performance on the Iowa Gambling Task (IGT) compared to controls. On the IGT, ADs make more disadvantageous decisions, reflecting choices that favor immediate rewards at the cost of long-term losses (Fein et al., 2004; Kim et al., 2011; Mazas et al., 2000). It is clear that ADs have behavioral deficits related to these tasks, but the neural mechanisms underlying these behavioral deficits in ADs are only beginning to be understood.

While it is well documented that ADs make suboptimal decisions on tasks like the IGT and temporal discounting, these deficits may be exaggerated further when faced with decisions specifically about alcohol. Using an ecological task, we previously showed that, during high-risk decisions-to-drink, AD women activated regions of the salience network (SN), central executive network (CEN), and regions of the default-mode network (DMN), while control women deactivated regions of the SN and showed enhanced activation in regions of the DMN (Arcurio et al., 2013). Group differences were found only for decisions-to-drink, indicating they are specific to alcohol cues. Simultaneous activation of regions associated with the SN, CEN, and DMN in AD women suggests that their over-endorsement of high-risk drinking decisions may be due to a problem with switching between different neural networks. Additionally, our data pointed to six candidate regions that may play a critical role in AD specifically during high-risk decisions-to-drink, i.e. high-risk vs. low-risk alcohol decisions greater

than high-risk vs. low-risk appetitive and neutral decisions. The six regions that ADs activated significantly more than controls specifically during high-risk decisions-to-drink included the right anterior insula (rAIC), right inferior frontal gyrus, bilateral lateral occipital cortex, and cerebellar regions (vermis and crus I). The focus of the current study is on the functional connectivity of the rAIC during high-risk decisions-to-drink because of its role in switching between the DMN and CEN (Sridharan et al., 2008; Menon & Uddin, 2010) and in many features of alcohol dependence including cue reactivity and risk-taking (Naqvi et al., 2007, 2014; Schacht et al., 2013; Ishii et al., 2012; Mohr et al., 2010).

The role of the rAIC in alcohol dependence seems to be at odds when comparing the cue reactivity and risky decision-making literature. In regards to cue reactivity, in a recent meta-analysis, Schacht and colleagues (2013) investigated regions most commonly activated in functional neuroimaging studies during cue reactivity tasks using alcohol cues in those with alcohol use disorders and healthy controls. The anterior insula was among the regions most commonly activated in those with alcohol use disorders during cue reactivity tasks. Furthermore, using fMRI, Vollstädt-Klein and colleagues (2012) showed that attentional bias scores positively correlated with activation in the anterior insula during a cue reactivity task. Together, this research suggests that increased activation of the anterior insula in the presence of alcohol cues may serve to detect and orient to potentially rewarding stimuli. This is also in agreement with the anterior insula's role as a core region of the SN, which functions to

detect and orient to salient internal or external stimuli (Menon & Uddin, 2010; Menon, 2011).

Additionally, Naqvi and colleagues (2007) in a retrospective study demonstrated that patients who were smokers and subsequently acquired insular damage (mostly from stroke) were much more likely to "abruptly" quit smoking compared to patients with lesion damage elsewhere who had also quit smoking. Patients with insular damage who quit smoking were able to do so immediately and without relapse compared to patients with damage to other brain regions. This phenomenon may have been observed because of the insula's well-documented role in interoception (for a review, see Craig, 2009). The insula is a multimodal region, situated in the limbic system such that inputs carrying information regarding the external and internal environment may be integrated to guide further processing or action plans by recruiting the appropriate networks based on homeostatic needs (Paulus & Stewart, 2013; Naqvi et al., 2014). This evidence suggests that the insula may be a substrate of craving that represents the need to adjust homeostatic values and can guide behavior towards ingesting alcohol as the desired or optimal way of achieving homeostasis.

There is, however, another large body of literature that suggests the anterior insula plays a critical role in risky decision-making. Specifically in gambling tasks that use points or money, neuroimaging studies have shown that the anterior insula is particularly responsive to potential loss (Mohr et al., 2010; Kuhnen & Knutson, 2005; Preuschoff et al., 2008; Clark et al., 2008; Palminteri et al., 2012). For example, Kuhnen and Knutson (2005) showed that activity in the anterior insula preceded "riskless"

choices even in cases where choosing the riskless choice was suboptimal. In a meta-analysis of neuroimaging studies on risk processing, Mohr and colleagues (2010) showed that risk consistently activated the anterior insula and that it was primarily active for potential losses. Results of these studies suggest that the insula may be involved in representing risk or magnitude of potential loss and in recruiting risk-avoiding action plans (Gowin et al., 2013).

The anterior insula has consistently been identified as a structural and functional hub using network analyses, meaning that it is central to integrative and communicative processes (van den Heuvel & Sporns, 2013). In humans, the insula, dorsal prefrontal, posterior parietal, and visual cortices have been identified as outflow or 'driving' hubs, whereas the posterior cingulate, precuneus, and medial frontal regions have been identified as input or 'driven' hubs. Additionally, these hubs are highly connected to one another, constituting a 'rich club' (van den Heuvel & Sporns, 2013), meaning that severe impairments could occur when damage occurs to these regions or to tracts connecting these regions. Indeed, functional resting state studies show that network disruption is common in alcohol dependence and other forms of substance use (Schmaal et al., 2013; Chanraud et al., 2011; Liu et al., 2009; Cisler et al., 2013; Ma et al., 2011). Specifically, Chanraud and colleagues (2011) demonstrated that the functional connectivity of the DMN is disrupted in those with AD, and Schmaal et al. (2013) showed that the negative coupling (anti-correlation) between the CEN and DMN was reduced in those with AD. Given the anterior insula's role in switching between the CEN and DMN (Sridharan et al., 2008) and its role in cue reactivity and

risky decisions, a driving factor in these studies may be dysfunction in the anterior insula. Supporting this notion, Cisler and colleagues (2013) showed that functional connectivity of the right anterior insula during rest is altered in those with cocaine dependence, namely that the rAIC had greater functional connectivity with the dorsomedial prefrontal cortex, bilateral dorsolateral prefrtonal cortex, and the inferior frontal gyrus. Together, these studies demonstrate that functional connectivity analyses are critical to further understanding of alcohol dependence.

In the current study, we investigated the role of the right anterior insula in alcohol dependence during high-risk decisions-to-drink using a generalized form of psychophysiological interactions (gPPI) as our functional connectivity measure. We hypothesized that if this aspect of the rAIC is involved in generating approach or drug-seeking behavior, we would find increased functional connectivity between the rAIC and regions involved in approach behavior, such as reward regions. If this portion of the rAIC is more involved in summing up potential losses, we hypothesized we would find increased functional connectivity between the rAIC and regions involved in inhibition, such as dorsolateral prefrontal cortex or inferior frontal gyrus.

