2017

Neural and cognitive biomarkers of binge and heavy drinking

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Dissertation

NEURAL AND COGNITIVE BIOMARKERS OF BINGE AND HEAVY DRINKING

by

ARKADIY LEONIDOVICH MAKSIMOVSKIY

B.A., Cornell University, 2007

Submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

2017

Approved by

First Reader

Jasmeet Pannu Hayes, Ph.D.
Assistant Professor of Psychiatry

Second Reader

Regina McGlinchey, Ph.D.
Associate Professor of Psychology
Harvard University

Third Reader

Marlene Oscar Berman, Ph.D.
Professor of Neurology, Psychiatry, and Anatomy & Neurobiology

"*Just imagine a sheet of paper. We all live inside that flat sheet of paper…We just deduce the nature of our world…by looking at things. And watch what happens. You see a dot appear out of nowhere…We bring in our best theoretical physicists; they don't know anything. And what does the dot do next? It turns into a circle. And the circle gets bigger to a maximum size and then it shrinks back down, goes back to a dot, and…then disappears. Then all the academics go back to the chalkboards and they try to figure it out. And all it is, is a sphere passing through the two dimensions of your universe."*

- Neil deGrasse Tyson (Tyson, 2016)

ACKNOWLEDGEMENTS

First and foremost, I would like to express my deepest gratitude to my advisor, Professor Regina McGlinchey. Dr. McGlinchey's everlasting patience, encouragement, support, and feedback have allowed me to transform my initial ideas into a final project. Despite a myriad number of research roles and responsibilities, Dr. McGlinchey has looked at every single one of my dissertation drafts and has always provided thorough and kind feedback, encouraging me to do more.

I would also like to thank Professors Milberg and McGlinchey for allowing me to use their laboratory's resources, providing the funding for my education and training purposes, and protecting my time for professional development.

In no particular order, I would like to thank the remainder of my dissertation committee: Professors Marlene Oscar Berman, David Salat, Jasmeet Hayes, and Danny Kaloupek. They have all been incredibly generous with their time in listening to my ideas, reading through countless drafts, and always offering constructive and helpful feedback.

Additionally, I would like to thank the Chair of my Dissertation committee, Professor Carole Palumbo. I am incredibly grateful for Dr. Palumbo's guidance and advice throughout this process; her door has always been open for impromptu meetings and discussions.

Furthermore, I would like to thank Professor Milberg for taking the time to discuss various aspects of my project and always offering helpful feedback for my ideas.

Whether I barged into his office or sent emails at odd hours of the night, Dr. Milberg has always taken the time to listen and point me in the right direction.

I would like to thank Professor Esterman for being so generous with his time and providing feedback on certain aspects of my dissertation. His expertise has been invaluable and I greatly appreciate his input.

I would like to express my gratitude to the entire TRACTS team for a myriad number of aspects pertaining to participant recruitment, data processing, collection, and verification. These data would not have been available without the entire laboratory's joint efforts and I am incredibly grateful for the opportunity to work with such a talented and energetic team.

I would also like to express my gratitude to Rebecca Dobrzynski for her help with proofreading and editing the dissertation.

NEURAL AND COGNITIVE BIOMARKERS OF BINGE AND HEAVY DRINKING

ARKADIY LEONIDOVICH MAKSIMOVSKIY

Boston University School of Medicine, 2017

Major Professor: Jasmeet Pannu Hayes, Ph.D., Assistant Professor of Psychiatry

ABSTRACT

Background: Theories suggest two motivations that drive people to consume alcohol at pathological levels: (1) seeking of short-term pleasurable effects and (2) alleviation of unpleasant states. The former is associated with Binge Drinking (BD; i.e. high intake during fewer occasions) and the latter with Heavy Drinking (HD; substantial intake during more occasions). Although direct comparisons have not been made, BD has been associated with impairments in top-down executive control (related to frontal-parietal regions) and HD has been linked to bottom-up changes in internal mentation (related to the default mode network anatomical structure and function). This dissertation compares the two drinking patterns with the goal of testing for differential neurocognitive and neuroanatomical characteristics that would be indicative of two disorder subtypes.

Methods: The sample consisted of adult participants with a history of adolescent onset: BD (N = 16), HD (N = 15), and Healthy Controls (HC; N = 21). All groups were equated on age, education, amount of lifetime alcohol consumed (BD and HD groups), as well as other factors. The study compared group performance on an affective go/no go task and group differences in brain volume and cortical thickness based on structural MRI.

Results: Behavioral results showed a higher number of errors for the HD group, in comparison to other groups. Volumetric results indicated a smaller bilateral ventral diencephalon in both BD and HD, in comparison to the HC, and smaller bilateral globus pallidus in BD only. Cortical thickness analyses revealed a thinner left superior parietal region (overlapping with the dorsal attention and fronto-parietal networks) in BD, whereas a left medial occipito-parietal region was thicker in HD (overlapping mainly with the visual network). **Conclusion**: These data, interpreted in the context of prior studies, suggest that BD findings might be indicative of an executive control dysregulation that could contribute to continued BD. HD findings might be indicative of tissue damage due to frequent drinking. Prior research has found the occipital region to have the highest concentration γ-Aminobutyric acid receptors that are affected by alcohol, which might explain the thicker occipital region findings in the HD group.

PREFACE

In the spirit of the sentiment expressed by Neil deGrasse Tyson, I am hoping for this dissertation to serve as a small stepping stone towards improving our measuring tools for a better scientific understanding of psychopathology. I believe that a great deal of scientific progress comes from the integration and reinterpretation of empirical knowledge with the goal of improving the accuracy and elegance of our best models.

This project is thus an attempt to integrate the published, as well as newly collected neurological, developmental, and cognitive data with the goal of enhancing our understanding of alcohol use disorders.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

3T ..... 3 Tesla

AGN ..... Affective Go/No-Go

ANOVA ..... Analysis of Variance

AUD ..... Alcohol Use Disorder

BD ..... Binge Drinking

BDs ..... Binge Drinkers

CAPS ..... Clinician Administered PTSD Scale

DASS ..... Depression Anxiety Stress Scales

DODS ..... Different Offset, Different Slope

DRRI ..... Deployment Risk and Resilience Inventory

DSM ..... Diagnostic and Statistical Manual of Mental Disorders

eTIV ..... Estimated Total Intracranial Volume

FDR ..... False Discovery Rate

fMRI ..... Functional Magnetic Resonance Imaging

FSL ..... Functional MRI of the Brain Software Library

FWHD ..... Full-Width/Half-Max

GABA ..... γ-Aminobutyric acid

HCs ..... Healthy Controls

HD ..... Heavy Drinking

HDs ..... Heavy Drinkers

HSD ..... Honest Significant Difference

ICD ..... International Classification for Diseases

IQ .....Intelligence Quotient

JMP ..... John's Macintosh Project

LDH ..... Lifetime Drinking History

MM .....Millimeters

MPRAGE .....Magnetic Pulse Rapid Gradient Echo

MRI.....Magnetic Resonance Imaging

MS..... Multiple Sclerosis

MS.....Milliseconds

mTBI.....Mild Traumatic Brain Injury

NOS .....Not Otherwise Specified

OEF..... Operation Enduring Freedom

OID .....Operation Iraqi Freedom

OND..... Operation New Dawn

PFC ..... Pre-Frontal Cortex

PTSD..... Post-Traumatic Stress Disorder

ROI.....Region of Interest

RR&D .....Rehabilitation Research and Development

rsMRI .....Resting State Magnetic Resonance Imaging

SAT..... Speed Accuracy Tradeoff

SCID-5 ..... Structured Clinical Interview for DSM-5

T1 ..... Spin-lattice Relaxation (T1) Weighted Image

TBI ..... Traumatic Brain Injury

TE..... Echo Time

TRACTS ..... Translational Research Center for TBI and Stress Disorders

VA ..... Department of Veterans Affairs

WTAR ..... Wechsler Test of Adult Reading

SPECIFIC AIMS

Aim 1: Examine differential inhibitory and attention processing capacity, using the Affective Go/No-Go and Simple Reaction Time tasks (used as a control measure), between Binge Drinkers, Heavy Drinkers, and Healthy Controls.

Hypothesis 1.1: Binge Drinkers will show a higher number of inhibitory errors (commission) in response to positive stimuli as compared to Healthy Controls, while Heavy Drinkers will show a higher number of inhibitory (commission) as well as attention (omission) errors on the Affective Go/No-Go task in response to all valence stimuli.

Hypothesis 1.2: There will be no significant group differences on the Simple Reaction Time Task (used as a control measure).

Aim 2: Examine whole-brain subcortical volumetric differences between Binge Drinkers, Heavy Drinkers, and Healthy Controls.

Hypothesis 2.1: Both pathological drinking groups (Binge and Heavy Drinkers) will show an altered volume within the ventral striatal structures, as compared to the Healthy Control group.

Aim 3: Examine whole-brain cortical thickness differences between Binge Drinkers, Heavy Drinkers, and Healthy Controls.

Hypothesis 3.1: Binge Drinkers will show significantly impacted dorsal attention network regions (within the top-down processing hubs: frontal and parietal regions), as compared to Heavy Drinkers and Healthy Controls.

Hypothesis 3.2: Heavy Drinkers will show significantly impacted default mode network regions (within the bottom-up processing hubs: posterior cingulate cortex and the precuneus regions), as compared to Binge Drinkers and Healthy Controls.

CHAPTER 1 – INTRODUCTION

Significance

Recent theories suggest that certain problem drinkers consume alcohol because of its pleasurable effects (positive reinforcement), while others drink in order to alleviate an unpleasant state (negative reinforcement) (Koob & Volkow, 2010; Volkow, Koob, & McLellan, 2016). The former is attributed to a binge drinking pattern, which involves consuming large amounts of alcohol over short periods of time (Koob & Le Moal, 2001). The latter is attributed to a heavy drinking pattern, which involves drinking pathological amounts of alcohol frequently (Koob, 2004). Although the two types of drinkers have not been directly compared, there are a number of neurological and cognitive findings that might differentiate them from one another. For example, in comparison to healthy controls, Binge Drinkers (BDs) seem to have impaired regulatory abilities with volitional control (Koob & Volkow, 2010). Specifically, they have been characterized by *reflection impulsivity*, which is the trait of making premature decisions at the prospect of a reward prior to considering all relevant information (Banca et al., 2015). Anatomically, BDs were found to have a smaller striatal as well as left frontal and parietal regional volume (in comparison to healthy controls), which correlate with reflection impulsivity (Banca et al., 2015). Heavy Drinkers (HDs), on the other hand, appear to have a neurocognitive disruption of automatic (unconscious) processing of information (Koob & Volkow, 2010). HDs are characterized by *compulsive* traits, which are repetitive thoughts or actions that occur in order to alleviate discomfort (Koob & Volkow, 2016). They were

shown to have reduced functional connectivity within regions of the default mode network (including the posterior cingulate cortex and the precuneus), in comparison to healthy controls (Shokri-Kojori, Tomasi, Wiers, Wang, & Volkow, 2016). The different characteristics of BDs and HDs seem to imply that the two drinking patterns might constitute distinct Alcohol Use Disorder (AUD) subtypes. However, empirical findings that directly compare BDs and HDs to one another are lacking. Additionally, despite numerous findings of impaired inhibitory abilities in AUD, it is unclear whether they occur in only one of the drinking patterns or in both. Exploring the differential correlates of BDs and HDs will enhance our understanding of AUD by (1) determining whether the two types of drinkers differ in their respective neurocognitive characteristics, and, if so, (2) identifying the cognitive and anatomical characteristics that are unique to each drinking subtype. This information will serve as a stepping-stone for future research and offer clinical implications for more targeted treatment of AUDs. This dissertation aims to accomplish these goals by directly comparing individuals that fall within each of the respective drinking patterns. In order to best isolate the correlates of drinking patterns, all subjects will have begun drinking during adolescence and be equated for their current age and total quantity of lifetime alcohol consumed, as well as other relevant characteristics. Results of this dissertation will serve as the first empirical investigation into whether BDs and HDs constitute two distinct AUD subtypes.

Scope of Alcohol Use Disorders in the US

According to the National Institute on Alcohol Abuse and Alcoholism, 16.3 million adults in the U.S. were diagnosed with an AUD in 2014, and approximately

679,000 adolescents under 18 had an AUD (N.I.A.A.A., 2016a). Of these, almost 25% of adults engaged in binge drinking (BD; characterized by consuming five or more drinks for men and four or more drinks for women, within the course of two hours (N.I.A.A.A., 2016b)) and 6.7 percent engaged in a heavy drinking (HD; characterized by binge drinking on five or more days per month (N.I.A.A.A., 2016b)) pattern of pathological alcohol consumption (Substance Abuse and Mental Health Services Administration, 2014). Almost 88,000 people die from alcohol-related causes per year, making it the fourth most preventable cause of death in the United States (Stahre, Roeber, Kanny, Brewer, & Zhang, 2014). AUDs are estimated to cost the U.S. $249 billion in an annual economic burden (Sacks, Gonzales, Bouchery, Tomedi, & Brewer, 2015). These data underscore the urgency and the importance of advancing AUD research aimed at enhancing understanding of these disorders and helping those who are effected.

Background

Alcohol is produced from the process of fermentation, which involves chemically altering an organic substance such as grain, honey, barley, or fruit (Foundation for a Drug-Free World, 2016). Largely because of the pleasurable sensation that alcohol consumption can produce to the human experience (see the **Acute Effects of Alcohol** section below), people have engaged in fermentation for thousands of years all over the world. Historically, perhaps the earliest signs of alcohol use dates back to the Stone Age; jugs discovered from the Neolithic period (circa 10,000 B.C.) are indicative of alcohol consumption. Following that, numerous references to alcoholic beverages were found from early Egyptian Civilization, China (as early as 7,000 B.C.), India (between 3,000

and 2,000 B.C.), Babylon, and Ancient Greece (Foundation for a Drug-Free World, 2016). Despite its pleasurable effects, there is evidence to suggest that the harmful effects of alcohol abuse were also recognized. For example, ancient Chinese texts contain numerous warnings pertaining to the consequences of pathological drinking (Patrick, 1952; Williams, 1913). Similarly, Egyptian carvings depict women suffering from the effects of alcohol, men standing on their heads from drunkenness, and people being carried due to the effects of excessive drinking (Williams, 1913).

Despite anecdotal knowledge about the ailments that can be associated with alcohol use, only relatively recent advancements have allowed for a quantifiable *scientific* understanding of its potential harmful effects. Perhaps one of the major breakthroughs in treating AUDs was the recognition that alcoholism is not one disease but rather consists of multiple alcohol sub-type disorders that are classified under one umbrella term (McGovern & White, 2002). An early scientific theory of alcoholism introduced in the 1940s argued that alcoholism consists of subtype drinking disorders with varying degrees of impairment (Jellinek, 1960); these were proposed to consist of social, psychological, and occupational issues (Jellinek, 1960). Roughly a decade later, the first edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) classified alcoholism as a subset of psychological diagnoses including neurosis and personality and homosexuality disorders (American Psychiatric Association, 1952); the second edition expanded on the same criteria (American Psychiatric Association, 1968). Following numerous research findings, the third DSM edition reclassified alcoholism as an independent disorder which, for the first time, was classified under the *substance use disorders* category (American

Psychiatric Association, 1980). This change reflected the new recognition that alcoholism is a distinct pathology with unique symptoms. It was also indicative of the collected body of research that showed that alcoholism warranted its own sub-criteria: abuse and dependence (American Psychiatric Association, 1980). The three DSM updates that followed continued to modify the abuse and dependence categories to better reflect ongoing clinical research (see (American Psychiatric Association, 1987, 1994, 2000)). In the first significant change in the conceptualization of pathological alcohol use, the DSM-5 replaced the term *alcoholism* with *alcohol use disorders* (American Psychiatric Association, 2003). Additional changes involved removing the dichotomous *abuse* and *dependence* categories and instead applied three levels of AUD severity: mild, moderate, and severe (American Psychiatric Association, 2003). This change was based on the most recent scientific advances indicating that AUDs consist of multiple sub-types of severity, which are best captured by non-dichotomous criteria.

In parallel to the American diagnostic criteria (as documented in the DSM versions), the International Classification for Diseases (ICD) has undergone a similar series of changes from the 1960s up until through the present day. The early ICD version in the late 1960s classified alcohol drinking together with personality disorders (W.H.O., 1967). An update in the late 1970s separated alcoholism into two categories: abuse and dependence (W.H.O., 1977, 1978), with the 10th version of the ICD being most similar to DSM-IV criteria (W.H.O., 1992). The 11th ICD revision draft, which is slated to be released in 2018, contains sub-categories of "harmful patterns of alcohol use" as well as "alcohol dependence" (W.H.O., 2016).

Classification of AUDs into recognizable sub-types and identifiable patterns that are quantifiably distinguishable from one another is a major step towards developing more targeted treatment methods, more accurate prognostication, and more thorough understanding of the disorder. This dissertation aims to contribute to these advancements by examining two distinct AUD subtypes with differential biomarkers, based on quantifiably unique and commonly occurring drinking patterns.

The sections below contain brief summaries of research that is related to AUDs and addiction. While each of the reviewed fields is large and complex, these sections are meant merely to serve as brief introductions to each of the areas of research, as well as to highlight their respective relevance to the current project.

Acute Effects of Alcohol

Immediate effects of alcohol typically include a pleasurable sensation due to a combined impact of positive and negative affective factors (Koob, 2003a). Neurochemically, alcohol causes a short-term increase in dopamine (DA), opioid, and γ-aminobutyric acid (GABA) neurotransmitters, which result in positive affect (Barbaccia et al., 1999; Carta, Mameli, & Valenzuela, 2004; Yoshimoto, McBride, Lumeng, & Li, 1992). Additionally, alcohol decreases the Corticotropin-releasing hormone (CRF), which can result in decreased negative affect (for instance, associated with stress) (Ketchesin, Stinnett, & Seasholtz, 2016; Zhou, Colombo, Gessa, & Kreek, 2013). In healthy individuals, the levels of these neurotransmitters return to a normal baseline state after alcohol consumption, following a brief rebound period (see decay time description

(Kumar et al., 2009)). Brain regions that are known to send pleasurable signals include the nucleus accumbens (NAcc), basal ganglia, and parts of the limbic system (Makris et al., 2008). The orbitofrontal cortex and the NAcc have been shown to be selectively involved in opioid release during alcohol consumption (Mitchell et al., 2012). Additionally, physiologically depressant effects have been observed in the form of slowed breathing and decreased heart-rate (Porges & Byrne, 1992). During a state of increased GABA levels in the brain, frontal lobes function with a decreased ability to inhibit inappropriate information and a diminished ability to make advantageous decisions (Field, Wiers, Christiansen, Fillmore, & Verster, 2010). At early stages of intoxication, individuals might feel more "at-ease," relaxed, and disinhibited (Dubowski, 1957). Further, progressively acute stages of intoxication increase the levels of these states, as alcohol depresses the central nervous system even more (Dubowski, 1957). If levels of intoxication exceed the liver's ethanol processing capacity, the nervous system depresses the cardiac and respiratory function, which can be fatal (Dubowski, 1957). Following non-lethal levels of intoxication, the organism rebounds via decreased levels (lower than pre-intoxication levels) of GABA, CRF, along with various physiological factors that often lead to a "hangover" cluster of symptoms including nausea, headaches, and fatigue (Swift & Davidson, 1998). In healthy individuals, these symptoms are short-lasting as individuals return to a pre-intoxication state of functioning within several hours (Swift & Davidson, 1998).

Long Term Effects of Alcohol

When examining the long-term effects of pathological alcohol consumption, it is important to make the distinction between uncomplicated and complicated problem drinkers (Zahr, Kaufman, & Harper, 2011). The former term refers to purely alcohol-related pathology, while the latter term refers to alcohol with comorbid conditions common in AUD that are associated with their own neurotoxic effects (Svanberg, Withall, Draper, & Bowden, 2014). At the most extreme end of the complicated AUD spectrum is the well-studied condition of Wernicke-Korsakoff's syndrome (Victor, Adams, & Collins, 1971). This syndrome develops following an acute episode of Wernicke's encephalopathy resulting from a thiamine deficiency in heavy chronic drinkers. It is characterized by a severe memory disorder secondary to damage in the diencephalic regions of the brain (McGlinchey‐Berroth et al., 1995). Recent policy guidelines for adding thiamine to alcoholic beverages, as well as increased availability of vitamin B-1 (containing thiamine) in hospital emergency rooms have resulted in a steady drop of new Korsakoff's Syndrome cases (Klooster et al., 2013). Other complicated AUD cases often include co-occurring SCID Axis I and II diagnoses, such as depression and bipolar disorders, as well as various health complications, such as alcohol-induced hypertension (see (Compton, Conway, Stinson, Colliver, & Grant, 2005; Grant & Harford, 1995; Klatsky, Friedman, Siegelaub, & Gérard, 1977; Mellos, 2009; Pirkola et al., 2005) for examples).

Most consistent findings pertaining to brain changes related to uncomplicated AUDs have been reported from studying participants with decades of heavy and chronic

alcohol consumption. Although definitions vary between studies, the uncomplicated chronic AUD population generally consumes about 35 drinks/week for men and 28 drinks/week for women (Oslin, Atkinson, Smith, & Hendrie, 1998). Brain changes have been found to be heterogeneous and lay on a continuum of severity (Lisdahl, Thayer, Squeglia, McQueeny, & Tapert, 2013; Savage, 2014). The amount of damage seems to depend on factors such as the age of onset of drinking, years of drinking, age at the time of study assessment, and the amount of lifetime alcohol consumed (Savage, 2014).

Neuropathological studies provided some of the earliest evidence of brain changes associated with alcohol use. For example, some of the earliest such evidence comes from in-vitro post-mortem examinations. For example, one study found a total reduction in the number of neurons within the frontal cortex in cases with alcoholic history, as compared to healthy controls (Harper, Kril, & Daly, 1987). This study used the motor cortex as a control brain region to indicate a selective frontal neural loss (Harper et al., 1987). Follow-up pathology studies have shown that neural loss occurs within the soma of larger (pyramidal) neurons, and is affected within the frontal regions as well as the cerebellum (Harper, 1998; Harper & Kril, 1989).

In vitro, imaging studies have shown more general global cerebral atrophy (Cala, Jones, Mastaglia, & Wiley, 1978). Computerized Tomography (CT) scan studies have documented global shrinkage of the entire cortex (Carlen, Wortzman, Holgate, Wilkinson, & Rankin, 1978; Ron, 1983). More recent Magnetic Resonance Imaging (MRI) studies have confirmed these findings, indicating a smaller grey and white matter

volume in alcoholics, as compared to healthy controls (Fortier et al., 2011; Savage, 2014). Additional common alcohol-related in-vivo neuroanatomical findings include ventricular enlargement (Savage, 2014; E. V. Sullivan & Pfefferbaum, 2009) and cerebellar volumetric reduction (Harper, 1998; Lishman, 1990; Pfefferbaum et al., 1992).

While in-vivo and in-vitro studies seem to converge on the directionality of alcohol impact (as indicated by volumetric reduction), there are some discrepancies when it comes to alcohol's effect on specific structures. Among the subcortical grey matter structures, specific findings include volumetric reductions within the thalamus and hypothalamus (Beaunieux, Eustache, & Pitel, 2014), cingulate cortex (Savage, 2014), and insula (Savage, 2014). Finally, diencephalic shrinkage has also been reported (Antony Harding, Halliday, Caine, & Kril, 2000), which was accompanied by functional loss only in Wernicke's patients (Savage, 2014). While in-vivo MRI studies having found that the hippocampus is reduced (Pitel et al., 2009; E. V. Sullivan & Marsh, 2003), post-mortem pathological examinations have not confirmed hippocampal reduction (AJ Harding, Wong, Svoboda, Kril, & Halliday, 1997). Although definitive reasons for this inconsistency are unknown, it is suggested that it might be due to the impact of white matter loss on grey matter hippocampal structures, which could be biasing the structural MRI results (Savage, 2014). Additionally, pathology studies have the advantage of examining types of neurons, at a cellular level that is not yet possible with neuroimaging. Findings pertaining to frontal lobe alcohol damage do seem to converge between study methodology, as they all point to a specific frontal lobe vulnerability to alcohol

neuropathology (see (Pfefferbaum, Lim, Desmond, & Sullivan, 1996) and (Harper & Matsumoto, 2005)).

In addition to anatomical studies, a great deal of research has examined the impact of long-term alcohol abuse on neuropsychological function. Similar to anatomical results, alcohol seems to impact a wide array of neuropsychological domains. While this is a broad and complex field of research, a recent review has identified the following components to be affected: psychomotor abilities, executive function, memory function, emotional processing and psychosocial abilities, and visuospatial skills (Fulton T Crews et al., 2005; Oscar Berman et al., 2014; E. Sullivan, Rosenbloom, & Pfefferbaum, 2000; E. V. Sullivan, Fama, Rosenbloom, & Pfefferbaum, 2002). The functions vary widely in their restorative capacity (Oscar Berman et al., 2014) and in cases of abstinence, and they are associated with respective neurological circuit impairment (Oscar Berman, Kirkley, Gansler, & Couture, 2004).

Risk Factors

Inherited Risk Factors

Studies have identified a number of genetic traits that are associated with various aspects of AUDs (Hendershot, Wardell, McPhee, & Ramchandani, 2016; Koob, 2003a; Tawa, Hall, & Lohoff, 2016; Wall, Luczak, & Hiller-Sturmhöfel, 2016). One such trait is the individual acute response to alcohol intake, which has been shown to be partially genetically mediated (Hendershot et al., 2016). Specifically, individuals who inherit the

combined traits of heightened hedonic response and lower sedation from alcohol intake appear to be at an elevated risk for developing an AUD (A. C. King, De Wit, McNamara, & Cao, 2011; A. C. King, McNamara, Hasin, & Cao, 2014; Schuckit, 1994; Schuckit & Smith, 2000). Furthermore, several genetic factors relating to the metabolization of alcohol have been identified; these are important vulnerability markers because individuals who take longer to reach intoxication might be at a higher risk for consuming larger amounts of alcohol in a given period of time. Specific alleles that were linked to ethanol metabolizing enzymes include the ADH1B*, ADH1C, and ALDH2*2 (Tawa et al., 2016). Additionally, the ADH1B* and ALDH2* polymorphisms were found to be associated with slower intoxication (Koob, 2003a).

Inherited risk factors pertaining to the hedonic experience of alcohol use, craving aspects, stress processing, and negative affect during withdrawal have been identified as well. The C-AMP dependent protein (Koob, 2003a) has been linked to an increased hedonic experience from alcohol consumption. This is an important risk factor, as heightened pleasurable experience that results from alcohol consumption might make alcohol use more appealing and consequently contribute to the development of an AUD. When it comes to craving, dopaminergically mediated mechanisms are some of the most relevant, as DA has been shown to be involved in motivation and desire (Berridge & Robinson, 1998). In this line of research, DA receptor function has been shown to be associated with two inherited alleles: TaqI and RFLP (Grandy et al., 1989), indicating that craving aspects of AUDs may be at least partially innate (Noble et al., 1994).

The ability to deal with stress is another important risk factor for AUD development (Marlatt, 1976; Silberman et al., 2009). Given that acute effects of alcohol involve increased GABA levels (Santhakumar, Wallner, & Otis, 2007), and that GABA has a sedating effect by decreasing anxiety (Cryan & Kaupmann, 2005), individuals who have difficulty managing stress have been shown to be at an increased risk for self-medication via alcohol (Brady & Sonne, 1999; Crum, Muntaner, Eaton, & Anthony, 1995; Higley, Hasert, Suomi, & Linnoila, 1991). Additionally, the speed and efficiency of GABA synthesis is an important factor of self-medicating (Farooqi & O'Rahilly, 2007); (Sałat et al., 2012), and a major component of innate risk factors (Gorwood, Schumann, Treutlein, & Adès, 2006; Tabakoff et al., 2009). In this vein of research, both GABA synthesis (found to be mediated by the aldehyde dehydrogenase 1a1 (*ALDH1a1* polymorphism)) (Marchitti, Brocker, Stagos, & Vasiliou, 2008) and stress processing have been linked to hereditary factors (Higley et al., 1991). Specifically, engaging in rapid alcohol consumption via Binge Drinking (BD) was shown to decrease stress by means of GABA synthesis (Koob, 2003a). Heavy alcohol consumption, on the other hand, was also shown to decrease stress but was linked to a different polymorphism: the rs1876831, C allele (Koob, 2003a). Finally, experiencing heightened negative affect during withdrawal stages can be a risk factor for further drinking and relapses. The CRF_1 receptor gene (*Corticotropin releasing factor hormone receptor 1*) polymorphism was found to be associated with negative affect during hangover/withdrawal periods within adolescent BD (Koob, 2003a).

Non-Inherited Risk Factors

Environmental factors can either serve as crucial trigger points that exploit the inherited vulnerability or increase resilience towards developing an AUD. The first environmental influence in human development occurs within the fetal environment. It was shown that alcohol consumption during pregnancy has an impact on prenatal development (Rosett et al., 1983) that can lead to damaged brain tissue before the offspring is even born (K. L. Jones, 2011). At the most severe end of prenatal alcohol exposure is a group of conditions that make up the Fetal Alcohol Spectrum Disorders that can result when a mother consumes large amounts of alcohol during pregnancy (Sokol, Delaney-Black, & Nordstrom, 2003). The conditions include abnormal facial characteristics, short height, low body weight, small head, and cognitive and behavioral problems. These types of damage have been attributed to the effects of alcohol since they were evident in infants whose mothers drank during pregnancy, in contrast with those who did not (K. L. Jones, 2011). Additionally, mothers who stopped drinking during the second trimester had children with lesser damage, in contrast to those who continued to drink during pregnancy. In turn, these changes are believed to add to vulnerability and contribute to a greater likelihood of developing an AUD during adolescence and throughout adulthood (Streissguth et al., 2004).

During post-fetal development, a nourishing and loving relationship between a child and her parents has been shown to be associated with resilience towards stress

(Masten, Best, & Garmezy, 1990; Rutter, 1987). Conversely, unhealthy attachment with parents characterized by a neglectful and/or abusive upbringing has been predictive of substance and alcohol abuse in adulthood (Kumpfer & Bluth, 2004). It is possible that the effects of neglectful upbringing work synergistically with inherited genetic risks (Tsuang, Bar, Stone, & Faraone, 2004), increasing even more the likelihood of developing an AUD.

Another environmental factor that has been significantly associated with alcohol and substance abuse is trauma (Clark, Lesnick, & Hegedus, 1997; Skinner, Holt, Schuller, Roy, & Israel, 1984; Stewart, 1996). Women who have experienced childhood sexual trauma, for instance, are more likely to self-medicate with alcohol than their healthy counterparts (Wilsnack, Vogeltanz, Klassen, & Harris, 1997). Veterans who have developed a Posttraumatic Stress Disorder (PTSD) or an acute stress disorder due to a history of traumatic event(s), often self-medicate with alcohol (Khantzian, 1997; McGlinchey, Milberg, Fonda, & Fortier, 2017; McGlinchey, Milberg, Fonda, & Fortier, In press). As mentioned earlier, alcohol's sedating impact via GABAnergic transmitters, are an appealing short term "solution" for reducing the distressing symptomatology of traumatic stress.

A major factor relating to AUDs, particularly for the adolescent population, is the social environment (Beattie et al., 1993). Similarly to parenting styles, the social milieu can be either a protective factor linked to resilience or a risk factor linked to vulnerability (Enoch, 2006). In either scenario, close peers tend to provide social rewards and pressure

towards socially acceptable activities, as well as threat of ostracism as a deterrent from unaccepted acts (Werner, 2000). Indeed, groups that favor BD (such as fraternities) encourage and pressure their members to engage in those acts (Borsari & Carey, 1999). Such social environments have been shown to be one of the major risk factors for adolescent BD (Larimer et al., 2001; McCabe, 2002). On the contrary, groups that value non-drinking activities (such as prayer groups) would serve as deterrents from pathological alcohol consumption. Similarly to other environmental factors, the co-occurrence of a risky social environment with other existing risk factors (inherited or environmental) raises the chances of developing an AUD (Repetti, Taylor, & Seeman, 2002; Sher, Grekin, & Williams, 2005).

Adolescent Onset AUD

Introduction

Adolescence is defined as the developmental period that occurs between the ages of 12-25, and it is the time during which the brain reaches full maturity (Casey, Jones, & Hare, 2008; F. Crews, He, & Hodge, 2007; Giedd et al., 1999; Shaw et al., 2006; Linda P Spear, 2000). This point is reached via massive brain restructuring which, amongst other changes, involves decreases in frontal grey matter and an increase in whole-brain white matter (F. Crews et al., 2007). Importantly, there is a considerable overlap in brain systems that undergo most of the adolescent restructuring and those that are affected in AUD (described above); specifically, the forebrain systems that are related to the cognitive executive processing of motivation towards reward, stress processing, and

related attention and inhibitory functions (Galvan, 2010; Monk et al., 2003; Romer, 2010). Not surprisingly, AUDs most often begin during adolescence and start to emerge in the form of either BD or HD patterns (Chassin, Pitts, & Prost, 2002; Donovan, 2004; Schulenberg & Maggs, 2002). Each drinking pattern seems to be associated with different cognitive and motivational mechanisms that are involved in alcohol consumption.

Adolescent Development

Among a broad range of physiological and cognitive changes that occur during adolescence, the PFC undergoes a sort of "sculpting" as a result of genetic and environmental influence (Lewis, 1997). Grey matter within the PFC decreases as a result of synaptic pruning and white matter connectivity increases, interconnecting the PFC with other brain regions to a greater extent than before adolescence (Andersen, Thompson, Rutstein, Hostetter, & Teicher, 2000). The maturational changes that are the most relevant to AUD vulnerability are those that underlie reward motivation and stress processing (Galvan, Hare, Voss, Glover, & Casey, 2007; Romeo & McEwen, 2006; Van Leijenhorst et al., 2010). Anatomically, PFC-striatal-limbic connections are restructured, which impacts the activity of attention and inhibitory systems (F. Crews et al., 2007). Cognitive traits associated with maturing, such as impulsivity and changes in stress processing, also begin to emerge (Arnett, 1999; Romer, 2010). Healthy developmental changes during adolescence involve non-linear thinning of the entire cortical surface (Shaw et al., 2008a). This occurs partially due to synaptic pruning (F. Crews et al., 2007)

and accompanies white matter reorganization (via myelination) below the cortical surface of the brain (Paus, 2010). Most regional cortical thinning has been shown to follow a cubic trajectory, reaching peaks in thickness at the onset of adolescence and thinning until 25 years of age ((Shaw et al., 2008a); see Figure 1 below). The two exceptions to this trajectory seem to be localized within the insula, anterior cingulate cortex, and inferior regions of the brain (Shaw et al., 2008a). Insula and the anterior cingulate cortex were shown to follow quadratic curves; reaching peak thickness at approximately 17 years of age, and thinning after that point onward (Shaw et al., 2008a). Some regions within the orbitofrontal cortex, frontal operculum, piriform cortex, medial temporal cortex, subgenual cingulate cortex, and medial occipitotemporal cortex appear to follow linear trajectories of cortical thinning (Paus, 2010). Figure 1 shows a visual summary of these changes (Shaw et al., 2008b).

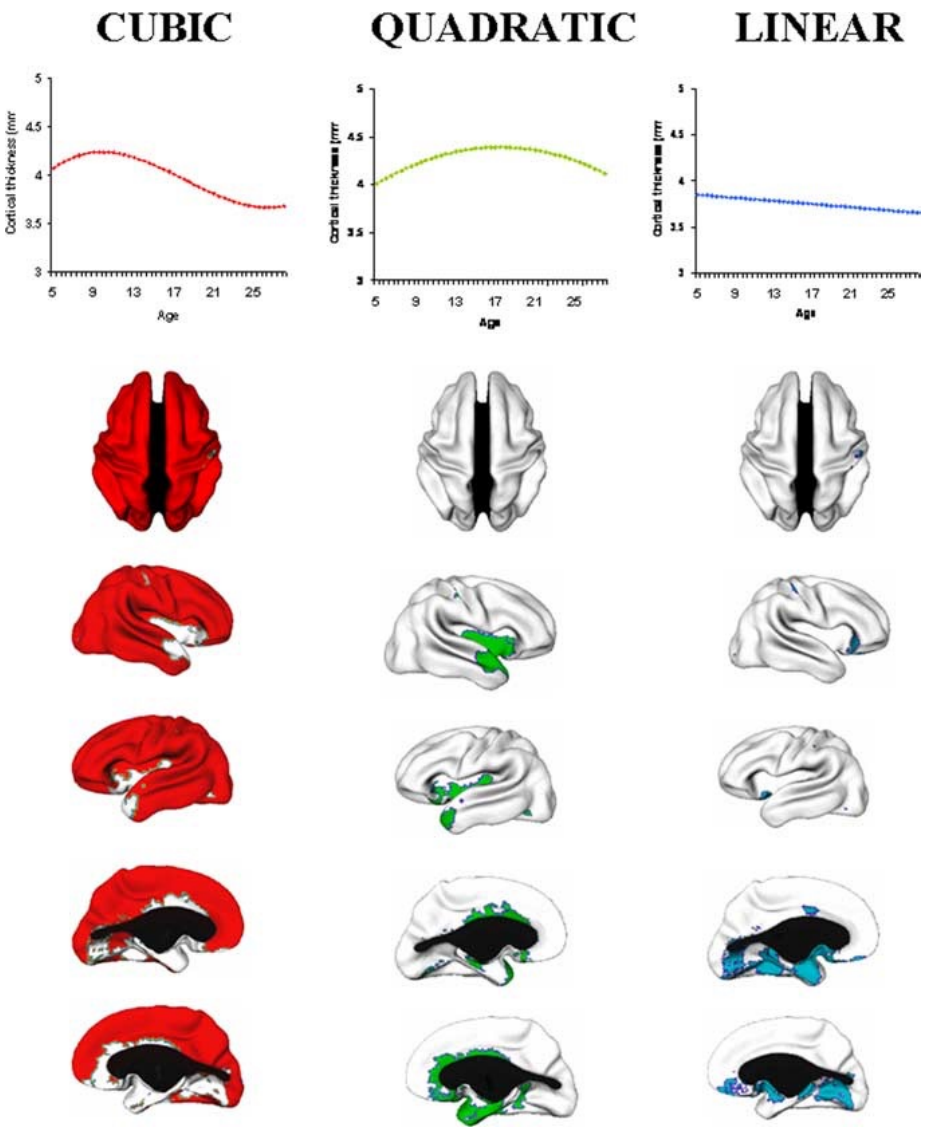

Figure 1. Trajectories of Cortical Grey Matter Adolescent Development.

These images depict multiple trajectories of cortical thinning throughout adolescence based on age, and snapshots of several locations along the linear and non-linear functions. Reprinted with permission from (Shaw et al., 2008a); permission obtained on 10/13/16 (Shaw et al., 2008b).

Within the developing PFC-basal ganglia circuits, globus pallidus plays a specific role in goal-oriented motivation. Specifically, bilateral global pallidum lesions are associated with impaired learning of new rules, as measured by the Wisconsin Card Sorting Task (Olzak et al., 2006), as well as impaired attention towards new rule learning (Scott et al., 2002). Damage within the pallidum regions that project to orbitofrontal and ventromedial prefrontal cortices have resulted in clinical apathy (this condition was slightly alleviated with dopaminergic treatments) (Adam et al., 2013). Cell activity recordings of the globus pallidus during deep brain stimulation have shown higher activity during reward presentation (Howell et al., 2016), as well as a cessation of learned compulsive symptoms (Smeets et al., 2016). A recent animal study with monkeys who had undergone pallidoctomies, has shown impairments within reward motivated behavior via impaired performance on a reward task (Piron et al., 2016). Additionally, it was found that volumetric reduction within the globus pallidus is associated with decreased ability to make causal inferences in adolescents: an ability that is critical to learning (Griffiths, Lagopoulos, Hermens, Hickie, & Balleine, 2015).

Adolescent development of the globus pallidus is associated with the emergence of motivational traits (Lamm et al., 2014). These traits become pathological in AUD, as motivation is increased towards the consumption of unhealthy quantities of alcohol and is often decreased in relation to other goals (Heinz et al., 2014b). Both BD and HD individuals have been shown to have increased motivation (often referred to as incentive salience) towards alcohol, and decreased motivation towards pursuing other, healthier activities (Lau-Barraco, Linden-Carmichael, Hequembourg, & Pribesh, 2016;

Marczinski, Fillmore, Henges, Ramsey, & Young, 2013). Interestingly, a single case study examining damage to the globus pallidus, via ischemic injury, reported an associated cessation of substance abuse (Moussawi, Kalivas, & Lee, 2016). These findings show that the globus pallidus is not only involved in pathological motivation towards substance abuse, but it also appears to be necessary for the maintenance of pathological drinking.