4.2. Methods

Methods regarding participants, assessment materials, imaging materials and procedure, scanning session procedure, imaging parameters, and imaging analysis have been reported in full in Chapter 2 of the current volume.

Psychophysiological Interactions Analysis. A generalized PPI (gPPI) model was used in order to model all conditions of interest (high-risk alcohol, food, and household items) (McLaren et al., 2012). We performed a seed-based analysis on the region of the right anterior insula (rAIC) that was significantly active in the 3-way interaction of Stimulus (alcohol > food and items) x Risk (high > low-risk) x Group (ADs > controls) reported in the whole-brain GLM analysis in Chapter 2 of this volume. Generalized-PPIs were computed by creating a psychophysiological interaction term consisting of the element-by-element product of the non-deconvolved physiological activity from the seed region (demeaned time series within the seed region) and our psychological task predictors (mean-centered task time course for high-risk alcohol, high-risk food, and high-risk household items) (Kim & Horwitz, 2008). Crucially, three regressors representing the main effects of condition (high-risk alcohol, food, and items) and a fourth regressor representing the time course of the seed region were added to the model as covariates of no interest. By including task and seed region time course as covariates, the gPPI analysis will only uncover regions that are functionally connected to the seed region at a level over and above what could be accounted for by either task or seed region BOLD changes (O'Reilly et al., 2012).

4.3. Results

Behavior. Behavioral results have been described in full in Chapter 2 of this volume. Behavioral results directly pertaining to the current study are described below.

Likelihood of endorsement. Briefly, a repeated-measures ANOVA with endorsement rate as the dependent variable, stimulus and risk as within-in-subject factors, and group as a between-subject fact showed highly significant effects (Chapter 2, Figure 2.2., pg. 70). Especially pertinent for the current analysis, there was a main effect of risk [$F_{(2,29)}$ =122.380, p=0.000] where both groups endorsed high-risk stimuli significantly less than the low-risk stimuli, demonstrating that our risk manipulation was successful. There was also a significant 3-way interaction of group x stimulus type x risk [$F_{(2,58)}$=3.994, p=0.024] where post-hoc pairwise tests using Tukey's honestly significant difference (HSD) revealed that the only significant between-group difference in endorsement was observed in the high-risk alcohol condition where ADs responded that they would drink significantly more high-risk alcoholic beverages than controls [$q_{(2,58)}$=4.46].

Reaction Time. Briefly, a repeated-measures ANOVA with endorsement rate as the dependent variable, stimulus and risk as within-in-subject factors and group as a between-subject factor showed significant effects (Chapter 2, Figure 2.3., pg. 71). Notably, there was a main effect of risk [$F_{(2,29)}$=20.334, p=0.047] where both groups took a significantly longer amount of time to make high-risk decisions compared to low-risk. There was also a significant 3-way interaction of group x stimulus type x risk [$F_{(2,58)}$=6.552, p=0.003] where post-hoc pairwise tests using HSD revealed that the ADs took a significantly longer amount of time to make high-risk alcohol decisions compared with low-risk alcohol decisions [$q_{(2,58)}$=3.84].

fMRI: GLM. BOLD fMRI data were analyzed in a 3 x 2 x 2 x 2 full-factorial, whole-brain GLM analysis with stimulus cue (alcohol, food, item), risk (high, low), and phase (follicular, luteal) as within-subject factors and group (controls, ADs) as a between-subject factor. Procedurally, menstrual cycle phase was included as a factor due to hypotheses about its influence on face/sex decisions. Because face/sex decisions were not analyzed for this article, there was no specific hypothesis made about the influence of phase on stimulus cue activation. For completeness, phase was included as a factor in the overall analysis. However, for alcohol decisions, phase did not interact with risk, nor did it interact with group. As such, the results below are reported collapsed across phase (i.e., two sessions worth of data per participant).

Decisions-to-Drink: Low-risk. These results have been described in full in Chapter 2 of this volume. The low-risk maps were generated by comparing alcohol decisions to food and item decisions in the low-risk condition (i.e., $2 \times (ALC^{Low\text{-}risk}) - (FOOD^{Low\text{-}risk} + ITEM^{Low\text{-}risk})$) for each group separately and for the two-way stimulus by group interaction. Briefly, no significant group differences were observed for low-risk decisions-to-drink. The activation pattern in both groups was mainly associated with greater activation of the default-mode network (DMN) for alcohol decisions, whereas both groups significantly deactivated (i.e., produced less activation with alcohol decisions compared to food and item decisions) regions of the medial occipital cortex.

Decisions-to-Drink: High-risk. The high-risk maps (Chapter 2, Figure 2.5., pg. 73) were generated the same way as the low-risk maps, except comparing all high-risk conditions (i.e., $(2 \times ALC^{High\text{-}risk}) - (FOOD^{High\text{-}risk} + ITEM^{High\text{-}risk})$). The results for high-

risk decisions were quite different from low-risk decisions. Here, ADs showed significantly greater activation than controls for alcohol decisions compared to food and item decisions in regions of the SN, including the substantia nigra, dorsal striatum, bilateral anterior insula, and pre-SMA (Figure 5a,b). ADs also showed significantly greater activation than controls for alcohol decisions compared to food and item decisions in regions of the CEN, including the mid-ventral lateral PFC (mid-vlPFC), which includes the inferior frontal sulcus (IFS) BA9, the inferior frontal gyrus (IFG) BA46/45/44, and the frontal operculum/insula, which will be referred to here as the fronto-insular cortex (FIC) (BA47/13) (Figure 5a). In addition to greater activation in regions of the SN and CEN, ADs also showed significantly greater activation for alcohol decisions in the LOC (BA19), FG (BA37), and cerebellum (crus 1, bilateral) (Figure 5b). There were no regions where controls showed significantly greater activation for alcohol decisions than other decisions relative to ADs.

Separate group maps for high-risk alcohol decisions (Chapter 2, Figure 2.5., pg. 73) were examined to determine what patterns of activation/deactivation were driving the interaction for different clusters. The map for controls only (Chapter 2, top rows of Figure 2.5.a,b, pg. 73) represents the "normative" pattern of activation for the high-risk alcohol decisions. It is worthwhile noting that this normative control pattern for high-risk decisions was very similar to the control pattern for low-risk decisions; controls showed greater activation for alcohol decisions than other decisions in regions associated with the DMN (posterior cingulate and vmPFC). However, unlike with low-risk decisions, for high-risk decisions controls also "deactivated" (i.e., produced less

activation with alcohol decisions than other decisions) core regions of the SN, including posterior and anterior portions of the insula, the dACC, and pre-SMA. In addition, controls showed significant deactivation of the medial occipital cortex.