In addition to the globus pallidus, other ventral striatal structures function together to process rewarding stimuli, and are particularly sensitive to reward during adolescence (Fliessbach et al., 2007; Takahashi, Langdon, Niv, & Schoenbaum, 2016; Telzer, 2016). Although their role does not seem to be as specific as that of the globus pallidus, they have been shown (via functional MRI (fMRI)) to consistently activate in response to rewarding stimuli (Schultz, 2000) and decrease in activation when rewards are absent (Schultz, Apicella, Scarnati, & Ljungberg, 1992). In the presence of rewards, the ventral striatum was shown to be hyperactive in adolescence, in comparison to healthy adults (Schultz et al., 1992). Additionally, these structures are hyperactive in response to alcohol cues within the AUD population (in adolescents as well as adults (Chambers, Taylor, & Potenza, 2003; Jana Wrase et al., 2007)). Taken together, these findings point to a crucial component of a reward system, the globus pallidus, which has altered functioning during adolescent development and appears to be malfunctioning within the AUD population.

Overview of Impulsive and Compulsive Traits

Prior to classifying AUD subtypes based on their respective impulsive and compulsive characteristics, it is worthwhile to review the latest literature on these endophenotypes. Impulsivity has been defined as a reckless action that lacks the proper foresight and evaluative thinking required to weigh all the positive and negative outcomes of an act (Durana, Barnes, Johnson, & Shure, 1993; Evenden, 1999; Voon & Dalley, 2015). Impulsive actions are often reinforced by positive goals; the desire to obtain a reward, also known as positive reinforcement (Koob & Le Moal, 2001; Voon & Dalley, 2015). Impulsivity is argued to involve a flaw in executive reasoning (Bickel, Jarmolowicz, Mueller, Gatchalian, & McClure, 2012). The construct of impulsivity has been broken down into several different domains involving motor and decision-making components. Motor impulsivity can be broken down into waiting impulsivity (restraining a response in anticipation of a reward) and response inhibition (stopping a proponent or an initiated response). Decision making impulsivity can refer to (1) delay discounting: the extent to which future rewards are devalued in comparison to analogous but immediate rewards, or (2) reflection impulsivity: lack of consideration of all necessary factors resulting in rash decisions.

While the neural underpinnings of impulsivity differ depending on the specific task, there are certain commonalities that are involved in most tasks that evoke impulsivity (Schilling et al., 2013). According to a recent review, the fronto-striatal and parietal regions are involved in most impulsivity tasks (Fulton Timm Crews & Boettiger, 2009). When participants attempt to inhibit an action, the PFC structures communicate

with the globus pallidus and the substantia nigra through either the NAcc or the caudate nucleus (Aron & Poldrack, 2006). Parietal regions are also involved and are believed either to play an evaluator role for judging the magnitude of potential reward or to focus volitional attention on the task at hand (Bisley & Goldberg, 2010b; Spechler et al., 2016). Smaller left parietal volume has been associated with greater impulsivity, which further suggests its role in inhibiting inappropriate behaviors (Banca et al., 2015). Given that parietal structures are involved in a broad array of tasks (see (Bisley & Goldberg, 2010a) for an overview), in addition to impulsivity, it is likely that they activate as part of a volitional control network when attention is focused on a given task.

Compulsivity, on the other hand, is defined as a repetitive pattern of behavior (in the form of thoughts or actions) that is aimed at reducing tension or discomfort (Koob, 2003a; Voon & Dalley, 2015). Compulsive acts are motivated by negative reinforcement (reduction of unpleasant states) and have been shown to be driven by involuntary (automatic) urges, as opposed to volitional motivation (Denys, 2014). Compulsion is typically measured by repetitive behaviors and cognitive inflexibility; the inability to reverse a previously learned behavior despite the updated instructional demands (Voon & Dalley, 2015; Voon et al., 2010). Attention set-shifting tasks have demonstrated deficiencies in the ability to perceive changing rules and perseverative behaviors in compulsive individuals (Voon & Dalley, 2015). This has also been reflected in the inability to reverse previously made associations (Banca, Harrison, & Voon, 2016).

In contrast to impulsivity, compulsive disorders were shown to involve disruptions within occipital regions, which serve as global attention hubs (Bagga et al.,

2014; Gonçalves et al., 2016; Migliaccio et al., 2016; Vossel, Geng, & Fink, 2014). These hubs constitute parts of dorsal (volitional) and ventral (involuntary) attention streams (Vossel et al., 2014). Involuntary attention is drawn towards cues that indicate tension when a certain craving or an "itch" needs to be satisfied (Euser, Oosterhoff, & van Balkom, 2016; Voon & Dalley, 2015). Voluntary attention is then deployed when the affected individuals makes the decision to focus on the reward of "scratching the itch," or drinking, in order to reduce negative symptoms associated with withdrawal (Stern et al., 2016; Stern & Taylor, 2014). Given that both types of attention are an organic entity of compulsive disorders, it is not surprising that the occipital attention hubs are affected.

Motivational Dysregulation in Binge Drinking

BD is associated with a disruption in the volitional decision making process that is driven by the hedonic rewards of alcohol consumption (Gil-Hernandez & Garcia-Moreno, 2016; Koob, 2004; Stock, Riegler, Chmielewski, & Beste, 2016). These dysregulations become apparent when teenagers become noticeably engaged in BD to a higher extent than healthy adolescents (Blakemore & Robbins, 2012; Fulton Timm Crews & Boettiger, 2009; Whelan et al., 2012). Studies show that BDs possess impulsive characteristics and are motivated to consume alcohol because of its rewarding effects (Koob; see Figure 2). This cohort of teenagers appears to possess certain neurocognitive vulnerabilities that are exploited during the first few BD episodes. When alcohol is first consumed, the reward centers of the brain release opioid and GABA neurotransmitters in all drinkers. Those who ultimately become BDs, however, seem to react differently to

this experience than their healthy counterparts. For example, they may begin to display trouble inhibiting (Balodis, Potenza, & Olmstead, 2009) actions that lead to more alcohol consumption (thus increased impulsivity) and start paying more attention to cues that relate to alcohol, versus all other stimuli (thus attention bias). Continued BD episodes, in turn, impact the developing neural structures that are associated with inhibition and impulsivity with changes persisting throughout adulthood. The neurocognitive changes are predictive of future BD episodes, as they motivate the affected individuals to keep re-experiencing the positive effects of alcohol intoxication (thus positive reinforcement). This type of reward-driven motivational dysregulation is associated with altered functioning of the developing PFC-basal ganglia network (Balodis et al., 2009). In more extreme cases, the neural system was said to be "hijacked" by the substance (Volkow & Wise, 2005).

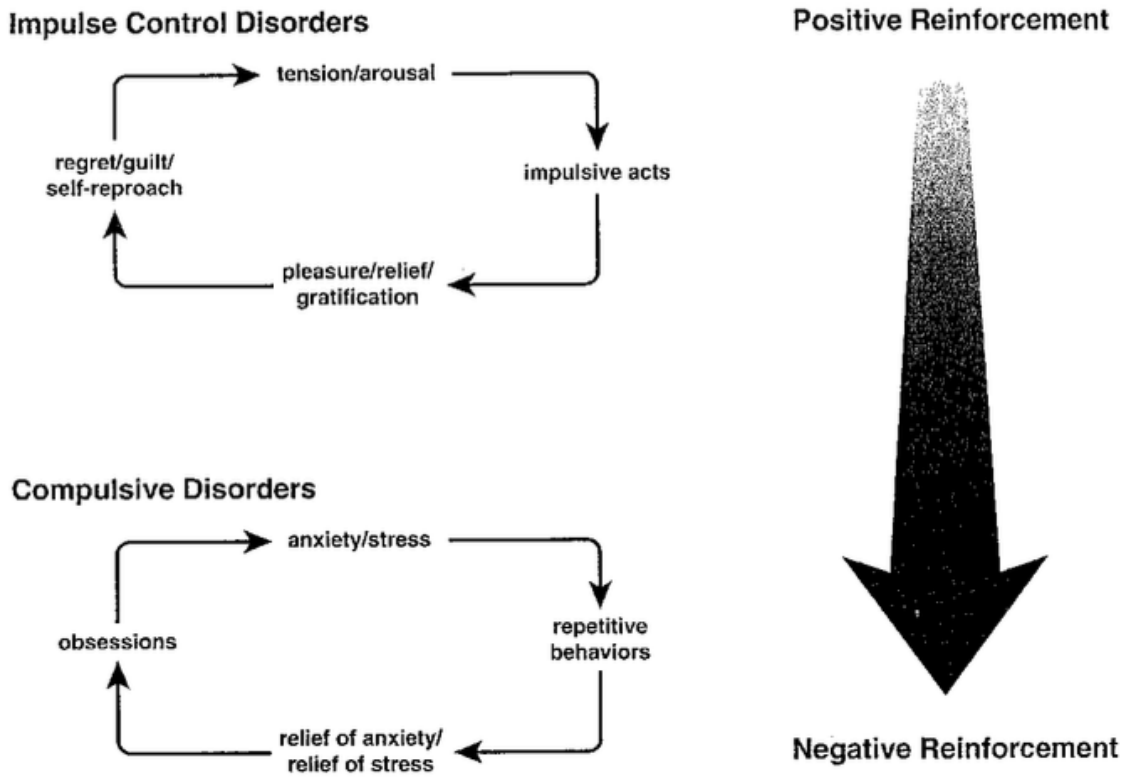

Figure 2. Compulsive and Impulsive Models of Substance Abuse.

This figure depicts the impulsive and compulsive models of addictive profiles. Each profile respectively involves positive and negative reinforcement as motivation. Adopted models of addiction from Koob and colleagues (Koob, 2003b). Permission to use the Figure obtained on 10/10/16 under the license number 3965571287529 and reprinted with permission.

Motivation Dysregulation in Heavy Drinking

HDs were shown to exhibit pathologically elevated obsessive and compulsive traits and are motivated to drink frequently via negative reinforcement (Anton, 2000; Anton, Moak, & Latham, 1995; Connor, Feeney, & Young, 2004; Flannery, Volpicelli, & Pettinati, 1999; Modell, Glaser, Cyr, & Mountz, 1992; Roberts, Anton, Latham, & Moak, 1999). HDs' day-to-day qualitative experience, as measured by self-report, is marked by

elevated levels of negative affect compared to non-problem drinkers (Colder & Chassin, 1993; Frone, Barnes, & Farrell, 1994; Hussong & Chassin, 1994). Their neurochemical composition includes chronically decreased GABA and elevated cortisol levels which "normalize" with steady alcohol intake (Enoch, 2008; Koob, 2004), contributing to ever increasing levels of alcohol tolerance. Importantly, the same $GABA_A$ receptors that are affected by alcohol also increase negative affect and stress (Enoch, 2008). Thus, HDs' reliance on alcohol is tied in to their desire to decrease stressful and uncomfortable states that are exacerbated in alcohol's absence.

Attention Overview

Among the developing neurocognitive systems during adolescence are the attention systems. Attention systems are divided into two distinct components; dorsal and ventral attention streams (Vossel et al., 2014). The ventral attention system was shown to activate in response to involuntary deployments of attention, an example of which is a saccade in response to a peripheral stimulus (Vossel et al., 2014). Regions most involved in this network include ventral frontal components, temporal-parietal junction, and the visual cortex (Vossel et al., 2014). The dorsal attention network underlies the volitional deployment of attention; for example, fMRI studies have demonstrated that it is activated during tasks involving voluntary action (Vossel et al., 2014). Neurologically, this system consists of bilateral frontal eye fields, lateral parietal regions (specifically, the intraparietal sulcus), as well as the visual cortex (Vossel et al., 2014). The superior

parietal lobule, within the lateral parietal region, is a particularly crucial task-positive component of this network, as it activates in response to a wide variety of tasks (Corbetta & Shulman, 2002; Gmeindl et al., 2016). Specifically, it is active during feature detection (Esterman, Tamber-Rosenau, Chiu, & Yantis, 2010; T. Liu, Slotnick, Serences, & Yantis, 2003), working memory (Tamber-Rosenau, Esterman, Chiu, & Yantis, 2011), sensory processing (Shomstein & Yantis, 2004), object processing (Serences, Schwarzbach, Courtney, Golay, & Yantis, 2004), and shifting between various spatial locations (Greenberg, Esterman, Wilson, Serences, & Yantis, 2010; Kelley, Serences, Giesbrecht, & Yantis, 2008; Vandenberghe, Gitelman, Parrish, & Mesulam, 2001; Yantis et al., 2002). Importantly, the frontal eye field region (more so on the right side) seems to play a more "fine-tuned" role in attention control; it engages and makes small adjustments during times when individuals are performing well on a given task (Esterman et al., 2015). It is important to note that while these attention systems occupy a distinct spatial distribution, the visual cortex is a global processing hub for both networks (Vossel et al., 2014). Additionally, although the basal ganglia structures are not directly a part of the attention networks, they provide value "assignments" along with the frontal systems for various tasks that might compete for attentional resources (Hazeltine, Grafton, & Ivry, 1997; Mason et al., 2007). This is important for attention in the context of positive information processing and motivation.

As evident by the review so far, the dorsal attention network is involved in a broad number of tasks and types of attention. The focus of this discussion will be on the sustained attention component of attentional processing, as it is most relevant to

developing AUD disorders. Sustained attention is defined as the ability to focus attention on a specific task for a prolonged period of time (Esterman, Noonan, Rosenberg, & DeGutis, 2012).

There are a number of competing theories with regards to the cognitive mechanisms of sustained attention processing underlying the dorsal attention network. The "resource theory" posits that sustained attention is an interplay between cognitive resource availability and the respective resource demands of various tasks (Grier et al., 2003). Failures in sustained attention occur when task demands become too high, and resources are stretched too thin, consequently causing suboptimal task performance (Warm, Parasuraman, & Matthews, 2008). This theory is problematic, however, because of ungrounded assumptions that participants are (1) fully motivated/engaged in doing the task, and (2) maximal effort is consistently exerted (Karen & Sasmita, 2016; Massar, Lim, Sasmita, & Chee, 2016; Nicholls, Loveless, Thomas, Loetscher, & Churches, 2015). Another problematic theory, often called the "underload theory," that attempts to explain the faulty mechanisms of sustained attention posits that performance decrements occur when task demands are too low to maintain arousal at optimal levels (Manly, Robertson, Galloway, & Hawkins, 1999). When this happens, unrelated thoughts and mental processes begin to form in order to fill the void in an under-stimulated attention network (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997). A major problem with this explanation is that it does not address why extended task performance is increasingly effortful, which, according to this theory, should not result in lower excitation (Warm et al., 2008).

Perhaps the “effortful allocation theory” is the most promising explanation for the functioning of sustained attention. This theory posits that the phenomenon of attention is a dynamic process involving the allocation of limited resources between the task at hand and other ongoing mental processes (Kurzban, Duckworth, Kable, & Myers, 2013; Thomson, Besner, & Smilek, 2015). According to this model, attention is inextricably linked to valence and motivational factors. Allocation of task resources is based on analyses and assignments of reward and opportunity cost to available tasks (Braver et al., 2014), which consequently impacts performance. If, for instance, a task is judged as boring without a sufficient reward for successful completion, resources might be divided between that task and other, more appealing, mental processes (i.e., thinking about what dessert to pick after dinner that evening). Additionally, as the agent gets more tired, fatigue would add to the cost of performing at peak effort (Boksem & Tops, 2008), which an ongoing re-evaluation of the task-resource allocation would take into account. Finally, it was recently shown that attention largely depends on how strongly a performance is linked to predicted outcomes; this takes past associative learning experience into account (Le Pelley, Beesley, & Griffiths, 2016). Past experience with alcohol engagement might be particularly important for reinforcement learning that often leads to addiction.

Ongoing mental processes that interfere with goal oriented attention have been shown to be associated with functional activation of the default mode network (Andrews-Hanna, Smallwood, & Spreng, 2014; Esterman et al., 2012). Briefly, as shown by numerous fMRI experiments, the default mode network consists of co-activating brain regions that increase in activation when participants are at rest and, comparatively,

decrease in activation during active engagement in tasks (Andrews-Hanna, 2012; R. Buckner, Andrews-Hanna, & Schacter; Spreng, Mar, & Kim, 2009). One of several mental processes that have been attributed to the default mode network is self-referential internal mentation (Andrews-Hanna et al., 2014). This refers to internally oriented thoughts that are not relevant, and are usually disruptive, to external tasks (Andrews-Hanna et al., 2014). External attention processes are thus disrupted when participants engage in a high level of internal mentation, as allocation of resources becomes strained (Esterman et al., 2012). Some of the internal mentation processes are not voluntary (thus bottom-up), and have been associated with the posterior regions of the default mode network (specifically, the precuneus and the posterior cingulate cortex) (Andrews-Hanna, 2012).

Attention Specific to Rewarding Stimuli

As evident from the above review, attentional and motivational systems are orthogonal to one another. Indeed, since one function of attention is to achieve the desired goals (Massar et al., 2016), it is not surprising that sustained attention is largely dependent on motivational factors. A recent study has shown that simply the prospect of a reward triggers activity within the attention network during task anticipation (Esterman, Poole, Liu, & DeGutis, 2016). Given that striatal and frontal regions are involved in assigning hedonic value to rewards based on past experience (Le Pelley, Beesley, et al., 2016; Le Pelley, Mitchell, Beesley, George, & Wills, 2016; Mason et al., 2007), this can be an additional point of vulnerability in AUD related disruptions. Since alcohol is often overvalued, while other unrelated tasks/objects are undervalued, it is not surprising that

AUD participants were shown to perform worse on tasks involving sustained attention (Crego et al., 2009; Parada et al., 2012; J. M. Townshend & Duka, 2005). Studies have shown that AUD participants were biased toward alcohol related cues (Fadardi & Cox, 2009; Garland, Franken, & Howard, 2012; McAteer, Curran, & Hanna, 2015; Schoenmakers, Wiers, & Field, 2008), which impacted their attention performance as well as craving (Fadardi & Cox, 2009). Additionally, the degree of attention bias depends on the amount of alcohol consumed throughout participants' lifetime (J. Townshend & Duka, 2001) and is predictive of treatment outcomes (Cox, Hogan, Kristian, & Race, 2002). Thus, the strength of associative learning impacts the hedonic value of immediate stimuli via biasing of attention resource allocation. Finally, it has been shown that altering attention biases via re-training procedures (away from alcohol cues and towards neutral cues) results in alcohol craving reduction (Fadardi & Cox, 2009).

As discussed, AUDs have been associated with widespread thinning of the entire cortex (Fortier et al., 2011). Results pertaining to thinning that is associated with adolescent onset AUD are not consistent across studies, which is likely due to the heterogeneity of AUD characterization (i.e., participants' drinking patterns). For example, according to a twin study conducted by Wilson and colleagues, pathological thinning that precedes developing an adolescent AUD is localized within the right superior, middle, and inferior frontal, as well as bilateral middle temporal regions (Wilson, Malone, Thomas, & Iacono, 2015). Contradictory to this, a review published a year later argued that a thinner cerebral cortex is a vulnerability marker of adolescent onset AUD (Lindsay M. Squeglia & Gray, 2016). Inconsistency of findings may be

related to a number of factors including a lack of attention to drinking severity, drinking patterns, and domain specific effects across studies. For instance, Fein and colleagues have shown that cortical grey matter reduction is a function of an interaction of age and alcohol use duration (G Fein et al., 2002; George Fein, Shimotsu, & Barakos, 2010). Others have argued that global effects on cortical thickness are dependent on AUD severity (Thayer et al., 2016). Finally, a recent study has shown that thinning in the dorsal attention network occurs independently of substance abuse (Holmes, Hollinshead, Roffman, Smoller, & Buckner, 2016).

Attention in Binge Drinkers

Given the wide array of neurocognitive aspects that are involved in attention processing, it is quite possible for different neurological changes (i.e., brain regions that constitute the default mode network versus the dorsal attention network) to result in similar attention deficits. Anatomical alterations that are specific to BDs (Müller-Oehring et al., 2013) are likely within the top-down regions supporting the dorsal attention network. Although definitive results have not been reported, several studies seem to support this theory. A recent study, for instance, measuring event-related potentials in BDs has shown that the dorsal attention regions have been altered in their event-related response in comparison to healthy controls (Watson, Newton-Mora, & Pirkle, 2016). Additionally, a resting state fMRI study has shown that the fronto-parietal aspects of the dorsal attention network have disrupted functional connectivity within BDs in comparison to healthy controls (Weiland et al., 2014). Interestingly, the parietal component of this network has been shown to be involved during the evaluation of

immediate versus delayed reward selection (Banca et al., 2015; Furl & Averbeck, 2011). Additionally, left parietal regional volume has been shown to be associated with greater impulsivity in BDs (Banca et al., 2015). These findings hint at a top-down volitional control attention disruption within BDs, characterized by less efficient and/or effective functioning during reward processing.