Because controls showed "deactivation" in some regions that also showed a significant stimulus by group interaction, it is possible that the interaction in those regions was driven by controls' deactivation for alcohol decisions relative to other decisions, rather than ADs' greater activation with alcohol decisions relative to other decisions. The AD-only map for high-risk alcohol decisions (Chapter 2, Figure 2.5.a,b, pg 73), showed significant activation for ADs in bilateral anterior insula, but not the pre-SMA. This suggests that the greater activation for alcohol decisions compared to other decisions in the pre-SMA for ADs over controls (i.e., the stimulus x group interaction) was driven by controls' "deactivation" (Chapter 2, Figure 2.5.a, pg 73) rather than ADs' "activation". However, in the anterior insula, the same two-way interaction appears to be a combined effect of ADs' greater activation with alcohol decisions over other decisions and controls' greater "deactivation" with alcohol decisions relative to other decisions. The AD-only map also showed another significant pattern of activation was not revealed in the group x stimulus interaction, namely greater activation with alcohol decisions than other decisions in core regions of the DMN (posterior cingulate and vmPFC) (Chapter 2, Figure 2.5.a, pg. 73). These were the same regions that controls activated -- and the *only* regions that controls activated -- for high-risk alcohol decisions. It is worthwhile noting that, unlike controls, ADs showed

no regions of significant "deactivation" for alcohol decisions relative to food or item decisions.

Decisions-to-Drink: High-risk > Low-risk. Lastly, we tested to see if there were any brain regions associated with a stimulus x risk condition x group interaction (i.e., ($ALC^{High\text{-}risk}$ - $ALC^{Low\text{-}risk}$) – (($FOOD^{High\text{-}risk}$ - $FOOD^{Low\text{-}risk}$) + ($ITEM^{High\text{-}risk}$ - $ITEM^{Low\text{-}risk}$)). Consistent with a comparison of low- and high-risk maps, the regions showing the greatest difference of high-risk and low-risk between ADs and controls included the right anterior insula (BA13), right FIC (BA44/13), right IFS (BA6), inferior temporal gyrus, ventral occipitotemporal aspect (BA37), fusiform gyrus (BA37), lateral occipital cortex (BA19), caudal inferior parietal sulcus (cIPS, BA 31) and cerebellum (vermis and bilateral crus I) (Chapter 2, Figure 2.6., pg. 75). In all of these clusters, the three-way interaction was driven by a greater difference in activation between alcohol decisions and food and item decisions that was greater for high-risk than low-risk situations, and that difference was greater for ADs than controls.

To further explain these results of the three-way interaction, we examined the two-way interactions between stimulus and risk for each group, by performing the same contrast (($ALC^{High\text{-}risk}$ vs. $ALC^{Low\text{-}risk}$) – (($FOOD^{High\text{-}risk}$ vs. $FOOD^{Low\text{-}risk}$) + ($ITEM^{High\text{-}risk}$ vs. $ITEM^{Low\text{-}risk}$)) in each group separately. This contrast showed no significant clusters of activation or "deactivation" for controls. However, there was a significant stimulus x risk interaction for ADs in all regions that showed the significant three-way interaction described above (stimulus x risk x group). In addition to those regions, ADs also showed a significant stimulus x risk interaction in the supramarginal

gyrus (BA40), middle frontal gyrus (BA8), IFG (BA46), frontopolar (BA10), orbital frontal cortex (BA11), precentral gyrus (BA4), postcentral gyrus (BA3), middle temporal gyrus (BA22), dACC (BA24), paracingulate gyrus (BA32), and lingual gyrus (BA18).

In sum, consistent across all regions, the three-way stimulus x risk x group interaction was driven by ADs' over-activation during high-risk alcohol decisions compared to high- and low-risk decisions with both appetitive and neutral control stimuli and compared to controls. The three-way interaction was seen in regions that are components of the SN (right anterior insula) and CEN (right IFG), as well as visual processing regions and the cerebellum.

fMRI: PPIs.

Right anterior insula cortex seed: high-risk decisions-to-drink. The right anterior insular cortex (rAIC) has been shown to play a causal role in switching between the DMN and CEN (Sridharan et al., 2008) and emerged as a critical region of interest in comparing high- and low-risk decisions-to-drink in ADs compared to controls. In ADs, the rAIC showed hyperactivation in high- compared to low-risk decisions-to-drink and compared to controls. Given its critical role in salience detection and network switching, we used the significant voxels belonging to the rAIC found in the GLM, 3-way interaction [$(ALC^{High\text{-}risk} - ALC^{Low\text{-}risk}) - ((FOOD^{High\text{-}risk} - FOOD^{Low\text{-}risk}) + (ITEM^{High\text{-}risk} - ITEM^{Low\text{-}risk}))$] results as the seed region of the subsequent PPI analysis.

The rAIC was used as a seed region to test for differences in functional connectivity between ADs and controls during the high-risk alcohol context compared to high-risk food and item contexts. We found significant differences in functional

connectivity between groups in the high-risk alcohol context where ADs had significantly less functional connectivity between the rAIC and the dorsal ACC (dACC), caudate body, regions of the DMN including the PCC (BA30), precuneus (BA7), middle temporal gyrus (BA39), angular gyrus (BA39), and hippocampus, and cerebellar regions compared to controls (Figure 4.1., Table 4.1.).

To further explain these results, we examined each group map separately. Controls did not show any significant differences in functional connectivity between the rAIC and any other voxels during high-risk decisions-to-drink. In contrast, ADs showed significantly decreased functional connectivity between the rAIC and regions of the DMN including the PCC (BA30), middle temporal gyrus (BA39), and precuneus (BA7), cerebellar regions, and frontal regions including the superior frontal gyrus (BA8/9), and middle frontal gyrus (BA8/9) during high-risk decisions-to-drink (Figure 4.2., Table 4.2.).

4.4. Discussion

This is the first study to investigate task-based functional connectivity using gPPI of the right anterior insula (rAIC) between AD and control women during an ecological, decisions-to-drink task. Our rAIC seed was chosen because this was the only portion of the insula to show hyperactivation during the high-risk alcohol condition in AD women compared with the low-risk alcohol condition and compared to control women, demonstrating that this aspect of the rAIC is highly specific to high-risk decisions-to-drink and may be critical in influencing neural activation in high-risk drinking

situations. Contrary to our hypotheses, we found significant differences in functional connectivity between groups in the high-risk alcohol context where ADs had significantly less functional connectivity between the rAIC and the dorsal anterior cingulate cortex (dACC), caudate body, regions of the default-mode network (DMN) including the posterior cingulate cortex (PCC), precuneus, middle temporal gyrus, angular gyrus, and hippocampus, and cerebellar regions including the vermis. The current findings, together with previous research connecting disruption of the DMN with alcohol dependence (Chanraud, et al., 2011; Schmaal et al., 2013) and our GLM results showing that control women primarily activate core regions of the DMN when making decisions about high-risk alcohol, highlights the importance of further investigating the role of the DMN in ecological, risky decisions.