Attention in Heavy Drinkers

Unlike BD, HD is characterized by chronic compulsive alcohol seeking behavior that is likely related to disrupted internal mentation (Koob & Le Moal, 2001). While the content of these thoughts has not been studied in the HD population, it might be related to alcohol (either related to the substance directly, or pertaining to thoughts about discomforts of being sober). It thus seems likely that fMRI findings pertaining to an altered default mode network within AUDs (Chanraud, Pitel, Pfefferbaum, & Sullivan, 2011) are related to the compulsive involuntary cognitive processes of HD population and driven by them. Indeed, volumetric differences have been found within non-alcoholic participants suffering from obsessive-compulsive thoughts within the precuneus node of the default mode network (Gonçalves et al., 2016). These findings point to a bottom-up dysregulation of the default mode network in HDs that could be associated with proposed attention disturbance.

Overview of Inhibitory Control

The ability to inhibit and excite information are two crucial aspect of the same mechanism (Galarreta & Hestrin, 1998; Okun & Lampl, 2008). Computationally,

inhibition is defined as expanding energy to suppress a certain signal (Aron, 2007). Excitation is the opposite, defined as expanding energy to bring a signal to the forefront of cognitive processing (Houghton & Tipper, 1996; Levine, 2000). Stop-signal inhibition tasks test for a specific type of inhibition, requiring participants to first perform a certain action over and over again, exciting the signals and cues that are associated with that action in the process (Aron & Poldrack, 2006). Then, when participants are cued to stop that action from occurring, neural energy has to be expanded in order to suppress the previously excited action (Verbruggen & Logan, 2008).

While the cellular computational models of inhibition are outside of the scope of this discussion (see (Kuffler, Nicholls, & Martin, 1976) for a review), certain brain systems have been identified as playing specific roles in exciting and inhibiting neural information from a systems neuroscience perspective (Aron, Robbins, & Poldrack, 2004; Knight, Staines, Swick, & Chao, 1999). Frontal lobe regions are generally associated with selecting which information to excite and inhibit (Ridderinkhof, Van Den Wildenberg, Segalowitz, & Carter, 2004; Shimamura, 2000). Specifically, it has been argued that the right inferior frontal gyrus acts as a "neural break" (Aron et al., 2004) (although this model is debated; see (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010)). Basal ganglia and limbic structures have been implicated in exciting neural information, specifically relating to emotionally valance stimuli (J. Brown, Bullock, & Grossberg, 1999; Groenewegen, 2003). This region's activity has been associated with the strength of excitation pertaining to specific signals (Carretié et al., 2009; Gujar, Yoo, Hu, & Walker, 2011). In this model, the frontal lobes and the limbic/striatal regions act in

opposition to one another (Hariri, Bookheimer, & Mazziotta, 2000; Karreman & Moghaddam, 1996). Once the frontal structures identify certain information as emotionally salient, basal ganglia and striatal structures excite that information. The signal is then classified by the frontal systems as either appropriate (thus excited), or inappropriate for immediate action (thus inhibited) (Goldin, McRae, Ramel, & Gross, 2008; E. E. Smith & Jonides, 1999).

Inhibitory Function in Binge Drinkers

The ability to inhibit positive information constitutes a major aspect of reward processing (Quay, 1988) and seems to be deficient in BD. In a dynamic process with frontal systems, striatal and limbic structures assign a hedonic value to the stimulus, (Dolcos, LaBar, & Cabeza, 2004; Samejima, Ueda, Doya, & Kimura, 2005). Consequently, basal ganglia produce a DA mediated incentive salience signal, which codes motivation for achieving the presented stimulus (Berridge, 2007; McClure, Daw, & Montague, 2003; Nicola, 2007; Niv, Daw, Joel, & Dayan, 2007). Given the complexity of day-to-day life, and a multitude of competing signals, the frontal lobe systems are related to the cognitive function of exciting certain stimuli and weighting them against the opportunity cost of missing other goals (Kennerley, Dahmubed, Lara, & Wallis, 2009). Individuals vary in their abilities and preferences for reward selection based on their states, experience, and personality characteristics (Cooper, Duke, Pickering, & Smillie, 2015; Duckworth, Tsukayama, & Kirby, 2013; Keller et al., 2013; Ridderinkhof et al.,

2004; Schlam, Wilson, Shoda, Mischel, & Ayduk, 2013; Zelazo & Carlson, 2012). It was shown that the ability to inhibit immediate actions towards immediate rewards begins to develop at a young age, might be innate (Anokhin, Golosheykin, Grant, & Heath, 2011; Balogh, Mayes, & Potenza, 2013), and continues to develop throughout adolescence.

Individuals suffering from AUDs have been shown to possess deficiencies in inhibiting positive information pertaining to immediate rewards in favor of delayed larger rewards (Dawe, Gullo, & Loxton, 2004; Dawe & Loxton, 2004; De Wit, 2009; Dick et al., 2010). For example, AUD individuals seem to be characteristically more impulsive, more likely to choose immediate rewards without opting for more long-term advantageous options (Claus, Kiehl, & Hutchison, 2011; De Wit, 2009; Dick et al., 2010; Petry, 2001; Verdejo-García, Lawrence, & Clark, 2008). Cognitive tests such as Go/No-Go, which test response inhibition, have shown that AUD participants commit a greater number of inhibitory errors than their healthy counterparts (Kamarajan et al., 2005). Additionally, fMRI studies have shown that AUD participants' striatal regions are hyper-responsive when presented with alcohol related cues, and hypo-responsive to neutral cues, in comparison to controls (Grüsser et al., 2004; Schacht et al., 2011; J Wrase et al., 2002). This exemplifies a positive information bias that interacts with deficient inhibitory function that is characteristic of BDs (MacKillop et al., 2011; Voon et al., 2010).

More recent studies that have focused on the BD pattern of AUDs seem to indicate that BDs account for the findings of impulsivity in the AUD population as a whole. BDs have been recently shown to have problems with impulse control and commit more inhibitory errors (Poulton, Mackenzie, Harrington, Borg, & Hester, 2016). fMRI

studies have demonstrated that BD adolescent participants' fronto-parietal and dorsal striatal regions deactivate during decision making tasks to a higher extent than healthy controls (S. A. Jones, Cservenka, & Nagel, 2016). Grey matter volume of the left parietal region in BDs was associated with higher impulsivity in comparison to healthy participants (Banca et al., 2015).

Inhibitory Function in Heavy Drinkers

The ability to inhibit negative information is instrumental in stress management and resilience to developing psychopathology (Degnan & Fox, 2007; Joormann, 2006; Southwick & Charney, 2012). Generally, negative information processing is a complex task involving the interaction of attention systems (discussed below) with inhibitory capacity, which is highly dependent on individual affective sensitivity to salient information (Beck & Clark, 1988, 1997; Goeleven, De Raedt, Baert, & Koster, 2006; Koster, De Raedt, Goeleven, Franck, & Crombez, 2005; Wentura, 1999). Malfunction in any one of these aspects can contribute to difficulties with processing and inhibiting negative information, which consequently increase the vulnerability for alcohol abuse and addiction (Markus & De Raedt, 2011; Pardini, Lochman, & Wells, 2004). Sensitivity to negative information, for instance, has been measured via self-report and physiological measures such as fMRI (Hamilton & Gotlib, 2008; Siegle, Steinhauer, Thase, Stenger, & Carter, 2002). Individuals who are more sensitive to negative salience (similar to stress

sensitivity) were found to rate negative information as more negative than less-sensitive individuals, and take longer to return to their baseline affective states (often referred to as affective recovery) (Ito, Larsen, Smith, & Cacioppo, 1998; Waugh, Panage, Mendes, & Gotlib, 2010). Additionally, fMRI studies have shown higher activity within the amygdala regions (within the healthy adult population) in response to negative information and lower activities within PFC (Kim, Somerville, Johnstone, Alexander, & Whalen, 2003). Given that one of the functions ascribed to the PFC is the interpretation and processing of negative information while the amygdala interprets and responds to fearful and affective stimuli, the described deficiencies demonstrate an affective processing deficit across multiple systems.

A disruption in inhibiting negative information from conscious awareness occupies cognitive resources that can be used to attend to other ongoing stimuli (Goeleven et al., 2006; Joormann, 2006; Wentura, 1999). Affective Go/No-Go (AGN) studies have investigated these possible disruptions by asking participants to inhibit their responses to negative information by NOT pressing a button (Erickson et al., 2005) in response to positive and negative valence, low probability stimuli. Participants who engaged in problem drinking had difficulties inhibiting their responses (Houben, Havermans, Nederkoorn, & Jansen, 2012; Houben, Nederkoorn, Wiers, & Jansen, 2011; Weafer & Fillmore, 2008). Additionally, other studies have demonstrated less BOLD activity in the frontal regions within this population (Chen et al., 2007), which was interpreted to indicate an impaired inhibitory capacity. Inability to properly inhibit negative information in a timely manner might leave individuals burdened with that

information for longer periods of time and at more intense processing levels (Whitmer & Banich, 2007; Zetsche, D'Avanzato, & Joormann, 2012). This occurrence creates a stressor that might drive individuals towards alcohol consumption as a self-medicating means of coping (Colder, 2001; Colder & O'Connor, 2002).

As mentioned earlier, stressful life events and the ability to cope with negative information are major risk factors for developing an AUD. Individuals who either are exposed to more stress or have compromised capacity for coping with day-to-day stress levels are at a particular risk for problem drinking (Crum et al., 1995; Sher & Levenson, 1982). A major reason for this link pertains to the sedating, stress reducing effects of GABA, a neurotransmitter that is increased as a result of alcohol consumption (Herman & Cullinan, 1997; Spivak et al., 2000). Healthy inhibitory capacity allows individuals to inhibit stressful stimuli, and excite positive (often goal-oriented) information, thus decreasing the need for self-medication (Franklin, Saab, & Mansuy, 2012). Compromised inhibitory capacity, on the other hand, not only increases the risk of self-medication but also decreases an individual's ability to withhold themselves from pathological self-medication, even against better judgment (Colder & Chassin, 1997; Fulton Timm Crews & Boettiger, 2009; Franklin et al., 2012; Kreek, Nielsen, Butelman, & LaForge, 2005).

Stress reactivity is a central aspect of processing and responding to stressful life events, which was shown to serve as an additional trigger point for developing an AUD (Kreek et al., 2005; Meaney, 2001). Certain individuals have been found to operate at higher baseline levels of stress, which is neurologically marked by altered levels of

diurnal cortisol and decreased levels of GABA (Barbaccia, Serra, Purdy, & Biggio, 2001; Ockenfels et al., 1995; Wood, Walker, Valentino, & Bhatnagar, 2010). Additionally, these individuals were found to have high stress reactivity, as measured by physiological and self-report indices; their skin conductance response, electrocardiogram indices, and pupil dilation were higher than average in response to stress (Bauer, Quas, & Boyce, 2002; Goleman & Schwartz, 1976; Jacobs et al., 1994; Kagan, Reznick, & Snidman, 1987; Notarius & Levenson, 1979; Linda Patia Spear, 2009; Tomaka, Blascovich, Kelsey, & Leitten, 1993; Travis, 2001). Self-report measures indicate higher levels of anxiety and negative affect when presented with information containing negative salience (Barrett, 1998; Mathews & MacLeod, 2002). Heightened states or stress reactivity, and physiological arousal in response to negative information, were identified as risk factors for alcohol consumption, perhaps because of their pacifying effects (S. A. Brown, Vik, Patterson, Grant, & Schuckit, 1995; Finn, Earleywine, & Pihl, 1992; Hellemans, Verma, Yoon, Yu, & Weinberg, 2008). A reversal in neurotransmitter levels occurs immediately after alcohol consumption; stress hormones decrease and GABA increases. Given the preexisting increased need for self-medication via alcohol, stress reactivity is an important risk factor for AUD (Colder, 2001; Sinha, 2001, 2008).

Due to pathologically altered states of sobriety that are physiologically and psychologically tasking, HDs' genetically compromised inhibitory capacity is predicted to be diminished in response to rewarding, as well as aversive, information. Studies show that decreasing levels of blood alcohol between heavy drinking phases are associated with physical as well as psychological discomforts (Spechler et al., 2016). Given that the

central nervous system adapts to frequent heavy levels of alcohol consumption, it becomes hyper-excited when alcohol levels begin to drop (Becker, 1998). These states are often accompanied by anxiety, hypervigilance, and irritability, among a number of other symptoms (Economidou et al., 2011). This produces a taxing effect on neural systems (Spechler et al., 2016) and exploits the vulnerable inhibitory capacity (Spechler et al., 2016). Consequently, the affected individuals have problems processing rewarding as well as aversive stimuli (Avila & Parcet, 2001). This evidence is supportive of the conclusion that, in case of HDs, rewarding (i.e., alcohol related) as well as negative cues are more difficult to inhibit, in comparison to those without a history of AUD.

Study Overview

The literature reviewed provides several important implications for the current study. First, evidence points to a differentiation between inhibitory and attention capacity in BDs and HDs. Recent studies have shown that BDs commit more inhibitory errors than their healthy counterparts (Poulton et al., 2016). This finding, interpreted in the context of other studies, might be indicative of a reward specific inhibitory impairment (Dawe et al., 2004; Dawe & Loxton, 2004; De Wit, 2009; Dick et al., 2010). HDs, on the other hand, may constitute a subgroup of individuals with AUD that have a more global impairment in both attention and inhibitory processing. It is proposed that because HDs are more likely to experience daily discomforts when not drinking (Spechler et al., 2016), their cognitive capacity may be diminished overall by stimulus-driven processes such as

anxiety, hypervigilance, and irritability (Economidou et al., 2011). The taxing effects of this pathological mentation, it is proposed, will likely diminish their attention and inhibitory capacity towards all stimuli (Avila & Parcet, 2001). ***Aim 1*** will ***examine the differential inhibitory and attention processing capacity, using the AGN and SRT tasks (the latter, used as a control measure), in BDs, HDs, and HCs. Hypothesis 1.1*** states that ***BDs will show a greater number of inhibitory errors (commission) in response to positive stimuli as compared to HDs, while HDs will show a greater number of inhibitory (commission) and attention (omission) errors on the AGN task in response to all valence stimuli.*** Since these predictions are not expected to result from a reaction time deficit, ***Hypothesis 1.2*** predicts that ***there will be no significant group differences on the SRT Task.***

Second, given the evidence showing that motivation dysregulation occurs in both pathological drinking patterns (BDs and HDs), it seems likely that they will both show altered ventral striatal volume, in comparison to HCs. These regions have been associated with reward processing (Takahashi et al., 2016), were shown to be altered in AUDs in general (Nicola, 2007; Spoelder et al., 2017), and will thus likely be altered in their morphometry within BDs and HDs. ***Aim 2***, is designed to ***examine whole-brain subcortical volumetric differences between BDs, HDs, and HCs.*** The whole-brain approach will be used in order to avoid biasing results to any specific area. ***Hypothesis 2.1*** states that ***both pathological drinking groups (BDs and HDs separately) will show an altered volume within ventral striatal structures, as compared to the HC group***.

Third, current evidence pertaining to cortical anatomy within the AUD population point to two distinct anatomical regions that might be associated with each of the proposed AUD subtypes. Given their impulsive characteristics, BDs are likely to have anatomical differences within fronto-parietal regions, responsible for top-down volitional control (Müller-Oehring et al., 2013; Weiland et al., 2014). On the other hand, given the compulsive internal mentation of HDs (Koob & Le Moal, 2001), they are likely show altered default mode network regions which goes in line with the previously reported AUD results (Chanraud et al., 2011), as well as recent findings from the obsessive-compulsive disorder population (Gonçalves et al., 2016). ***Aim 3*** will address these possibilities by ***examining whole-brain cortical thickness differences between BDs, HDs, and HCs***. ***Hypothesis 3.1*** states that ***BDs will show significantly altered dorsal attention network regions (within the top-down processing hubs: frontal and parietal regions), as compared to HDs and HCs. Hypothesis 3.2*** predicts that ***HDs will show significantly impacted default mode network regions (within the bottom-up processing hubs: posterior cingulate cortex and the precuneus regions), as compared to BDs and HCs.***

The current study uses a cross-sectional design to accomplish the above aims and address the specified hypotheses. Cortical thickness, volumetric, and behavioral measures (AGNG and SRT) were abstracted from the Translational Research Center for TBI and Stress Disorders (TRACTS) Data Repository (consisting of a sample of young veterans) for BD, HD, and healthy control (HC) participants. The respective drinking pattern status of each participant was determined by lifetime drinking history (LDH) interview data,

which has been designed to retroactively measure participants' drinking histories. Modified NIH guidelines will be used to define BD, HD, and HC groups. Only participants who had begun consuming alcohol during adolescence (12-25 years of age), and continued to drink in accordance with respective drinking patterns were included in the pathological drinking groups. All groups were equated on age, education, total quantity of lifetime alcohol consumed (weight adjusted), premorbid intelligence, psychiatric variables, as well as combat-related factors. ANOVA (for brain volume and behavioral measures) and t-tests (for cortical thickness) will examine group differences in the primary dependent measures, including covariates where necessary.

CHAPTER 2 – METHODS

Participants

The analyses have been conducted using the TRACTS Data Repository of the VA RR&D TBI National Network Research Center Translational Research Center for TBI and Stress Disorders (TRACTS) (McGlinchey et al., 2017). The TRACTS longitudinal cohort study recruits OEF/OIF/OND Veterans between the ages of 18 and 65, collecting an extensive battery of neuropsychological, clinical, physiological, and imaging measures. The exclusion criteria of the TRACTS cohort consists of the following factors: (1) history of neurological illness (Huntington's, Parkinson's, dementia, MS, etc.), (2) history of seizure disorders unrelated to head injury(ies), (3) current diagnosis of schizophrenia, bipolar or other psychotic disorder, (4) severe depression or anxiety, current active homicidal and/or suicidal ideation with intent requiring crisis intervention,

(5) cognitive disorder due to general medical condition other than TBI, and (6) unstable psychological diagnosis that would interfere with accurate data collection, determined by consensus of at least three doctorate-level psychologists. This study sample is an excellent cohort to conduct the proposed analyses, as at the time of the analyses there were 433 enrolled participants with a high rate of AUDs. The current project implemented additional inclusion, exclusion, and equating criteria, as described below, in order to select three subgroups of TRACTS participants that were equated across groups for critical confounding variables and that are best suited to accomplish the proposed aims.

The proposed aims have been accomplished using a final sample of 52 participants divided into the groups, as described below. The definitions for these groups are based on modified NIAAA criteria consistent with the following rationale. NIAAA defines BD as consuming at least 4 drinks for women and 5 for men within the course of 2 hours (N.I.A.A.A., 2016b). HD is defined as engaging in the BD pattern for 5 or more days in a month (N.I.A.A.A., 2016b). Further modification has been made based on our previous work, in order to avoid overlap and accommodate the lack of hour-by-hour accuracy in the retrospective interview. For the current analyses, individuals were classified as BDs if he/she consumed at least 4 drinks (women) and 5 drinks (men) on 12 or less days per month, whereas HDs consumed 3 drinks (women) and 4 drinks (men) on 16 or more days per month. HC consisted of participants who consume alcohol at healthy, non-pathological levels. BDs and HDs started drinking during adolescence (12-25) and continued to drink in this manner into adulthood and at the time of enrollment.

BD (N = 16): Operationally defined as an individual who reports a pattern of consuming ≥4 (females) or ≥5 (males) drinks per day on 12 or fewer occasions per month, without a history of HD episodes. Age of onset of the first BD period is between the ages of 12-25.

HD (N = 15): Operationally defined as an individual who reports a pattern of consuming ≥3 (females) or ≥4 (males) drinks per day on 16 or more occasions per month, without a history of BD episodes during adolescence. Age of onset of the first HD period is between the ages of 12-25.

HC (N = 21): Operationally defined as individuals who do not consume alcohol at pathological levels and are without any history of BD, HD, or any AUD (as measured by SCID DSM-IV). Most individuals in this group consists of socially drinking individuals, although 4 participants have not reported any alcohol consumption.

Study-specific Exclusion Criteria

(1) Participants with known factors that may impact neurological function (such as atrophy from malnutrition, anoxia, or congenital defects), neuropsychological performance (such as low IQ or English as a second language), or those who exhibit significant psychiatric conditions, such as psychosis not otherwise specified (NOS) or psychosis resulting from substance abuse or dependence.

(2) Participants with a history of moderate or severe TBI at any epoch (pre-deployment, deployment, or post-deployment).

(3) Participants with another unspecified and/or multidimensional concern that may impact functioning, such as an extreme outlier for blast exposure and other MRI measures.

(4) Any participants with missing data for a variable of interest in this project.

(5) History of any substance abuse or dependence, other than alcohol or nicotine.

Equating Study Groups

Group differences on the variables listed below have been examined using ANOVA tests. In cases when group differences were found to be significant, the respective variable(s) have been classified as covariates in the statistical models (see the *Covariates* section below).

(1) Psychiatric Variables (summarized in Table 1).

   a. Posttraumatic stress disorder (PTSD) total symptom severity score (as measured using Clinician Administered PTSD Scale for DSM-IV (Blake et al., 1995; Gray, Litz, Hsu, & Lombardo, 2004; Weathers, Keane, & Davidson, 2001; Weathers, Ruscio, & Keane, 1999)).

   b. Anxiety severity (measured by DASS) (Crawford & Henry, 2003).

   c. Depression severity (measured by DASS).

   d. Stress severity (measured by DASS).

   e. DSM-IV SCID Diagnosis.

(2) Demographic Characteristics (summarized in Table 2).

a. Estimated premorbid IQ (as measured by WTAR test of adult intelligence) (Wechsler, 2001).
b. Age at the time of testing.
c. Years of education.
d. Gender.

(3) Relevant Health Information.

a. Number of mild traumatic brain injury instances throughout the participant's lifetime.
b. Number of medications taken (total, psychotropic, and non-psychotropic).
c. Cigarette smoking status.

(4) Combat impact (summarized in Table 1).

a. Deployment Risk and Resiliency Inventory (DRRI) combat score (D. King, King, & Vogt, 2003).
b. DRRI "other" score.

(5) Alcohol consumption factors (summarized in Table 3).

a. Total weight-adjusted amount of alcohol consumed during the course of the participant's lifetime.
b. Age of onset of drinking onset.
c. Total length of all drinking episodes.

In addition to the variables described above, participants were equated on their dominant handedness as well as the total number of medications that participants were taking at the time of testing. Chi-square tests do not indicate a significant group

difference for handedness ($p > 0.05$) and an ANOVA does not show any significant group differences for the total number of medications that participants have been taking during the time of testing ($p > 0.05$). The total number of medications has been examined as well as psychotropic and non-psychotropic categories.

Covariates

The following eight variables have been identified as covariates, due to significant difference ($p < 0.05$) between the main groups (BD, HD, and HC) identified using ANOVA and post-hoc tests (either chai-square tests for dichotomous measures or Student's t-tests for continuous variables). See the **Aims Methods** sections for descriptions on how these covariates have been handled within each of the respective aims.

- Gender (number of females; HC > HD).
- Number of smokers (HD > BD/HC).
- Total CAPS severity Score (HD > BD/HC).
- DASS Anxiety sub-score (HD > BD).
- DASS Depression sub-score (HD > BD/HC).
- DASS Stress sub-score (HD > BD/HC).
- Number of current (at the time of testing) single depression episodes (HD > BD/HC).
- Number of lifetime recurrent depression episodes (BD < HD/HC).

Drinking Pattern		Psychiatric Variables				Combat Information	
		DASS Anxiety Total Score	DASS Depression Total Score	DASS Stress Total Score	CAPS Total Score	DRRI Combat	DRRI Other
Binge Drinking (BD) N = 16	**Mean:** **S.D.:** **Range:**	1.5 2.68 0-8	3.37 3.56 0-10	6.5 6.67 0-22	29.25 20.06 2-66	14.56 10.65 2-38	7 5.1 0-15
Heavy Drinking (HD) N = 15	**Mean:** **S.D.:** **Range:**	8.00* 11.56 0-40 HD > BD	11.47* 10.86 0-40 HD > BD/HC	14.00* 11.46 0-42 HD > BD/HC	61.87* (27.66) 4-99 HD > BD/HC	21.14 13.54 3-51	9.14 4.88 1-15
Healthy Controls (HC) N = 21	**Mean:** **S.D.:** **Range:**	3.37 5.12 0-20	3.56 4.88 0-16	5.68 6.74 0-24	33.19 (25.14) 0-75	13.11 11.41 0-37	5.94 4.45 0-14

Table 1. Psychological and Combat Information.

All standard deviation measures are noted in parentheses. Significance levels, marked by "*", have been set at $p < 0.05$, and group differences are indicated within the corresponding cells. Significant differences have been found in mean years of education (HD < HC), number of females, (HC > HD), number of smokers (HD > BD/HC), and mean CAPS scores (HD > BD/HC). Abbreviations: Standard Deviation (S.D); Depression and Anxiety S.S. (DASS); Clinician Administered PTSD Scale (CAPS); Deployment Risk and Resiliency Inventory II (DRRI).

Drinking Pattern		Demographic Characteristics				Health Information		
		Est. IQ	Age	Years of Edu.	Gender: Number of Females	Number of Smokers	Number of Military mTBI	Number of Meds. (Median)
Binge Drinking (BD) N = 16	**Mean:** **S.D.:** **Range:**	99.875 (12.53) 75 -119	34 8.35 23-46	14.13 2.16 12-18	1	3	0.375 (0.72) 0-2	0 (0.89) 0-3
Heavy Drinking (HD) N = 15	**Mean:** **S.D.:** **Range:**	99.93 (8.12) 83 -111	30.08 (7.17) 23-49	13.2 (1.23) 12-16	0	6* HD > BD/HC	1.9 (3.95) 0-16	1 (1.55) 0-5
Healthy Controls (HC) N = 21	**Mean:** **S.D.:** **Range:**	99.99 (9.33) 73 - 123	34.74 (10.19) 20-53	14.86 (2.22) 12-19	6* HC > HD	1	0.24 (0.54) 0-2	0 (0.29) 0-5

Table 2. Demographic and Health Information.

All standard deviation measures are noted in parentheses. Significance levels, marked by "*", have been set at $p < 0.05$, and group differences are indicated within the corresponding cells. Significant differences have been found in mean years of education (HD < HC), number of females, (HC > HD), number of smokers (HD > BD/HC), and mean CAPS scores (HD > BD/HC). Abbreviations: Estimated (Est.); Education (Edu.); Mild Traumatic Brain Injury (mTBI); Clinician-administered PTSD Scale (CAPS); Medications (Meds.).

Drinking Pattern	Alcohol Consumption Information					
		LDH total (weight corrected)	Mean Length of Total Drinking Time (in years)	SCID Alcohol Abuse	SCID Alcohol Dependence	Age of First Drink
Binge Drinking (BD)	**Mean:** **S.D.:** **Range:**	1,519.08 (582.13) 902.11 -3,189	17.09 6.89 7.4-30.6	Current: 1 Lifetime: 6	Current: 0 Lifetime: 4	17.25 2.35 13-21
Heavy Drinking (HD)	**Mean:** **S.D.:** **Range:**	2,437.42 (2,608.52) 254.5 -9,391.4	12.53 (9.12) 3 - 32.9	Current: 1 Lifetime: 2	Current: 3 Lifetime: 11	17.93 4.33 7-22
Healthy Controls (HC)	**Mean:** **S.D.:** **Range:**	*122.75 (239.68) 0 - 843.23 HC < BD/HD	N/A	Current: 0 Lifetime: 0	Current: 0 Lifetime: 0	17.48 6.23 0-24

Table 3. Alcohol Consumption Information.

All standard deviation measures are noted in parentheses. Significance levels, marked by "*", have been set at $p < 0.05$, and group differences are indicated within the corresponding cells. As expected, significant differences have been found between HD/BD groups and HC group in weight-adjusted LDH levels; HC < BD/HD. Although drinking onset age falls within the adolescent period (12-25), mean age of HD and BD onset was found to be significantly different; BD < HD. Abbreviations: Lifetime Drinking total (LDH), Structures Clinical Interview for DSM-IV (SCID). The "Age of First Drink" variable indicates the mean age at which a participant engaged in alcohol consumption for the first time, independent of pathological drinking patterns (these are denoted by the "Mean Age of

Comorbidity Information

Table 4 presents a breakdown of lifetime and current psychological disorders for each of the groups, as measured by the *Structured Clinical Interview for DSM-IV Axis I Disorders – Non-Patient Edition (SCID-I/NP)*. Numbers represent the number of individuals who met criteria for that diagnosis.

Psychiatric Diagnosis	Time of Diagnosis	Binge Drinkers (BD)	Heavy Drinkers (HD)	Healthy Controls (HC)	Significant Difference
Major Depressive Disorder - Single Episode	Current	0	3	0	HD > BD/HC
	Lifetime	3	1	3	None
	Both	0	2	0	None
Major Depressive Disorder - Recurrent	Lifetime	0	4	4	BD < HD/HC
Panic Disorder Without Agoraphobia	Lifetime	1	0	1	None
	Both	0	1	0	None
Social Phobia	Both	0	1	0	None
Specific Phobia	Both	0	1	0	None
Generalized Anxiety Disorder	Current	0	2	0	None
Alcohol Abuse	Current	1	1	0	None
	Lifetime	6	2	0	BD > HD/HC
Alcohol Dependence	Lifetime	4	8	0	HD > BD > HC
	Both	0	3	0	HD > BD/HC
Cannabis Dependence	Lifetime	0	1	0	None
Adjustment Disorder	Both	0	1	0	None
Total Diagnoses (Excluding Alcohol)	Current	0	5	0	HD > BD/HC
	Lifetime	4	6	8	None
	Both	0	6	0	HD > BD/HC
	Any	4	17	8	HD > BD/HC

Table 4. Psychiatric Diagnostic Information.

This table provides a breakdown of psychiatric diagnoses based on the DSM-IV SCID clinical interview. Frequencies of diagnosis that significantly differ between Groups have been verified using *Fisher's Exact* test, at a significance threshold level of $p < 0.05$. Specific group differences are indicated within the chart and highlighted. Abbreviations: HD = Heavy Drinkers; BD = Binge Drinkers; HC = Healthy Controls.

Aim 1 – Methods

Aim 1 examines the differential inhibitory and attention processing capacity using the affective Go/No-Go and Simple Reaction Time tasks. Tables 6 and 7 summarize the measures and statistical analyses used to evaluate this aim.

Go/No-Go task: Experimental Measures of Attention and Inhibition

The Go/No-Go task has been shown to be sensitive to the inhibitory and attention processing domains of cognitive function (Bezdjian, Baker, Lozano, & Raine, 2009). This test requires participants to quickly respond to a category of *Go Stimuli,* while withholding a response to stimuli that fall within the *No-Go* category (Murphy et al., 1999). Response biases, as evident by higher errors in response to specific stimuli and not others, are established after several blocks of this task (Elliott et al., 2004; Erickson et al., 2005). Impairments in inhibitory capacity are evident through errors of commission, which are defined as erroneous responses that should have been withheld (i.e., "go" responses to "no-go" stimuli) (Elliott et al., 2004; Erickson et al., 2005). Additionally, difficulties within the domain of inhibitory capacity can be evaluated via the response latency for commission errors: the amount of time, measured in milliseconds, that it takes for participants to make an erroneous response. Longer latency is evidence of delayed processing time and difficulties in processing the specific stimuli. Inattention is measured via errors of omission: not making a response within a designated amount of time, when a response is required (i.e., "no-go" responses to "go" stimuli).

The *affective* version of the Go/No-Go task (AGN) has been used as it contains stimuli that are divided into positive and negative valence categories (Murphy et al., 1999). These components are designed to examine affect-specific biases within attention and inhibitory function. This task consists of 10 blocks, 2 of which are practice and 8 are testing blocks. Each block consists of 18 stimuli divided into 9 negative and 9 positive stimuli, presented in a randomized and counterbalanced for valence. At the beginning of each block, the participant is told which valence stimuli is a target (i.e., which one they should press the button for, and which to ignore). Each stimulus is presented for 300 milliseconds, followed by a 900 millisecond inter-stimulus-interval. See Figure 3 for a sample schematic of an AGN task.

In the current study, AGN test was used to determine specific differential deficiencies in BD and HD participants within the domains of attention and response inhibition. Lapses in attention have been measured via omission errors, and examined within positive and negative affect stimuli. Inhibitory decrements have been measured via commission errors and also examined within positive and negative affect stimuli. Additionally, processing difficulties has been measured via delayed responses (latencies) in each respective condition. Finally, speed-accuracy tradeoff has been measured in each affective condition as an indicator of impaired performance under pressure (deficiencies in cognitive resource allocation).

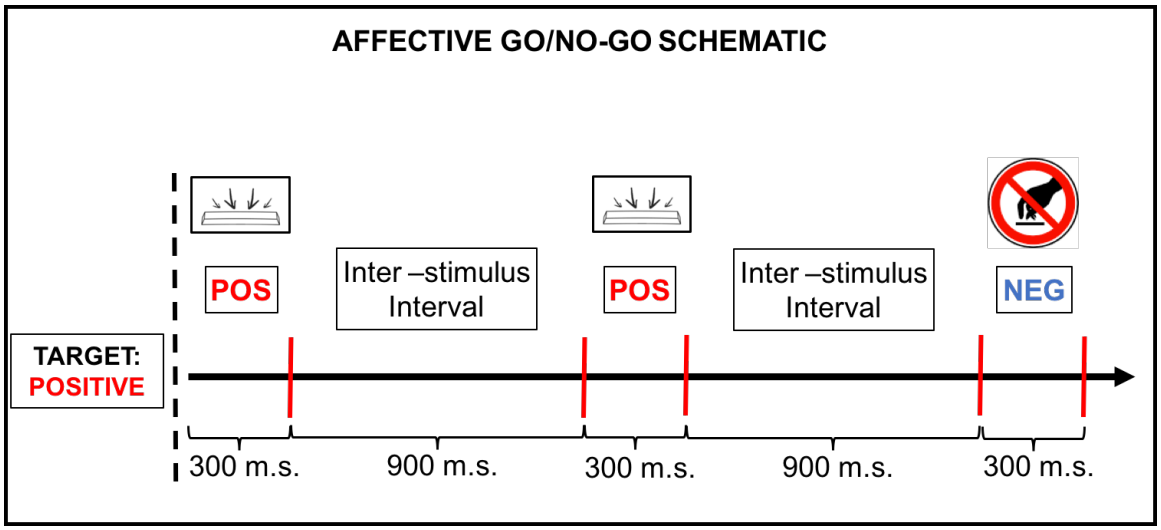

Figure 3. Affective Go/No-Go Schematic.

This schematic is an example of a portion of an Affective/Go/No-Go block. As evident from the left box, participants are presented with a target valence stimulus for which they are instructed to press a button whenever it appears. Stimuli with non-target valence words require participants to withhold a button press. Each stimulus was presented for 300 milliseconds, followed by a 900 millisecond inter-stimulus interval prior to the presentation of the next stimulus. There was a total of 10 blocks, divided into two practice and eight testing blocks. Each block consisted of 18 stimuli, divided into nine positive and nine negative valence types. The order of stimulus presentation has been pseudo-random, counterbalancing the order of target valence stimuli within and between blocks. Abbreviations: POS = Positive; NEG = Negative; m.s. = milliseconds.

Below are the definitions of the dependent measures that were used in the current analysis from the AGN task:

(1) Commission Errors: Inappropriate responses at times when they should have been withheld. These measures have been collapsed across all conditions: positive and negative stimuli.

(2) Omission Errors: Lack of responses at times when responses are required. These measures have been collapsed across all conditions: positive and negative stimuli.

(3) Response Latency: For all correct responses, response latency has been recorded. It is defined as the time it takes to make a response, after the stimulus has been presented.

(4) Speed Accuracy Tradeoff: This is a linear function used to assess whether participants perform worse (by making more errors) as their speed increases.

Simple Reaction Time Task: Control Measure of Reaction Time Speed

The Cambridge Neuroscientific Test Automated Battery *Simple Reaction Time Task* (Lowe & Rabbitt, 1998) was used as a control measure that was not expected to differ across our AUD groups. The following dependent variable has been used from this task:

Simple Reaction Time: This is the time it takes participants to make a button-press response after a presentation of a response-prompt.

Aim 1 - Analyses

Aim 1 examines attention, inhibitory, and reaction time differences between BDs, HDs and HCs. Tables 5 and 6 summarize the measures and statistical analyses used to evaluate this aim.

Aim	Statistical Model(s)	Independent Variables	Dependent Variables	Covariates	Corrections for Multiple Comparisons
1	Initial: ANOVA Post-Hoc: Tukey's HSD Tests	3 Groups: 1. Binge Drinkers 2. Heavy Drinkers 3. Healthy Controls	10 Affective Go/No-Go Variables: 1. Positive Stimulus Latency 2. Negative Stimulus Latency 3. Total Omission Errors 4. Total Commission Errors 5. Positive Stimulus Errors 6. Negative Stimulus Errors 7. Positive Commission Errors 8. Negative Commission Errors 9. Positive Omission Errors 10. Negative Omission Errors	1. Gender (number of females). 2. Number of smokers. 3. Total CAPS severity Score. 4. DASS Anxiety sub-score. 5. DASS Depression sub-score. 6. DASS Stress sub-score. 7. Number of single depression episodes (current). 8. Number of recurrent depression episodes (lifetime).	Group-wise: False Discovery Rate (FDR) Familywise: Tukey HSD

Table 5. Aim 1 Analysis Information.

This table summarizes the statistical models, variables, and corrections for multiple comparisons for Aim 1. None of the covariates have been found to be significant as a result of backward regression models (using total errors as a dependent measure) and, therefore, they have not been included in the final analyses. Abbreviations: ANOVA: Analysis of Variance; HSD: Honest Significance Difference; CAPS: Clinician Administered PTSD Scale for DSM-IV; DASS: Depression Anxiety Stress Scale.

Aim	Statistical Model(s)	Independent Variables	Dependent Variables	Covariates	Corrections for Multiple Comparisons
1	Initial: ANOVA Post-Hoc: Tukey's HSD Tests	3 Groups: 1. Binge Drinkers 2. Heavy Drinkers 3. Healthy Controls	1 Simple Reaction Time Variable: 1. Mean Correct Latency Reaction Time	1. Gender (number of females). 2. Number of smokers. 3. Total CAPS severity Score. 4. DASS Anxiety sub-score. 5. DASS Depression sub-score. 6. DASS Stress sub-score. 7. Number of single depression episodes (current). 8. Number of recurrent depression episodes (lifetime).	Group-wise: False Discovery Rate (FDR) Familywise: Tukey HSD

Table 6. Aim 1 Additional Analysis Information.

This table summarizes the statistical models, variables, and corrections for multiple comparisons for the control task of Aim 1. Abbreviations: ANOVA: Analysis of Variance; HSD: Honest Significance Difference; CAPS: Clinician Administered PTSD Scale for DSM-IV; DASS: Depression Anxiety Stress Scale.

Between-group differences in dependent measures have been assessed using an ANOVA model in JMP software (SAS Institute Inc., 1989-2016.). Significant results ($p < 0.05$) have been adjusted for multiple comparisons using the False Discovery Rate (FDR) correction. Student's t-tests have been conducted for all significant results, to examine specific between-group differences, with the corresponding correction for multiple comparisons. Tables 5 and 6 summarize all variables and statistical tests for these

analyses. Results surviving these corrections have been taken into account if the following conditions have been met:

(1) Visual inspections for outliers have been performed, making sure a few outliers do not drive results.
(2) Pathological drinking groups differ from the control group, as well as from each other. Since the objective of these tests is to identify differential characterization of pathological drinking patterns, satisfaction of both conditions is essential.
(3) Results are replicated after including the identified covariates in the statistical models.

Covariates

In order to determine the relative effect of covariates on the dependent measures, the steps below have been taken. This approach does not assume that all covariates impact the dependent measures in the same way and, consequently, allows for flexible models, with each model adjusted for the respective dependent measure. For example, the *depression* covariate might have an effect on temporal region dependent measure while the *anxiety* covariate might impact insular region dependent measure to a greater extent. Thus, separate models have been built for each dependent variable. This is a data-driven approach that allows for identification of significant covariates that are related to the dependent measures within the current sample. The following steps have been taken to identify covariates that might have impacted the dependent measures.

(1) Step-wise regression with backward substitution have been run for variables that have been identified as covariates (listed within the "**Participants**" section). These models used each of the identified covariates as independent measures. Covariates that showed a significant effect on the dependent measures have been included in the ANOVA models (see next step).

(2) The original ANOVA models have been re-run with the inclusion of identified covariates (as identified in Step 1).

(3) In cases when ANOVA showed significant results, post-hoc tests (using Student's t-tests comparisons) have been run.

Aim 2 – Methods

Aim 2 examines the whole-brain subcortical volumetric differences between BDs, HDs and HCs. Table 7 summarizes the measures and statistical analyses used to evaluate this aim.

Aim	Statistical Model(s)	Independent Variables	Dependent Variables	Covariates	Corrections for Multiple Comparisons
2	Initial: ANOVA Post-Hoc: Tukey's HSD Tests	3 Groups: 1. Binge Drinkers 2. Heavy Drinkers 3. Healthy Controls	Subcortical Brain Structures, Adjusted for Brain Volume.	1. Gender (number of females). 2. Number of smokers. 3. Total CAPS severity Score. 4. DASS Anxiety sub-score. 5. DASS Depression sub-score. 6. DASS Stress sub-score. 7. Number of single depression episodes (current). 8. Number of recurrent depression episodes (lifetime).	Group-wise: False Discovery Rate (FDR) Familywise: Tukey

Table 7. Aim 2 Analysis Information.