These results lead to new insights about how drinking persists despite the severe negative consequences experienced by those with alcohol dependence. First, our results showed that ADs have reduced functional connectivity between the rAIC and the PCC and precuneus, which have all been identified as cortical hubs (van den Heuvel & Sporns, 2013). That dysfunction of the rAIC leads to decreases in functional connectivity with other hub regions supports a 'rich club' organization model (van den Heuvel & Sporns, 2013) where dysfunction in one structural/functional hub would lead to observable differences in communication with other hub regions. Furthermore, the PCC and precuneus are primarily associated with the DMN along with the middle temporal gyrus, angular gyrus, and hippocampus. Decreased functional connectivity between the rAIC and these regions associated with the DMN could partly explain why

reduced anti-correlation between the DMN and CEN was observed in those with alcohol dependence (Schmaal et al., 2013). The rAIC has been shown to play a causal role in switching between the CEN and DMN (Sridharan et al., 2008), and if communication is broken down between the rAIC and key regions of the DMN, this could result in a reduced ability to switch between the DMN and CEN and reduced anti-correlation between default-mode and central executive networks.

Regions of the DMN have also been shown to activate significantly during temporal discounting tasks (Carter et al., 2010; Amlung et al., 2012) and prospective thought (Schacter et al., 2007). Temporal discounting and prospective thinking both have the future in common. In order to chose the future reward during temporal discounting tasks, the future self must be imagined. Indeed, Peters & Büchel (2010) showed that cuing participants to use episodic future thinking during a temporal discounting task resulted in a decrease of discounting future rewards. The hippocampus has been shown to be essential for both remembering the past and the future (Schacter et al., 2007), and the PCC has been shown to be sensitive to the rewarding value of a stimulus (Serences, 2008; McCoy et al., 2003). Given that the rAIC seed region was used based on it its selectivity to high-risk drinking decisions, it may be that a reduction in the functional connectivity between the rAIC and key regions of the DMN indicates that critical information about the future risk associated with the alcoholic beverage is not being integrated into a decision about whether or not to drink the high-risk drink.

We also observed reduced functional connectivity between the rAIC and dorsal anterior cingulate cortex (dACC). The dACC is highly involved in conflict monitoring (Carter & van Veen, 2007) and risk aversion (Brown & Braver, 2007) and has extensive connections with many regions of the prefrontal cortex (Ridderinkhof et al., 2004). Reduced functional connectivity of the rAIC and dACC could indicate that the dACC is not properly receiving information regarding risk and therefore is neither able to properly detect conflict nor instantiate appropriate plans for inhibition when the goal for the system is to avoid the negative consequences associated with the stimulus.

Lastly, we observed reduced functional connectivity between the rAIC and caudate body and cerebellum. In our GLM results, we found that the caudate and cerebellar vermis were significantly more active in ADs compared to controls during high-risk decisions-to-drink. We inferred that recruitment of the caudate (dorsal striatum) was associated with circuitry underlying the habitual or compulsive drive to drink alcohol (Arcurio et al., 2013; Koob & Volkow, 2010; Vollstädt-Klein et al., 2010). Activation of the caudate in ADs during high-risk decisions-to-drink may be in part due to reduced functional connectivity with the rAIC. This portion of the rAIC appears to be a critical component of representing the risk involved with high-risk decisions-to-drink, and decreased functional connectivity between these two regions may be a mechanism of the habit formation for drug seeking in alcohol dependence.

The vermis of the cerebellum is also a key region involved in habit formation (Yin & Knowlton, 2006). The vermis is involved in the recall of emotional memories associated with drug cues and has connections to the ventral tegmental area and

substantia nigra, both dopamine-rich regions involved in drug seeking and use (Miquel et al., 2009). Decreased functional connectivity between the rAIC and vermis may be another critical component of habit formation in alcohol dependence.

Decreased functional connectivity of the rAIC in alcohol dependence may occur for several reasons. Alcohol is neurotoxic and over the course of heavy drinking results in decreased gray matter, particularly in the right anterior insula (Momenan et al., 2012), and white matter damage (Harper et al., 1990). Disruption of white matter integrity has also been documented in heavy drinkers (Monnig et al., 2013). Furthermore, Monnig and colleagues (2013), using fractional anisotropy (FA), showed that FA values of nine white matter tracts were negatively correlated with BOLD responses to alcohol taste cues in the middle frontal gyrus, fusiform, thalamus, parahippocampal gyrus, cingulate, caudate, insula, and cerebellum. In the current study, we observed decreased functional connectivity between the rAIC and hippocampus, dACC, caudate, and cerebellum, among other regions. Further research needs to be conducted to determine whether changes to insular gray matter, damage to white matter tracts, or a combination of both are critical to the changes we observed in functional connectivity of the rAIC.

Additionally, Gilman and colleagues (2012) investigated the effect of intravenous alcohol on brain activation during risky decision-making in healthy social drinkers and found that compared to placebo, one of the greatest effects of alcohol was on dampening the neural response to both positive and negative feedback. Feedback responses were dampened in the thalamus, caudate, and insula. The results of Gilman

et al. (2012) emphasize the importance of these structures in learning the negative consequences experienced while drinking alcohol. Typically, negative consequences associated with alcohol do not occur immediately and occurrence is uncertain. This is in contrast to the relatively fast and reliable reward experienced while first drinking alcohol. These results suggest that the negative consequences experienced by those with alcohol dependence are not properly represented or encoded in the brain and that the insula and caudate are critically involved in this process.

Limitations. A limitation of using PPI to model functional connectivity is that we are unable to assess directionality, but previous research has shown that the rAIC plays a causal role in switching between the CEN and DMN (Sridharan et al., 2008).

Conclusions. We have highlighted the importance of the rAIC in high-risk decisions-to-drink and how disruption in functional connectivity between the rAIC and regions of the DMN, dACC, and regions involved in habit formation may be critical to the continuation of drinking despite the severe negative consequences experienced by those with alcohol dependence. The anterior insula is a large and heterogeneous region containing different cell types with varying inputs and outputs as you move along the anterior-posterior axis (Craig, 2009; Cauda et al., 2011, 2014). This may be one reason why the anterior insula has been shown to be highly involved in both approach behavior (craving and drug seeking) and avoidance behavoir (risk-aversion). Here, we show a particular region of the rAIC to be highly responsive to the risk associated with alcohol during high-risk decisions-to-drink; it is unclear, however, whether the pattern of activation and functional connectivity associated with this region is due to gray

matter or white matter damage individually or a combination of both. Given that the anterior insula contains a high number of von Economo neurons that have only been found in the rAIC and anterior cingulate of the human brain and are specialized for rapid communication, the effects of alcohol on this cell type should be investigated.

Our results also suggest that proper functioning of the DMN is critical for making ecological, high-risk decisions-to-drink. Much of the previous literature has focused on this network as primarily being active during 'rest' (Greicius et al., 2003). However, recent research is showing that categorizing the DMN as "task-negative" is misleading and that this network is critical for mentalizing about future and real-world decision-making (Spreng, 2012). Together, our findings underscore the importance of further investigating the physical properties of the rAIC and how alcohol may alter them, the relationship between DMN functioning and ecological decisions-to-drink alcohol, and how alcohol dampens the negative feedback response between the rAIC and regions involved in habit formation.

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Table 4.1. List of PPIs for Controls > ADs, Right Anterior Insula Seed

"PPIs for rAIC seed during high-risk decisions-to-drink" ($2xAlc_{High}$) > ($Food_{High}$+$Item_{High}$)							
Controls > ADs (N=31)							
Region	voxels	BA	x	y	z	z-max	p
Cluster 4	3044					4.05	0.0000
Posterior cingulate		30	6	-44	2	4.05	
Hippocampus, L		--	-32	-28	-14	3.75	
Precuneus		7	0	-64	44	3.69	
Precuneus, R		7	4	-62	48	3.67	
Cluster 3	894					4.17	0.0002
Lateral occipital cortex, superior aspect, R		19	34	-82	36	4.17	
Middle temporal gyrus, R		39	44	-68	22	3.74	
Lateral occipital cortex, superior aspect, R		19	40	-82	28	3.74	
Angular gyrus, R		39	42	-74	38	3.52	
Middle temporal gyrus, R		39	40	-74	24	3.49	
Precuneus, R		7	18	-78	46	3.30	
Cluster 2	609					3.76	0.0032
Anterior internal capsule, white matter		--	20	8	22	3.76	
Genu of corpus callosum		--	18	26	20	3.20	
Caudate, body		--	14	0	18	3.16	
Cluster 1	397					3.75	0.039
Superior corona radiate, L		--	-30	-10	28	3.75	
Superior corona radiate, L		--	-24	-10	26	3.75	
Middle frontal gyrus, L		6	-32	20	44	3.03	
Other Significant voxels							
Anterior cingulate cortex		32	12	30	24	2.97	
Posterior cingulate cortex		31	6	-42	34	2.33	
Anterior cingulate cortex, dorsal		24	2	8	32	2.64	
Cerebellum, anterior lobe, nodule		--	6	-60	-26	3.46	
Cerebellum, anterior lobe, nodule		--	2	-62	-20	3.07	
Temporal fusiform gyrus, L		20	-40	-24	-22	3.11	
Hippocampus, L		--	-32	-30	-12	3.53	

Note: maxima located in ventricles are not reported

Table 4.2. List of PPIs for ADs-Only, Right Anterior Insula Seed

"PPIs for rAIC seed during high-risk decisions-to-drink" ($2xAlc_{High}$) > ($Food_{High}$+$Item_{High}$)							
ADs-only (N=15)							
Region	voxels	BA	x	y	z	z-max	p
Cluster 5	517					-4.36	0.0092
Lateral occipital cortex, superior aspect, R		19	34	-82	36	-4.36	
Lateral occipital cortex, superior aspect, R		19	40	-74	24	-3.43	
Lateral occipital cortex, superior aspect, R		19	38	-70	24	-3.32	
Middle temporal gyrus, R		39	44	-74	32	-3.04	
Middle temporal gyrus, R		39	46	-70	22	-3.03	
Posterior thalamic radiation		--	36	-54	14	-2.86	
Cluster 4	509					-4.06	0.0101
Pyramis, posterior lobe		--	-6	-84	-26	-4.06	
Pyramis, anterior lobe		--	-2	-70	-28	-3.60	
Nodule, anterior lobe		--	4	-58	-28	-3.51	
Fastigium, anterior lobe		--	-8	-64	-20	-3.27	
Declive vermis, posterior lobe		--	0	-76	-18	-3.18	
Tuber of vermis, posterior lobe		--	4	-72	-28	-3.09	
Cluster 3	431					-3.45	0.0256
Precuneus		7	0	-66	54	-3.45	
Precuneus, L		7	-4	-56	42	-3.32	
Precuneus		7	0	-64	44	-3.17	
Precuneus, R		7	14	-50	38	-3.01	
Precuneus, R		7	6	-62	54	-2.97	
Precuneus, L		7	-2	-58	66	-2.83	
Cluster 2	415					-3.79	0.0312
Posterior cingulate, R		30	8	-52	14	-2.75	
Cluster 1	400					-3.97	0.0376
Superior frontal gyrus, R		8	24	40	42	-3.97	
Superior frontal gyrus, R		8	26	42	38	-3.53	
Middle frontal gyrus, R		8	26	26	40	-3.46	
Middle frontal gyrus, R		9	32	38	34	-3.35	
Superior frontal gyrus, R		9	12	58	34	-3.08	
Superior frontal gyrus, R		9	18	48	34	-3.08	