This table summarizes the statistical models, variables, and corrections for multiple comparisons for Aim 2. The "number of smokers" covariate has been found to have a significant impact on the dependent measure, and has therefore been included in the final model. Abbreviations: ANOVA: Analysis of Variance; HSD: Honest Significance Difference; CAPS: Clinician Administered PTSD Scale for DSM-IV; DASS: Depression Anxiety Stress Scale.

MRI structural data was acquired in the Neuroimaging Research for Veterans Center (NeRVe) at VA Boston using a Siemens 3T TIM Trio system with a 12-radiofrequency channel head coil. For each subject, two T1-weighted MPRAGE scans were collected [3D sequence, flip angle 7°, acquisition matrid= 256×256, echo time=3.32 ms, repetition time=2530 ms, slice thickness=1 mm, TE= 3.32, in-plane resolution= 1.0 mm^2, 176 sagittal slices] and then averaged to increase the signal to noise ratio. The data was stored and processed at the NeRVe Image Processing Cluster.

Aim 2 – Analyses

Image Preprocessing

Volumetric neuroimaging data were preprocessed using the standard FreeSurfer processing stream (Fischl & Dale, 2000). The volumetric preprocessing stream generated 31 raw volumetric measurements (in mm^3) for grey matter subcortical segmentations and 68 volumetric measurements for white matter segmentations (Fischl et al., 2002; Hommer, Momenan, Kaiser, & Rawlings, 2001). The measurements have been calculated using the Desikan 2006 and Salat 2009 atlases (Desikan et al., 2006; Salat et al., 2009). Prior to measuring the volumetric regions of interest, the data went through an affine registration using the Montreal Neurological Institute atlas (MNI305) space with the correction of the B1 bias field (generated from the radiofrequency pulse). The total volume was then labeled using the subject-specific measurements, as well as a probability atlas for greatest accuracy (Fischl et al., 2002).

Given the identified effects of subcortical structural scaling with total head size, correcting those structures for total brain volume is important before analyses can be done. The subcortical structures in these analyses have been corrected for the estimated total intracranial volume (eTIV). eTIV has been derived automatically by calculating the linear transformation factor between the total intracranial volume and the MNI305 space (R. L. Buckner et al., 2004). Since total intracranial volume has been found to correlate with the transform matrix, as derived from spatial normalization, this method was expected to provide a reasonable estimate. The volume of each individual structure was then corrected by taking the ratio of that structure to the eTIV.

Identification of Covariates

Covariates have been identified and handled using the same approach as described within the *covariate* section for **Aim 1**.

Volumetric Analyses. Ten ANOVA tests were conducted with Drinking Groups as the independent variable, and each volumetric ROI used as a dependent measure (independently) without any covariates. Volumetric ROIs with alpha levels below 0.05 have been identified and corrected for multiple comparisons using the FDR adjustment. The original regression was then re-run with the identified significant covariates included from the stepwise regression (method described within the *Covariate* section above). Age was added as a covariate to all analyses due to previous findings indicating its effect on brain tissue. Post-hoc tests, using the Student's t-test comparisons have been run on the resulting dependent measures that remain significant.

Aim 3 – Methods

Aim 3 examines whole-brain cortical thickness between BDs, HDs, and HC.

Table 8 summarizes the measures and statistical analyses used to evaluate this aim.

Aim	Statistical Model(s)	Independent Variables	Dependent Variables	Covariates	Corrections for Multiple Comparisons
3	2-tailed t-test.	Binge Drinkers Versus Healthy Controls Heavy Drinkers Versus Healthy Controls	Whole brain voxel-based cortical thickness.	1. Gender (number of females). 2. Number of smokers. 3. Total CAPS severity Score. 4. DASS Anxiety sub-score. 5. DASS Depression sub-score. 6. DASS Stress sub-score. 7. Number of single depression episodes (current). 8. Number of recurrent depression episodes (lifetime). 9. Age.	Cluster-wise correction for multiple comparisons (simulation with 5,000 iteration). Voxel-wise correction for multiple comparisons.
3	1-tailed t-test (negative)	Binge Drinkers Versus Heavy Drinkers	Whole brain voxel-based cortical thickness.	Same as above.	Same as above.

Table 8. Aim 3 Analysis Information.

This table summarizes the statistical models, variables, and corrections for multiple comparisons for Aim 3. Abbreviations: HSD: Honest Significance Difference; CAPS: Clinician Administered PTSD Scale for DSM-IV; DASS: Depression Anxiety Stress Scale.

Cortical thickness is a measure of thickness of grey matter tissue on the surface of the brain with strong evidence linking it to a number of pathological conditions (Fischl & Dale, 2000). A common way of measuring brain tissue in this manner is to use structural MRI scans, and superimpose a mesh around the brain using the FreeSurfer software (Desikan et al., 2006). This method (explained in more detail below) computes grey matter thickness measures in millimeters squared (mm^2) for regions that can be identified via customizable and standardized atlases (Fischl, Liu, & Dale, 2001; Fischl, Sereno, Tootell, & Dale, 1999; Ségonne, Pacheco, & Fischl, 2007). A particular advantage of this approach is the power to localize and compare regional brain differences between pathological samples and healthy controls (Rosas et al., 2002; Salat et al., 2004). This method has been validated by using manual methodology (Kuperberg et al., 2003; Salat et al., 2004) as well as histological approaches (Rosas et al., 2002). In addition to gaining anatomical information, these measures are relatable to various trait and cognitive components of participant's psychological functioning (see (Kühn, Schubert, & Gallinat, 2011; Rajkowska et al., 1999) for examples). The data have been collected and stored using the same methods as described in the **Aim 2** section for subcortical volume.

Aim 3 – Analyses

Image Preprocessing

Two T1-weighted MPRAGE scans have been averaged together for each subject, using a combination of FreeSurfer and FSL tools (Desikan et al., 2006; Fischl et al.,

2004; S. M. Smith et al., 2004; Woolrich et al., 2009). First, Different-Offset, Different-Slope (DODS) files have been created for each analysis along with corresponding contrast matrix files; the matrix files reflected the main contrast of each analysis, along with nuance measures (covariates described below). Each subject's data was then resampled into common space (using FreeSurfer's fsaverage subject), and concatenated into a single file. The data have been smoothed at 15 full-width/half-max (FWHD) for each hemisphere. Most of these preprocessing steps have been repeated for each analysis listed below, using different covariates and contrasts and for each hemisphere.

Statistical Analyses

The main contrasts using 2-tailed t-tests have been run comparing each group, with "age" as a covariate for whole-brain analyses; planned comparisons included: (1) BD vs. HC, (2) HD vs. HC, and (3) BD vs. HD (to confirm unique signature of each pathology). Age was included as a covariate in all analyses due to prior work indicating the sensitivity of brain tissue to aging. The analyses have been rerun to include other covariates in the models, and are described in the *Covariate* section below. Vertex and cluster-wise corrections for multiple comparisons have been applied using the $p < 0.05$ as a threshold.

Cluster-wise correction for multiple comparisons involves using a simulation producing maximal cluster size measures under a null hypothesis (i.e. BD = HC). The simulation has been produced by synthesizing a smoother z map of the data thresholded at the designated significance level. After the resulting clusters have been identified from

each simulation run, the area of the maximal cluster has been recorded, and the simulation process has been repeated for 5,000 iterations. The original data was then thresholded using the same level for each cluster.

Covariates. As mentioned above, "age" has been included as a covariate in all statistical analyses, due to its noted effects on brain tissue. Variables that have been identified as significantly different between the Main Groups **(**BD, HD, and HC) were also included as covariates in separate models. In order to examine their maximal effects on brain thickness, a separate analysis has been run, including each of the variables as a covariate, in addition to "age." All analysis steps above were repeated for each of the 9 models. Table 8 summarizes all variables and statistical test for these analyses.

Resulting clusters have been taken into account if and only if they satisfy the following three conditions: (1) significantly differ between each pathological group (BD ≠ HD), as well as the control group (BD | HD ≠ HC); (2) survive the voxel and cluster-wise correction for multiple comparisons; (3) remain significant in in each of the models, controlling for covariates.

Obtaining Final Clusters. Finally, given the lack of 100% overlap between the clusters, their combined effect has been calculated. This has been accomplished by calculating the geometric intersection of all clusters, after overlaying them over one another. Geometrically, the intersection of several ROIs can be expressed as follows, in terms of hypothetical smaller ROI sets:

If: $ROI_1 = \{ROI_a, ROI_b, ROI_c, ROI_d, ROI_e\}$
$ROI_2 = \{ROI_b, ROI_e, ROI_g, ROI_w\}$
Then:
$ROI_1 \cap ROI_2 = \{ROI_b, ROI_e\}$

The logic motivating this approach is akin to that of a Venn diagram; only the overlapping effect that remains significant after all covariate effects are taken into account is of interest. The resulting cluster region-of-interest (ROI) is thus shrunk to represent the surviving effect of pathological drinking patterns.

Effect of Drinking Patterns on Yeo Networks. In order to localize and better identify the spatial effect of drinking patterns on cortical tissue, the generated ROI(s) from the above process has been quantified according to their impact on brain networks. The Yeo cortical network atlas has been used, comprising a 7-network solution. The geometric intersection was calculated between each of the ROIs and the type and percentage of networks that they impact. This provided quantifiable information pertaining to the extent and type of an effect that drinking patterns have on major brain networks. See Figure 4 for a Yeo Network atlas overview.

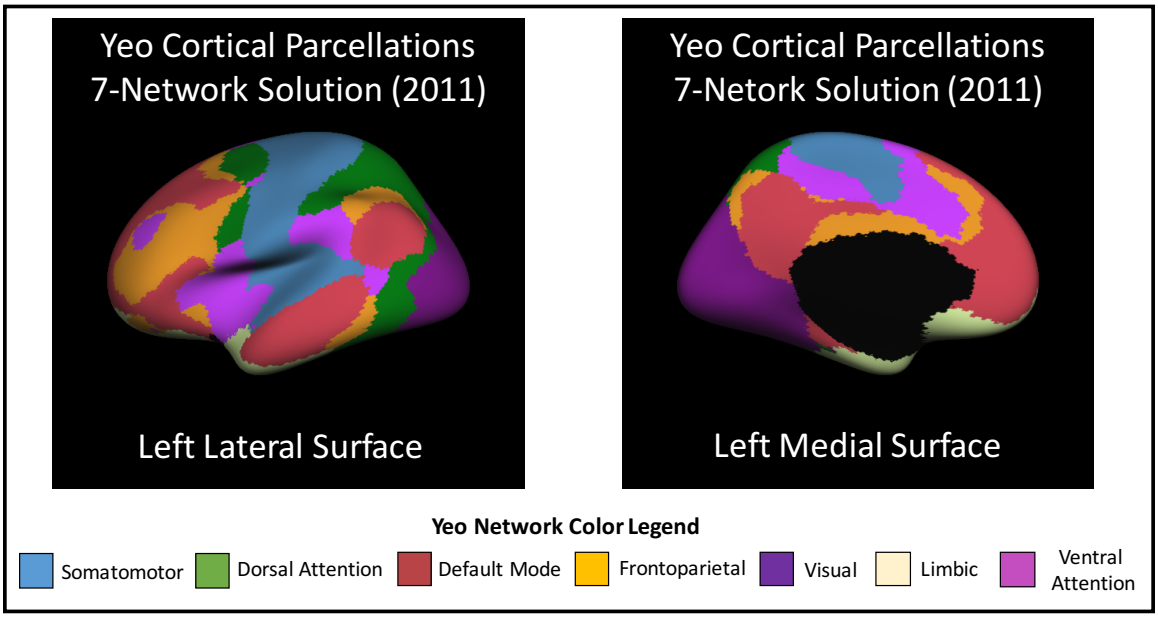

Figure 4. Yeo 7 Network Solution.

Cortical parcellation atlas (left) and confidence measures (on the right) of the Yeo brain networks – 7 Network Solution. Original images have been obtained from (Yeo et al., 2011) and modified to better fit with the focus of this project; permissions are not required for this type of a replication (as indicated by RightsLink).

CHAPTER 3 – RESULTS

Aim 1 – Cognitive Function Results

Summary

Behavioral results indicate that pathological drinking patterns are associated with differential findings on the AGN task. The HD group has shown a diminished inhibitory and attention performance in comparison to other groups (BDs and HCs), while BD participants were not found to have diminished performance in any of the measures in comparison to other groups. All results have been corrected for multiple comparisons using the FDR correction. Additionally, the ANOVA results have survived the stepwise backward regression models in order to test for covariates' effects.

Affective Go/No-Go Task

Heavy Drinkers. ANOVA and post-hoc t-tests revealed that the HD group produced significantly more errors on the AGN task, in comparison to BD and HC participants ($F(2,49) = 5.17$, $p = 0.009$; HD > BD, $p = 0.0106$; HD > HC, $p = 0.0046$). Errors have been further broken down into different types (valence type, commission, and omission), in order to examine whether the total elevated number of errors was driven by a specific error subtype.

Analyses examining errors of commission, indicated an elevated rate of this error type in the HD group in comparison to other groups ($F(2,49) = 5.23$, $p = 0.009$; HD > BD, $p = 0.0099$; HD > HC, $p = 0.0045$). Additional analyses aimed at separating errors of commission into positive and negative valence stimuli showed that both valence stimuli

were significantly higher in HDs. Specifically, total commission errors in response to positive valence stimuli ($F(2,49) = 5.38$, $p = 0.008$; HD > BD, $p = 0.0051$; HD > HC, $p = 0.0066$) were significantly higher in the HD group, as compared to BD and HC groups. Similarly, total commission errors in response to negative valence stimuli ($F(2,49) = 4.3$, $p = 0.02$; HD > BD, $p = 0.0349$; HD > HC, $p = 0.0066$) followed the same pattern.

Errors of omission were shown to be elevated in HDs in comparison to other groups, at a level that approached significance ($F(2,49) = 4.4$, $p = 0.0899$; HD > BD, $p = 0.042$; HD > HC, $p = 0.071$). Given the lack of significant findings for omission errors, follow-up statistical tests aimed at examining valence interactions were not conducted.

Analyses aimed at examining errors in response to valence types (positive and negative), collapsed across omission and commission conditions, revealed an elevated number of errors in the HD group for both valence categories, in comparison to BDs and HCs. Specifically, total errors in response to positive valence stimuli ($F(2,49) = 5.24$, $p = 0.008$; HD > BD, $p = 0.0097$; HD > HC, $p = 0.0045$), as well as negative valence stimuli ($F(2,49) = 4.31$, $p = 0.0189$; HD > BD, $p = 0.02$; HD > HC, $p = 0.0089$) have been found to be higher in HDs, in comparison to other groups. Figure 5 displays the main results of these findings.

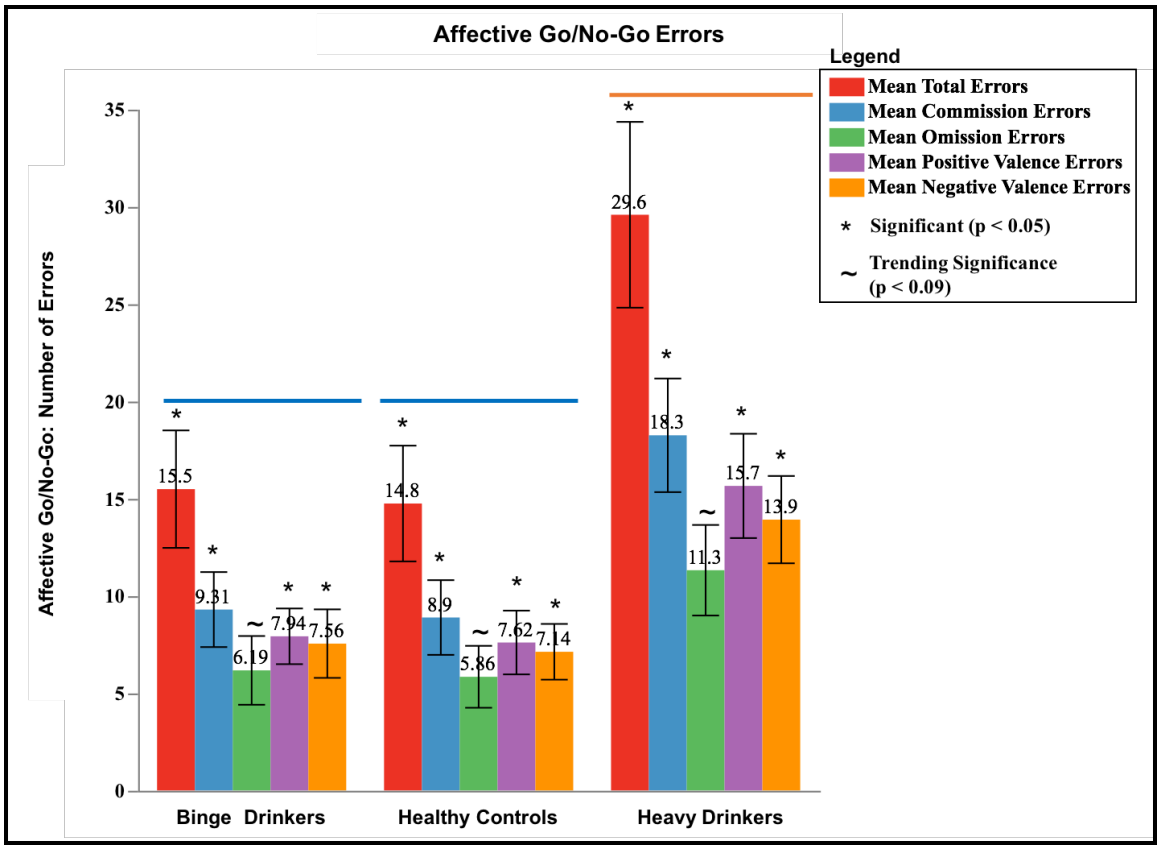

Figure 5. Affective Go/No-Go Errors.

The Heavy Drinking (HD) group has shown a significantly higher number of total valence errors in comparison to the Binge Drinking (BD) and Healthy Control (HC) groups. Additionally, mean commission errors, mean omission errors, mean positive, and mean negative errors were significantly higher within the HD group, in comparison to other groups. Mean omission errors were shown to trend significance within the HD group, in comparison to other groups. BD Mean = 15.5, BD Standard Deviation = 3.69; HD Mean = 29.6, HD Standard Deviation = 3.8; HC Mean = 14.76; HC Standard Deviation = 3.22. ANOVA: $p < 0.0092$; Student's t-tests: BD < HD $p < 0.028$; HC < HD $p < 0.013$.

Binge Drinkers. The BD group was not found to have a higher number of commission or omission errors in comparison to other groups ($p = 0.5$).

Simple Reaction Time Task

As predicted the SRT measure did not reveal any significant group differences for the HD group ($F(2,49) = 0.96$, $p = 0.39$). See Figure 6 for a graphical representation of these findings.

These results indicate a possible global attention and inhibitory processing deficit within HD participants that is likely independent of valence, since both valence stimuli are associated with higher errors. Lack of significant findings within the control SRT task indicates a dissociative finding specific to inhibitory impairment, rather than a more general reaction time deficit.