Note: maxima located in ventricles are not reported

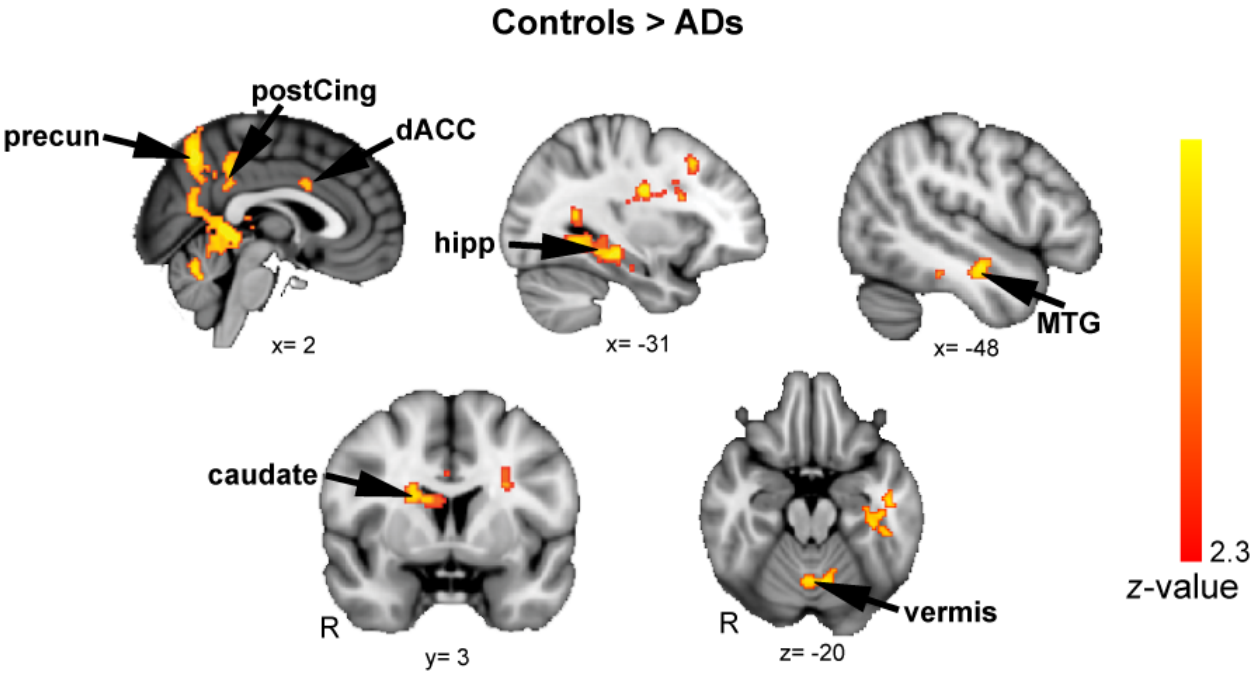

Figure 4.1. Psychophysiological interactions of the right anterior insula in controls greater than alcohol dependent women. Abbreviations: precun, precuneus; postCing, posterior cingulate cortex; dACC, dorsal anterior cingulate cortex; hipp, hippocampus; MTG, middle temporal gyrus. For region of activity detail, see Table 4.1.

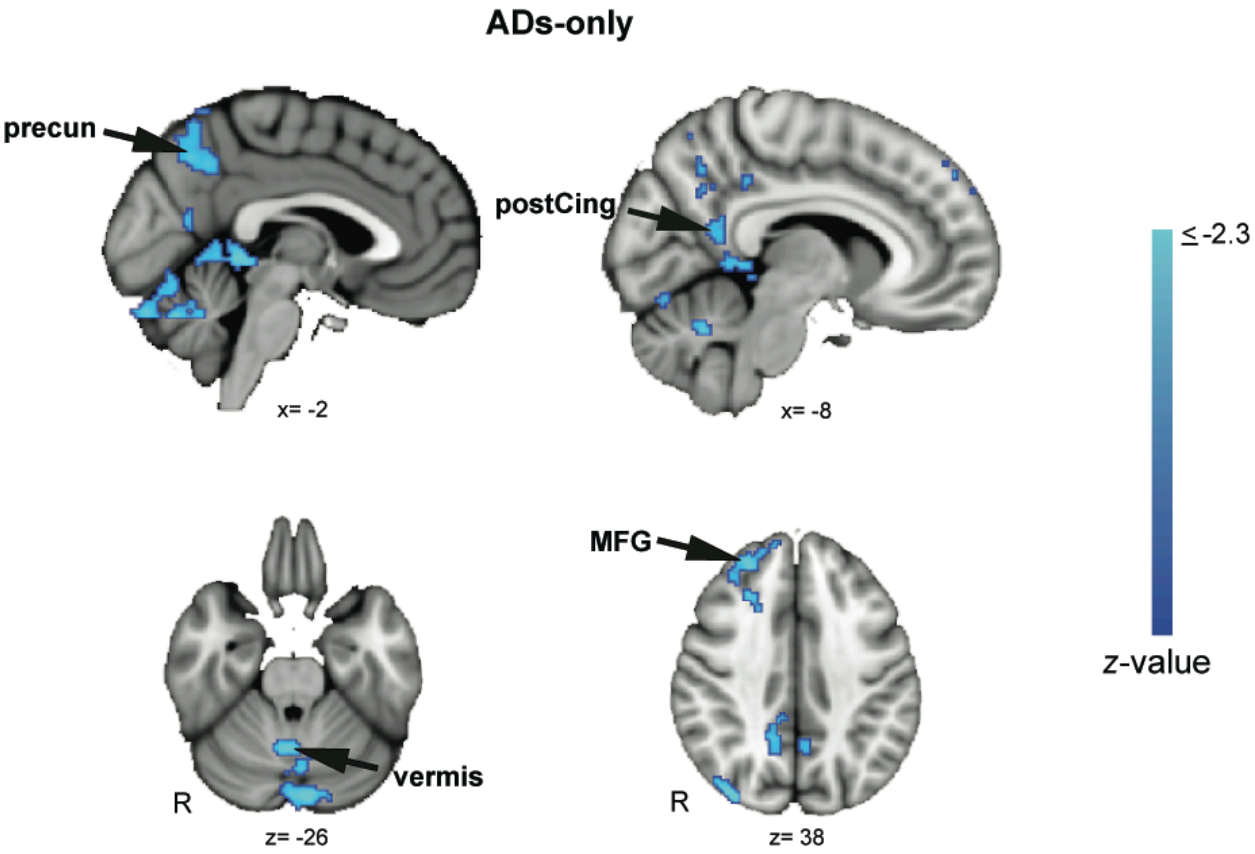

Figure 4.2. Psychophysiological interactions of the right anterior insula in alcohol dependent women. This map shows regions that had significantly less functional connectivity with the right anterior insula during the high-risk alcohol condition compared to the high-risk food and high-risk item decisions in alcohol dependent women. Abbreviations: precun, precuneus; postCing, posterior cingulate cortex; MFG, middle frontal gyrus. For region of activity details, see Table 4.2.

CHAPTER 5

GENERAL DISCUSSION

5.1. Ecological Decisions

In this dissertation, I used a novel ecological decisions task to better understand the neural circuitry involved in high-risk appetitive decisions in alcohol dependent women (ADs). This approach to decision-making and investigating alcohol dependence was very successful, leading to many new insights and future directions. By taking an ecological approach, decision-making inherently happens from a brain-body-environment perspective, meaning that the participant imagines himself or herself in a particular environment (e.g. high-risk drinking scenario), which evokes particular goals unique to each individual. This element is non-existent in most cognitive tasks, but it is critical when investigating how decision-making happens in the real world.

5.1.1. Low-Risk Appetitive Decisions

Interestingly, there were no behavioral or neural differences between ADs and control women for low-risk decisions across all stimulus types (alcohol, faces, food, items). The fact that there were no differences in the low-risk context demonstrates that risk or uncertainty is critical for evoking group differences. Additionally, these results show that both groups use the same neural circuitry to the same degree within the low-risk context. For both low-risk alcohol and sexual decisions, regions of the default-mode network (DMN) were activated along with reward regions such as the nucleus accumbens, other limbic regions, and visual areas. A direct comparison between alcohol and sexual decisions was not examined here.

5.1.2. High-Risk Appetitive Decisions

The high-risk context produced drastic group differences for alcohol decisions. Control women continued to activate regions of the DMN, while also deactivating regions associated with approach behavior, such as pre-supplementary motor area, anterior insula, and anterior cingulate cortex. However, alcohol dependent women activated regions associated with the default-mode, central executive, and salience networks during high-risk alcohol decisions, indicating that there may be a problem with switching between different networks (Menon & Uddin, 2010). Alcohol dependent women did not deactivate any regions while making high-risk alcohol decisions.

For sexual decisions, group differences were observed only when testing for main effects of stimulus, i.e. group x stimulus interaction. There was no group x stimulus x risk interaction for sexual decisions. One reason that the 3-way interaction was not observed could be that participants considered all sexual decisions as high-risk. Supporting this idea is that face stimuli were endorsed significantly less than all other stimulus categories for both groups. Future research investigating risky sexual decisions should modify the task such that the difference between high- and low- risk decisions is significant.

While data for alcohol and sexual decisions was not statistically tested against each other, an interesting pattern emerged when observing the results from the alcohol and sexual decisions analyses. High-risk alcohol decisions in alcohol dependent women produced no significant voxels of deactivation, and a very similar pattern was also present in ADs for sexual decisions. For sexual decisions, control women

deactivated many different regions involved in sexual arousal, whereas ADs did not deactivate any of these regions. Based on this observation, it may be that an inability to deactivate brain regions during ecological, risky decisions is a hallmark of alcohol dependence. Future research should investigate why ADs do not show the same pattern of deactivation as controls during these tasks.

5.2. Single vs. Dual Systems

The majority of research investigating addictive behavior frames addiction as a dual systems problem where reward and central executive systems are said to compete for behavior. This idea is appealing, however, it is unlikely that a biological system is build with two systems that fight for behavior (Keren, 2013; Keren & Schul, 2009). My research used that framework to guide specific hypotheses, however, the results are not in agreement with a dual systems solution. Instead, the results are in agreement with behavior being the product of a single system. For example, AD women continued to endorse high-risk alcohol even though they significantly activated regions of the central executive system. One could argue that this activation represents failed attempts of inhibition, however, it is equally valid that activation here represents planning for how to avoid the potential negative consequences if they should encounter them. The latter explanation is more likely given that there is no *real* reason to inhibit behavior, i.e. the possible negative consequences are uncertain and unknown.

5.3. Null Effect of Phase

While it was hypothesized phase would interact with appetitive decisions, especially sexual decisions, I did not find any effect of phase for any contrast tested across all three experiments. An effect of phase could not have been observed for several reasons. I most likely did not observe an effect of phase in the current studies because hormonal assays were not evaluated to assure that each participant's hormone levels are congruent with the follicular and luteal phases. It may be that some participants would be excluded from an analysis specifically investigating effects of menstrual phase after analyzing the hormone assays. Another reason that phase effects were not observed could be that phase interacts with very specific aspects of a decision. The current protocol was not designed to examine brain activity associated with different aspects of the decision phase, i.e. stimulus evaluation and choice. It could be that phase interacts more with the initial stimulus evaluation and that effects of phase wash out across the entire decision time course. Future research should test for phase interactions within specific stages of the decision process.

5.4. Risk Factors

Alcohol dependence is genetically heritable by 50 to 60 percent (Heath et al., 1997; Knopik et al., 2004). The high heritability of alcohol dependence brings into question how much of the observed differences in neural activation between groups was preexisting and how much was due to alcohol creating changes in gray and white matter. One way to answer this question is to include family history as a factor where

participants are categorized as "family history positive" (FHP) or "family history negative" (FHN). To be FHP, a first-degree relative has to have met criteria for alcohol dependence. Studies investigating differences in neural activation to appetitive stimuli between FHP and FHN participants have found differences in nucleus accumbens activation, where FHP participants have significant less activation that FHN participants (Andrews et al., 2011). Decreased activity in the dopaminergic system is observed with alcohol dependence and occurs by alcohol indirectly down-regulating the expression of dopamine receptors. Those with lower levels of dopamine to begin with may be more vulnerable to alcohol's effects and have a high risk of developing alcohol dependence. My results show that differences in neural activation between AD and control women are very specific to alcohol cues. If the dopaminergic system was compromised before heavy drinking occurred, I would expect to see differences in activation of the dopaminergic system between ADs and controls for all appetitive stimulus types. However, this is not what I observed. Future research should investigate the effect of family history of alcohol on ecological decisions-to-drink to disentangle the contribution of family history and experience with drinking alcohol.

5.5. General Limitations

This was the first protocol designed to test for neural mechanism related to ecological, appetitive decisions. As such, the protocol was designed to evoke large behavioral and neural differences between low- and high-risk contexts. While our protocol was successful in producing these differences, the protocol did not allow for

risk information to be crossed such that low- and high- risk information was presented together to create an even greater state of conflict when making decisions. Future research should aim to create risky situations that produce the greatest amount of conflict or uncertainty in participants to investigate the neural mechanisms associated across all levels of risk.

Additionally, I was unable to untangle the effects of stimulus and risk on decision-making because both the picture cue and risk information were always presented together. Future research should be aimed at creating a protocol where the reward and risk information are presented separately before making a decision to discover how neural mechanisms related to reward and risk interact to produce the behavioral choice.

Lastly, while hormonal assays were collected from each participant, this data was not used in the current studies to investigate the effects of phase. To fully understand the effects of menstrual phase, data from the hormonal assays need to be included in future analyses with this data.

5.6. Future Directions

For future research, I plan to use the results of this research investigate potential interventions for high-risk taking behavior. The current data demonstrate that ADs may have a problem with switching between different networks of the brain and this problem may be related to ADs inability to deactivate brain regions during ecological, high-risk decisions. Within- and between-network coherence are important measures

for examining network dynamics, including the level of anti-correlation between networks. There have been several papers published demonstrating how meditation and certain medications can alter neural network coherence and therefore, the level of correlation between networks. Specifically, Schmaal and colleagues (2013) have shown that modafinil alters the within- and between-network coherence of ADs. However, the relationship between network changes caused by modafinil and changes in risk-taking behavior is unknown. Bridging the gap between research like that of Schmaal and colleagues (2013) and behavior is the next step in building interventions to improve public health. My ultimate goal is to test how interventions that change network dynamics can reduce high-risk behavior in at-risk populations.