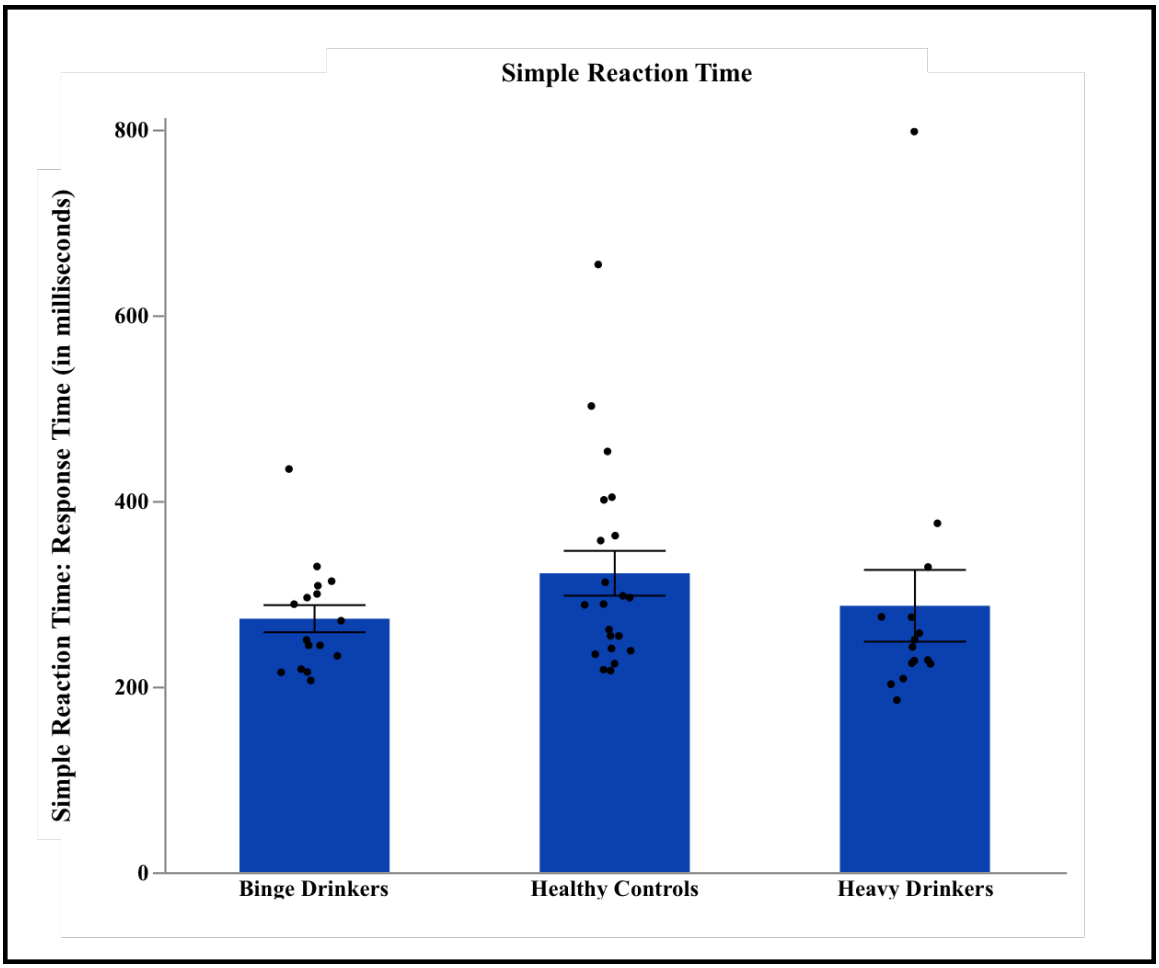

Figure 6. Simple Reaction Time.

This figure displays mean levels of performance on the simple reaction time task between the Binge Drinkers (Mean = 272.916), Heavy Drinkers (Mean = 286.836), and Healthy Controls (Mean = 321.829) as measured by the analysis of variance test (ANOVA). The mean differences between groups were not found to be significant ($p > 0.05$).

Aim 2 - Volumetric Results

Summary

ANOVA examining group differences in the volumetric data revealed a significant overall effect for the bilateral globus pallidus ($F(2,49) = 6.63$, $p = 0.0028$). Post-hoc t-tests showed that the levels are smaller within the BD group as compared to HD group (BD < HD, $p = 0.0007$), as well as between the BD group as compared to HC group (BD < HC, $p < 0.0234$). Additionally, analyses have shown a significant overall effect for the ventral diencephalon region in both pathological drinking groups ($F(2,49) = 5.23$, $p = 0.0087$). The region was reduced in BD in comparison to HC (BD < HC, $p < 0.0023$) and reduced at a level approaching significance in HD in comparison to HC (HD < HC, $p < 0.0969$).

These analyses have been adjusted for intracranial volume, tested with the relevant covariates, as well as corrected for group and familywise multiple comparisons. Stepwise backward regression models revealed “smoking status” and “age” to be significant covariates for the ventral diencephalon measure and therefore have been included in the final linear models; results remained significant after the inclusion. Figures 7 and 8 display the individual and group means for the bilateral globus pallidus and ventral diencephalon structures, respectively. As evident in Figure 8, the bilateral diencephalon measure shows two outliers within the HC and HD groups; the models were re-tested after the removal of the outliers and were confirmed to remain significant.

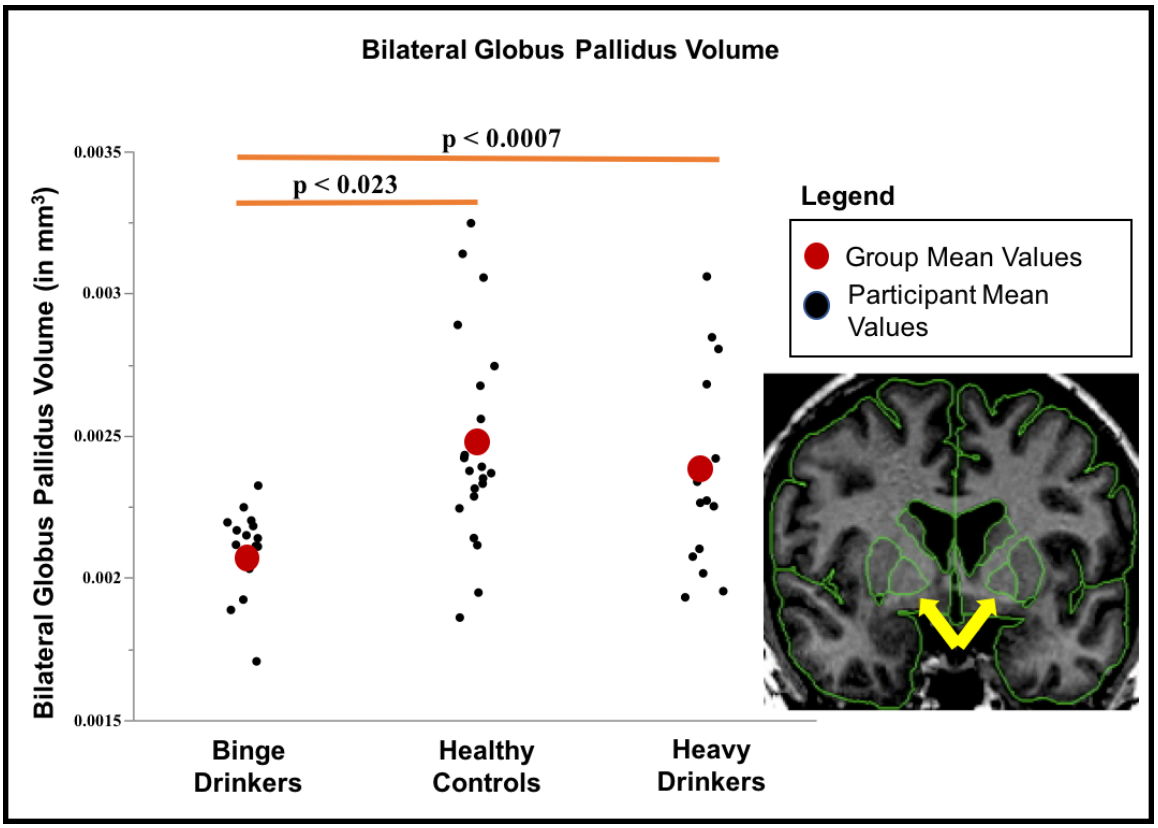

Figure 7. Bilateral Globus Pallidus Volume.

The black dots represent subject-specific mean values (in mm^3) for the bilateral globus pallidus volume. The red dots indicate mean values for each of the respective groups (Binge Drinkers: 0.0021 mm^3, Heavy Drinkers: 0.0024 mm^3, Healthy Controls: 0.0025 mm^3). The Binge Drinking group's volumetric mean values are smaller in comparison to Healthy Controls' ($p < 0.023$) and Heavy Drinkers' ($p < 0.0007$). The image on the right is an example of a one-slice segmented FreeSurfer volume with the globus pallidus indicated by the yellow arrows.

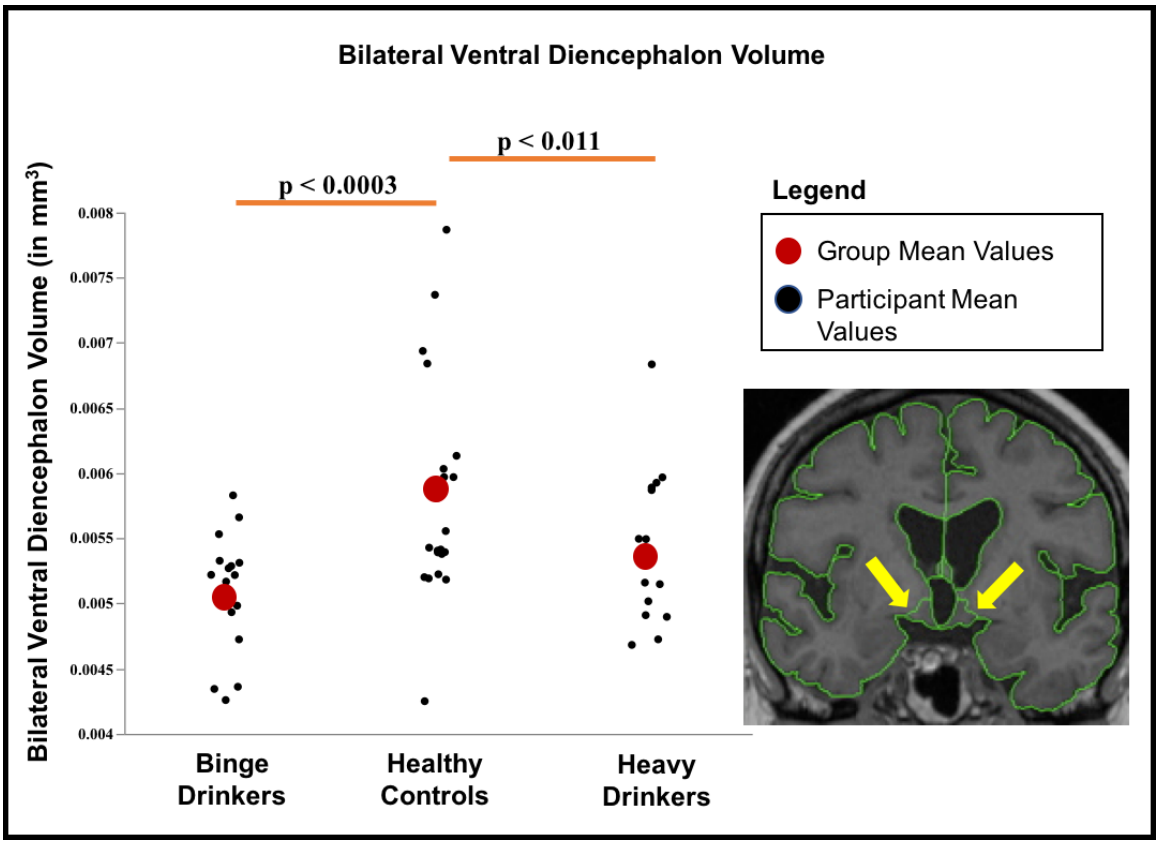

Figure 8. Bilateral Ventral Diencephalon Volume.

Black dots represent subject-specific mean values (in mm^3) for the bilateral ventral diencephalon volume. The red dots indicate mean values for each group (Binge Drinkers: 0.0051 mm^3, Heavy Drinkers: 0.0054 mm^3, Healthy Controls: 0.0058 mm^3). Both pathological drinking groups show volumetric mean values that are smaller in comparison to Healthy Controls ($p < 0.05$). The image on the right is an example of a one-slice segmented FreeSurfer volume with the ventral diencephalon indicated by the yellow arrows.

Aim 3 – Cortical Thickness Results

Summary

Reduced cortical thickness was found in the BD group in the left superior parietal region compared to the HD and HC groups. The resulting cluster overlaps with volitional control attention networks. The HD group had larger left occipital cortical thickness compared to the BD and HC groups, which primarily overlaps with the visual network, as well as other networks to a lesser extent.

Binge Drinkers

Cortical thickness analyses revealed a significantly smaller cluster within the left superior parietal region in the BD group, as compared to HD and HC groups (BD < HD, $p < 0.05$; BD < HC, $p < 0.05$). Smoothing was set at 15 FWHD and $p < 0.05$ threshold was used for vertex as well as cluster values. Age was included as a covariate in all analyses, and t-tests have been rerun with the inclusion of each potential confounding variable (identified in the previous chapter) separately. Results remained significant after the inclusion of covariates. Results from group comparisons are presented in Figure 9, and significant cluster group, as well as individual subject, mean values are displayed in Figures 10 and 11.

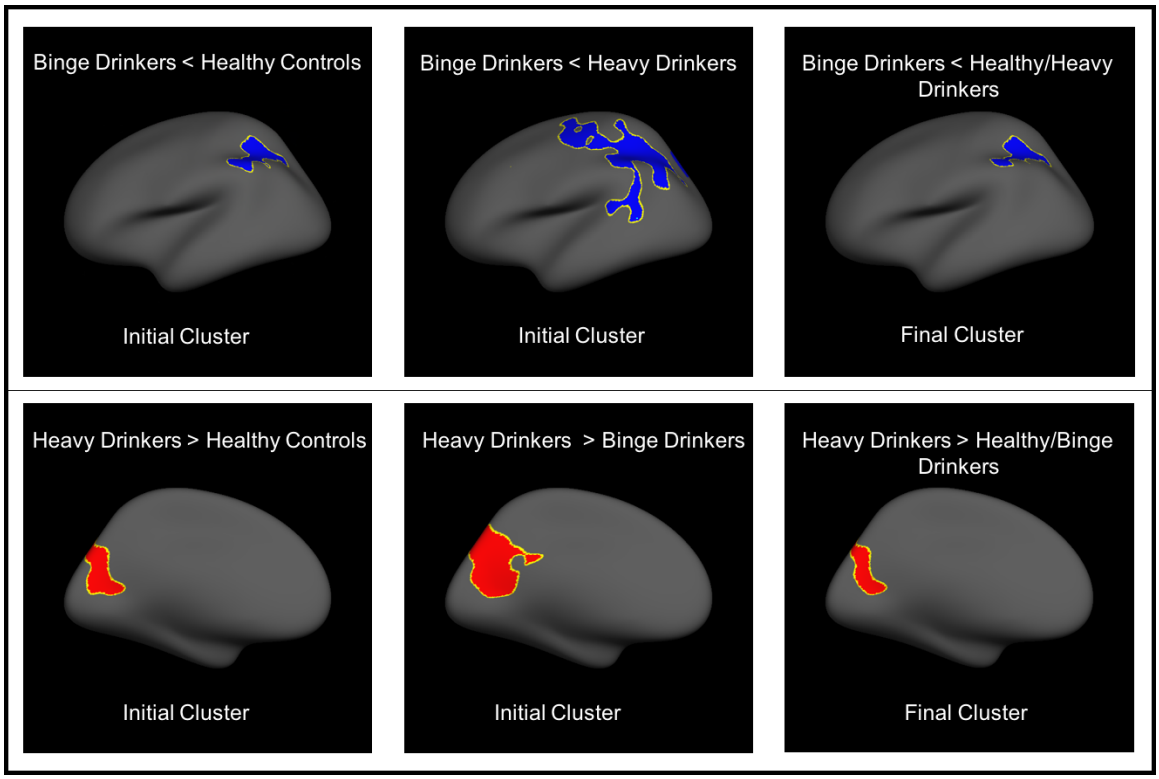

Figure 9. Significant Clusters for Group Comparisons.

These images are a visual representation of t-test results. The tests were used to compare pathological drinking groups to one another, as well as to healthy controls. The vertex and cluster p-values have been set at $p < 0.05$ and smoothing has been set at 15 FWHD. Age has been used as a covariate in these analyses and additional nuisance variables have been examined separately. Clusters within the upper row (in blue) show significantly smaller cortical thickness values localized to the left superior parietal region within the Binge Drinking Group, as compared to Healthy Controls (upper left), Heavy Drinkers (upper middle), as well as the geometric intersection of the two clusters (upper right). The upper right cluster indicates a differential effect of Binge Drinking as compared to all other groups. The lower row displays an effect of Heavy Drinking via larger cortical thickness values within the left occipital cortex (in red). The bottom left image indicates higher values within the Heavy Drinking group as compared the healthy controls, the bottom middle image indicates higher values within the Heavy Drinking group as compared Binge Drinkers. The bottom right image indicates a geometric intersection of these two clusters, showing differentially larger values within the Heavy Drinking group, as compared the Healthy Controls as well as Binge Drinkers.

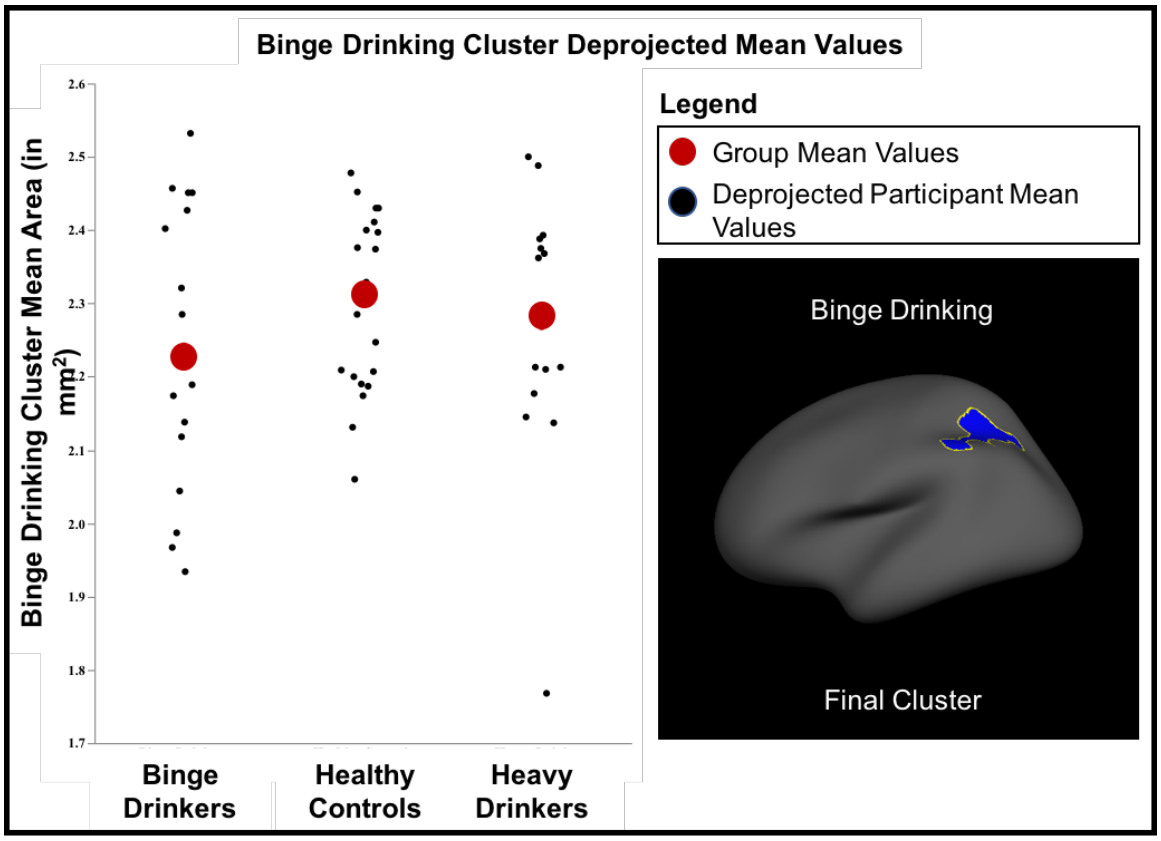

Figure 10. Group and Individual Mean Values for the Binge Drinking Cluster.

The scatterplot on the left indicates individual (in black) and group (in red) mean values for Binge Drinkers (Mean: 2.24 mm^2, Standard Deviation: 0.2), Heavy Drinkers (Mean: 2.27 mm^2, Standard Deviation: 0.18), and Healthy Controls (Mean: 2.3 mm^2, Standard Deviation: 0.12). These mean values are extracted from the Binge Drinking cluster displayed on the right-hand side of the image (Binge Drinking < Heavy Drinking/Healthy Controls; $p < 0.05$; FWHD = 15).