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APPENDIX A: PERMISSION FROM PUBLISHER

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Education

Indiana University – Bloomington, Indiana August 2008– June 2014 GPA: 3.91

Ph.D. in Psychology, individualized minor in Cognitive Psychology,
Thesis advisor: Dr. Thomas W. James

Indiana University of Pennsylvania – Indiana, Pennsylvania August 2002 – May 2008 GPA: 3.53

B.A, Psychology, Honors Program,
B.S., Natural Science,
Minor in Statistics,
Minor in Biology

Research Experience

Perception and Neuroimaging Lab (PAN Lab) August 2008 – present

- Brain imaging, using functional magnetic resonance imaging, of appetitive decision-making in alcohol dependent women
- Brain imaging, using functional magnetic resonance imaging, of how risk-taking behavior influences adolescent brain development
- Brain imaging, using functional magnetic resonance imaging, of how face features are integrated across multiple levels of signal to noise ratio

Teaching at Indiana University

- Instructor for the undergraduate lab for Research Methods in Psychology (PY 211) January 2012 – May 2012
- Instructor for the undergraduate lab for Research Methods in Psychology (PY 211) May 2013 – July 2013
- Invited Guest lectures for Introduction to Psychology (PY101), "Sleep and Dreaming", Fall 2009
- Invited Guest lectures for the undergraduate lab in Neuroimaging Methods and Statistics (PY 433), Spring 2011
- Invited Guest lecture for Cognitive Neuroscience (PY 349), "Risky Decision-Making", 11/14/2013

Skills

- Magnetic resonance imaging (MRI) operator – received training at the Imaging Research Facility at Indiana University, August 2012 – May 2013
- Brainvoyager
- FSL
- Functional Connectivity using Psychophysiological Interactions (PPIs)

Lindsay R. Arcurio

- Matlab
- SPSS

Volunteer/Mentorship

- Mentored "Science, Technology, Engineering, and Math" (STEM) student – introduced student to behavioral research in risky decision-making, taught how to analyze, interpret, and present statistical data (Summer 2013)
- Mentored "Summer Experiences for the Economically Disadvantaged" (SEED) student – taught how to run an experiment using fMRI, taught how to analyze fMRI data (Summer 2013)
- Group leader for the Brownie Math and Science Day (November, 2011 and 2012)
- Volunteer for the Brownie Math and Science Day (November, 2010)

Awards

Provost Travel Award for Women in Science, $700, used for conference travel, received January 2013

Research Spotlight, my research was nominated and showcased on the IU psychology website, January 2013

Publications

(In prep). **Arcurio, L.R.**, Finn, P.R., James, T.W. Functional connectivity during high-risk decisions-to-drink in alcohol dependent women.

(In prep). **Arcurio, L.R**., Fridberg, D.J., Heiman, J.R., Finn, P.R., James, T.W. Sexual decision-making in alcohol dependent women.

(Under review). Hensel, D.J., **Arcurio, L.R**., James, T.W., J.D., Fortenberry. Feasibility of fMRI to examine adolescent risk-taking.

Arcurio, L.R., Finn, P.R. & James, T.W. Neural mechanisms of high-risk decisions-to-drink in alcohol-dependent women. *Addiction Biology*, 2013.

James, T.W**.**, **Arcurio, L.R**., & Gold, J.M. (2013). Inversion effects in face-selective cortex with combinations of face parts. *Journal of Cognitive Neuroscience*.

Arcurio, L.R., Gold, J.M., & James, T.W. (2012). The response of face-selective cortex with face parts and part combinations. *Neuropsychologia, 50*, 2454-2459.

Conference Papers/Presentations

Arcurio, L. R. "Neural Mechanisms of High-Risk Decisions-to-Drink in Alcohol Dependent Women", **invited talk** to be given at the Indiana University, April 11, 2014, Bloomington, Indiana.

Lindsay R. Arcurio

Arcurio, L. R. "Neural Mechanisms of High-Risk Decisions-to-Drink in Alcohol Dependent Women", **invited talk** at the National Institute on Alcohol Abuse and Alcoholism, January 17, 2014, Bethesda, Maryland.

Arcurio, L.R., Finn, P.R., James, T.W. "Neural Mechanisms of High-Risk Decisions-to-Drink in Alcohol Dependent Women", poster presented at Indiana Neuroimaging Symposium, October 25, 2013, Bloomington, Indiana. [**Featured poster** – Chosen by the Indiana Neuroimaging Symposium Executive Committee]

Arcurio, L. R. "Neural Mechanisms of High-Risk Decisions-to-Drink in Alcohol Dependent Women", talk given at the Indiana University Clinical Colloquium, September 06, 2013, Bloomington, Indiana.

Kruse, S., **Arcurio, L.R.**, James, T.W. "The Influences of Immediate Reward and Negative Punishment on Decision Making in Alcohol Dependent Women", poster presented at the Groups Scholars Summer Research Experience Program Poster Symposium, July, 2013, Bloomington, Indiana.

Selzer, A., Bromfield, D.W., **Arcurio, L.A.**, James, T.W. "Activation of the Fusiform Face Area (FFA) Through Object Recognition", poster presented at the Groups Scholars Summer Research Experience Program Poster Symposium, July, 2013, Bloomington, Indiana.

Arcurio, L.R., Finn, P.R., James, T.W. "Neural Mechanisms of High-Risk Decisions-to-Drink in Alcohol Dependent Women", poster presented at Research Society on Alcoholism, June, 2013, Orlando, Florida.

Arcurio, L. R. "Neural Mechanisms of High-Risk Decisions-to-Drink in Alcohol Dependent Women", talk given at the Indiana University Cognitive Neuroscience Seminar, March 18, 2013, Bloomington, Indiana.

Hensel, D.J., **Arcurio, L.R.**, James, T.W. "Feasibility of fMRI to Examine Adolescent Risk Taking", oral presentation given at the Annual Meeting of the Society for Adolescent Health and Medicine, March, 2013, Atlanta, Georgia.

Dachille (Arcurio), L. R., Gold, J. M., James, T. W. "The Influence of Face Feature Combination on Fusiform Cortex Activity", poster presented at Vision Sciences Society. May 2010, Naples, Florida.

Dachille (Arcurio), L. R. "The Influence of Face Feature Configuration on Fusiform Cortex Activation", talk given at the Indiana University Neuroimaging Group (IUNG), December, 2009, Bloomington, Indiana.

Media Coverage

2/2014 Press release *IUB Newsroom*, "Study uncovers surprising differences in brain activity of alcohol-dependent women"

2/2014 *The Indiana Daily Student*, "Study: alcohol-dependent women misinterpret risk"

2/2014 *The Herald-Times*, "Study: Alcohol-addicted women more prone to risky behavior"

3/2014 *Elements Behavioral Health*, "Study shows differences in risk tolerance for alcohol-dependent women"