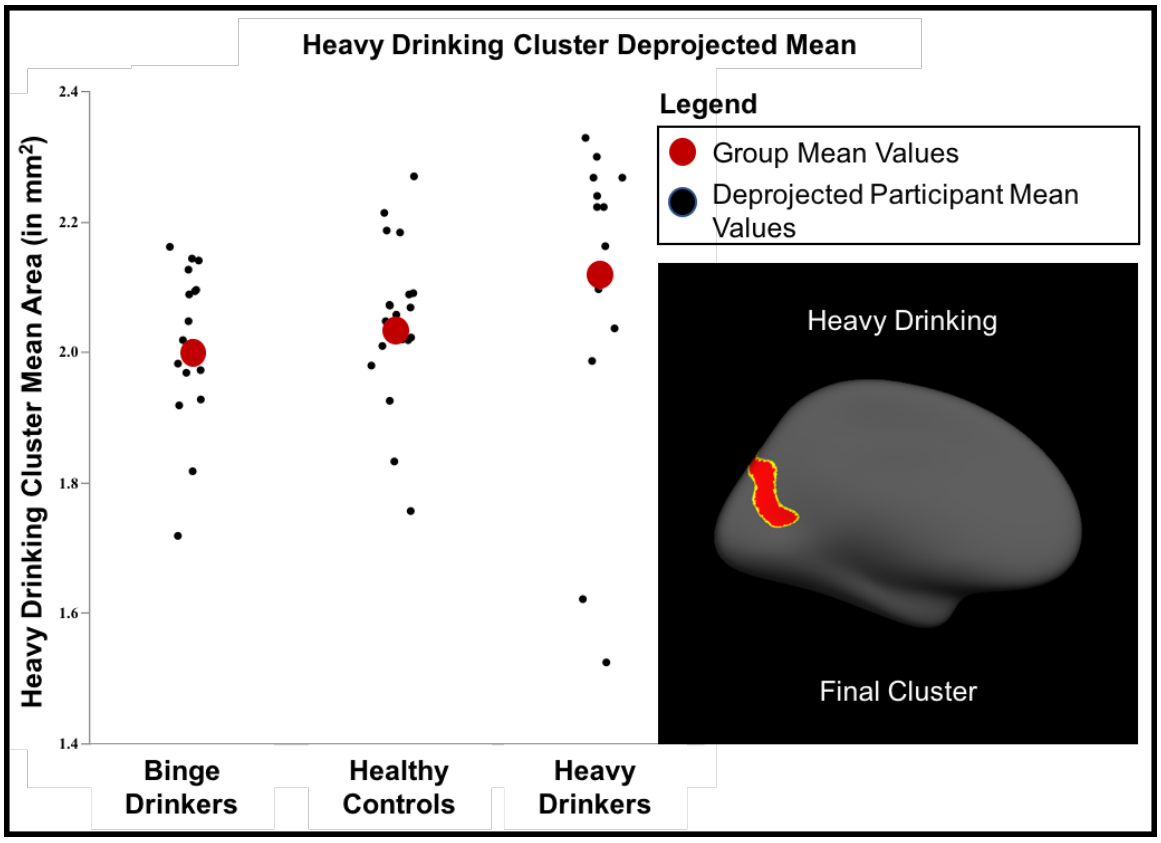

Figure 11. Group and Individual Mean Values for the Heavy Drinking Cluster.

The scatterplot on the left indicates individual (in black) and group (in red) mean values for Heavy Drinkers (Mean: 2.1 mm^2, Standard Deviation: 0.24), Binge Drinkers (Mean: 2.01 mm^2, Standard Deviation: 0.12), and Healthy Controls (Mean: 2.05 mm^2, Standard Deviation: 0.12). The mean values have been extracted from the Heavy Drinking cluster displayed on the right-hand side of the image (Heavy Drinking > Binge Drinking/Healthy Controls; $p < 0.05$; FWHD = 15).

Given that each t-test (BD vs. HD, BD vs. HC, as well as a separate model for each of the covariates) generated overlapping but slightly different clusters, the initial result (described above) has been shrunk in order to isolate the main effect of each drinking pattern. This has been done by taking an intersection of all resulting clusters ($CLUSTER_1 \cap CLUSTER_2 \cap CLUSTER_n$), and generating a final ROI, which consists of areas that all t-test results have in common. The final BD ROI is presented in the top row of Figure 12, representing the unique and differential effect of BD.

Heavy Drinkers

Results for the HD group show a larger cluster within the left medial occipital lobe in comparison to the BD and HC groups (HD > BD, $p < 0.05$; HD > HC, $p < 0.05$). Smoothing has been set at 15 FWHD, and $p < 0.05$ threshold has been used for vertex as well as cluster values. Age has been included as a covariate in all analyses, and t-tests have been rerun with the inclusion of each potential confounding variable (identified in the previous chapter) separately.

Results from the HC vs. BD comparison are presented in Figure 9 and significant mean values for cluster group and for individual subjects, mean values are presented in Figure 11.

Binge versus Heavy Drinkers

The significant region has been reduced to accommodate covariates' effects, following the same procedure as described for BD analyses. Results of the resulting cortical cluster intersections are presented in the bottom right hand side of Figure 12.

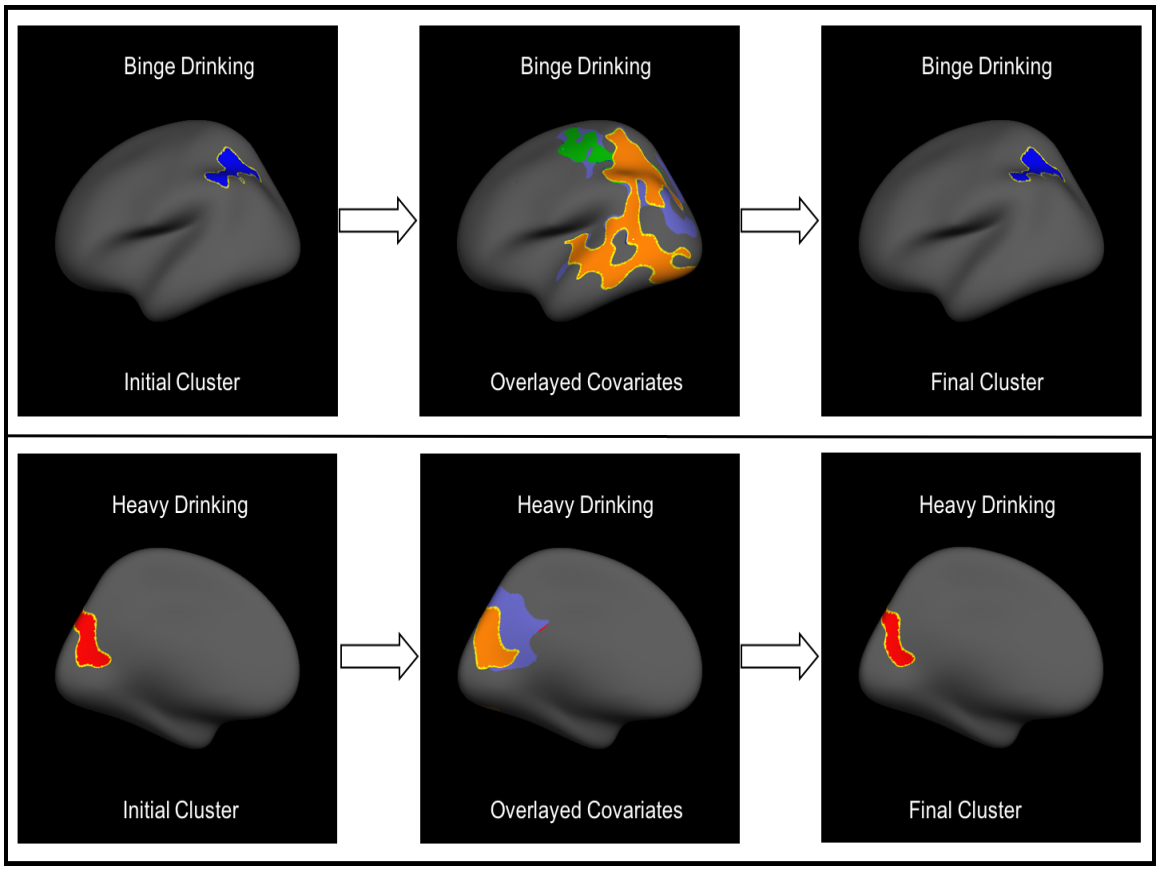

Figure 12. Distinguishing the Effect of Drinking Patterns from Nuisance Factors.

This is a visual display of the process that was followed in order to isolate the effects of drinking patterns from the covariates. The original clusters, as generated by t-tests ($p < 0.05$, FWHD = 15), are displayed on the left column; Binge Drinking cluster is on the top row (in blue) and the Heavy Drinking cluster is on the bottom row (in red). The middle column indicates a few exemplary resulting clusters from various t-tests with the inclusion of each of the covariates. Visible covariates include the total CAPS score (in orange), DASS Anxiety Score (in green), and smoking status (in purple). Note that not all of the covariate results are displayed, because of the high overlap (they would simply not be visible due to the nontransparent superimposition). The right row column displays the final clusters that have been generated after including only the geometric intersection of all covariates, and excluding all of the extra surface results. These are indicative of the cortical thickness effects of Binge and Heavy Drinking groups, with minimal effects from nuisance variables. Abbreviations: CAPS = Clinician Administered PTSD Scale; DASS = Depression and Anxiety Stress Scale.

Drinking Pattern Network Overlap

Significant BD and HD clusters, which have been generated from the process described above, were examined for the degree of spatial overlap with major cortical brain networks. Commonly used networks have been selected from the Yeo 7-Network solution cortical parcellation atlas (see Figure 4).

BD ROI Network Overlap

The amount of overlap has been calculated between the corresponding portions of the networks (within the superior parietal region) and the BD ROI. Results indicate that the BD ROI mainly overlaps with the volitional attention networks. Specifically, it overlaps with the posterior region of the Dorsal Attention Network by 615.794 mm^2 and with the fronto-parietal network by 594.938 mm^2. Overlap with the ventral attention and default mode networks are comparatively minimal, at 1.313 mm^2 and 0.676 mm^2, respectively. Figure 13 shows visual overlap of the BD ROI with Yeo networks and a quantifiable metric for comparison purposes is presented in Figure 14.

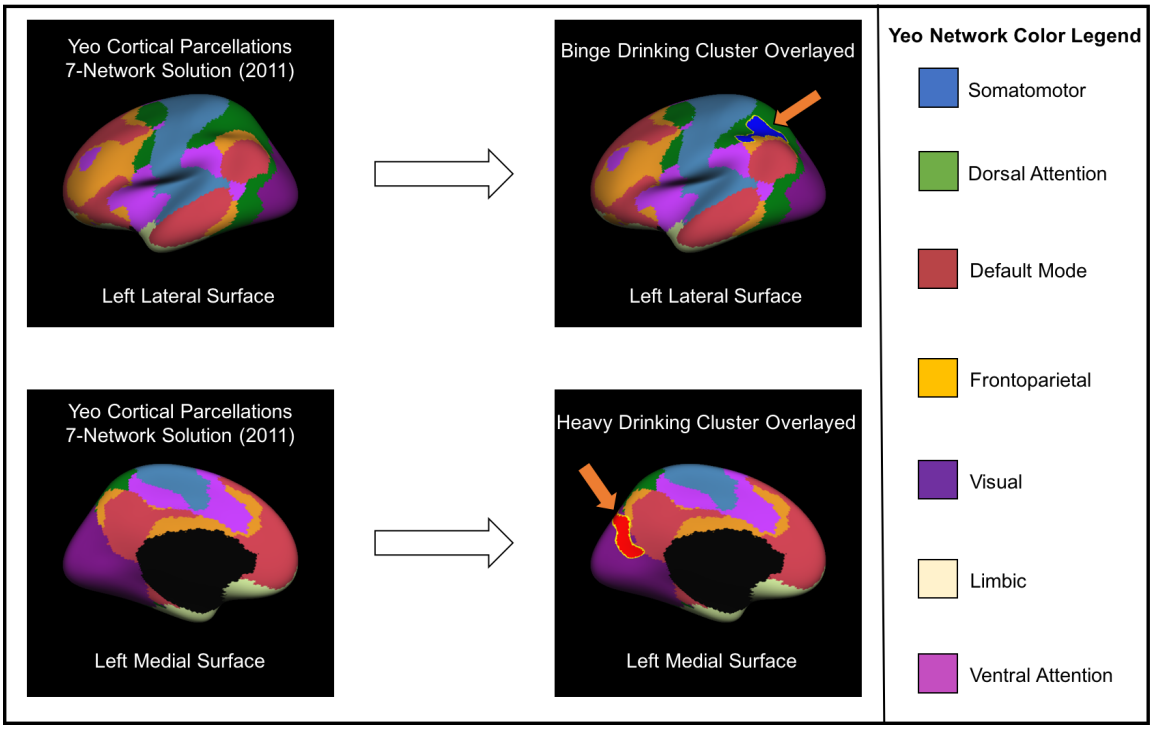

Figure 13. Intersection of Significant Clusters with Yeo Networks.

Images on the left column indicate the Yeo 7-Network solution cortical parcellation overlay. The two images in the middle column show the superimposed Binge (top, in blue) and Heavy Drinking (bottom, in red) clusters on top of the Yeo 7-Network atlas. This superimposition has allowed for a quantification of the degree and extent to which each of the networks is affected by the clusters. Upper right image contains a legend for the 7 major Networks and the bar graph on the bottom right summarizes the extent to which each Network is affected; Heavy Drinking overlap is in red and Binge Drinking overlap is in blue. As shown, the Heavy Drinking cluster primarily intersects with the visual network at 1,201.023 mm^2 and to a much lesser extent with the Default Mode Network (44.367 mm^2), Dorsal Attention Network (50.508 mm^2), and the Frontoparietal network (46.357 mm^2). The Binge Drinking cluster intersects with the Dorsal Attention Network (615.794 mm^2) as well as the Frontoparietal Network (594.938 mm^2).

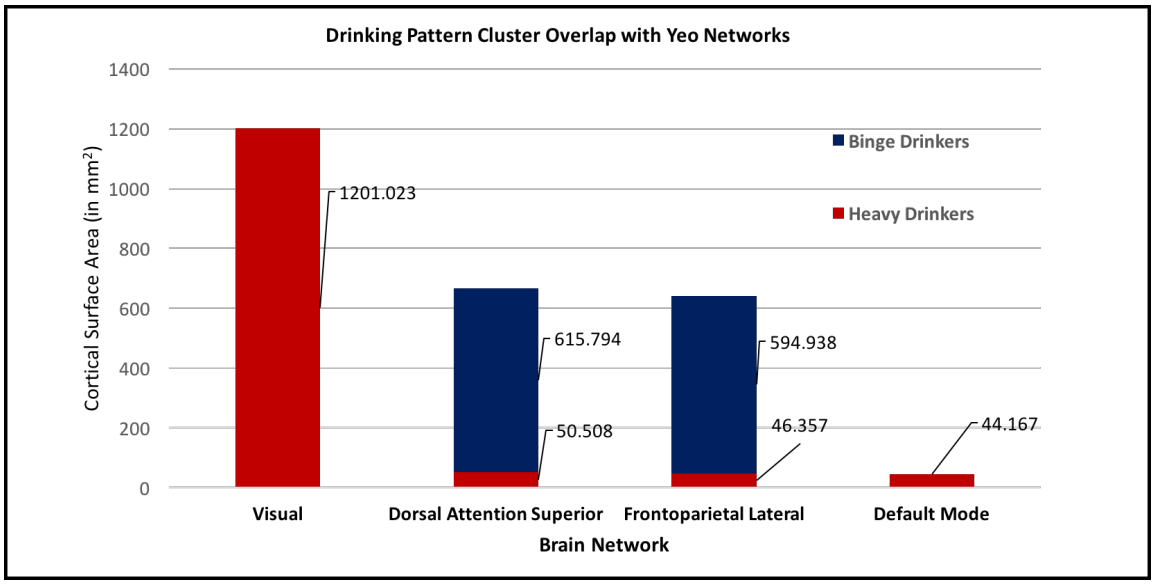

Figure 14. Quantified Intersection of Significant Clusters with Yeo Networks.

This graph is a quantified representation of the drinking pattern cluster overlap with the Yeo 7-Network solution cortical parcellation atlas. Relatively negligible intersection measures (below 1.5 mm^2) have not been included as they account for less than ~ 0.35%, as compared to an average size of presented intersections.

HD ROI Network Overlap

Results indicate that the HD ROI cluster overlaps with distinctly different networks, as compared to the BD cluster described above. The HD ROI mainly overlaps with the dorsal attention network (50.508 mm^2 overlap), as well as the visual network (1,202.023 mm^2 overlap). Other networks overlap to a relatively smaller extent; these include the frontoparietal lateral superior region (0.149 mm^2 overlap), frontoparietal medial superior region (46.357 mm^2 overlap), ventral attention lateral region (0.297 mm^2 overlap), ventral attention medial region (0.483 mm^2 overlap), the default mode network lateral region (0.361 mm^2 overlap), and the default mode medial region (43.806 mm^2 overlap). These results are visually summarized in Figure 14.

CHAPTER 4 - DISCUSSION

Results of this comprehensive study examining neuroanatomical and cognitive differences in individuals with a history of BD and HD, revealed the following main findings. Results from the cognitive function experiment indicate a higher rate of inhibitory and attention errors within the HD group, in comparison to the BD and HC groups. Results from the volumetric analyses show a smaller volume of the bilateral diencephalon within BD and HD group, in comparison to the HC group, and a smaller volume of the bilateral globus pallidus within the BD group in comparison to both other groups. Cortical thickness analyses reveal thinner tissue within the superior parietal region in the BD group, in comparison to other groups, and a thicker medial occipito-

parietal tissue within the HD group, in comparison to other groups. Cortical thickness findings for the BD group primarily impact the fronto-parietal brain networks, while findings for the HD group mostly effect the visual network but also several other networks to a smaller extent.

Aim 1: Cognitive Function

The primary finding with regard to the affective Go/No-Go task was the deficit in the HD group compared to both the BD and HC groups. While BD group did not differ from the HD or HC groups; post-hoc analyses revealed that these errors were not driven by any one stimulus type. HDs were shown to have elevated commission errors, errors in response to positive stimuli, errors in response to negative stimuli, as well as omission errors (approaching significance). Given that HDs' reaction time was not significantly different that of other participants', these results imply a potential inhibitory and an attention deficit in the HD group that is not a result of merely faster button pressing, and one that is not present within the BD or HC groups.

These findings are in line with prior literature showing an impairment in day-to-day functioning for individuals who drink heavily and frequently (Mangione et al., 1999). Additionally, prior work has shown that individuals with AUDs, with unspecified drinking patterns, are impaired in inhibitory functioning (Campanella et al., 2016) as well as in attention abilities (Clerkin, Magee, Wells, Beard, & Barnett, 2016). The current findings also suggest that inhibitory and attention impairments relating to stopping

uninitiated actions might not be present in all types of drinkers, but specific to the HD pattern.

This is an important distinction for differentiating between the two presently investigated AUD subtypes, as it indicates that a more frequent alcohol consumption pattern might be uniquely associated with global attention and inhibitory impairments. These data should not be misinterpreted as supporting a conclusion that BDs do not have *any* inhibitory or attention impairments in comparison to HDs or HCs. On the contrary, as discussed earlier, numerous studies have found that BDs are more impulsive than HCs in the presence of rewarding stimuli (Poulton et al., 2016) and show an altered attention response to alcohol cues (Petit et al., 2012) in comparison to controls. These types of cognitive processes have simply not been measured in the current study using the AGN task. For instance, the positive valence stimuli on the AGN task might not have been rewarding enough for BDs. Furthermore, the negative valence stimuli might not have been stress-inducing, and therefore has not resulted in a behavioral effect. While this does not take away from the importance of the AGN findings pertaining to HDs, differential correlates of BDs remain to be explored with additional measures.

Aim 2: Brain Volume

Analysis of brain volume revealed smaller bilateral globus pallidus only in BDs, in comparison to other groups. This was in contrast to the hypothesis that both drinking groups will show reduced volumes. However, this finding is very consistent with recent literature suggesting a role of globus pallidus in reward oriented motivation and is also consistent with the notion that BDs are motivated to drink by positive reinforcement.

Studies examining brain activation during reward motivation via fMRI have shown that the globus pallidus is selectively more active during goal oriented tasks (when higher rewards are present (Lamm et al., 2014)), as well as when processing novel stimuli (Scott et al., 2002), in comparison to neutral conditions. Additionally, cellular activity of the globus pallidus was recently found to be higher during reward presentation (Howell et al., 2016). Lesions to the anterior globus pallidus regions (projecting to the orbitofrontal and ventromedial PFC) were shown to be associated with clinical apathy marked by severe amotivation towards rewarding goals that was alleviated with dopaminergic treatment (Adam et al., 2013). A recent animal study examining monkeys who have undergone pallidoctomies has shown impairments within reward motivated behavior via pathologically decreased performance on a reward task (Piron et al., 2016). Furthermore, findings show that a volumetric reduction within the globus pallidus is associated with decreased ability to make causal inferences in adolescents, an ability that is critical to learning (Griffiths et al., 2015).

Adolescent development of the globus pallidus is associated with the emergence of motivational traits (Lamm et al., 2014). These traits become pathological in AUD, as motivation is increased towards the consumption of unhealthy quantities of alcohol and often decreased in relation to other goals (Heinz et al., 2014b). Exemplary of this, both BD and HD individuals have been shown to have increased motivation (often referred to as incentive salience) towards alcohol, and decreased motivation towards pursuing other, healthier activities (Lau-Barraco et al., 2016; Marczinski et al., 2013). Interestingly,

damage to the globus pallidus, via ischemic injury, resulted in cessation of substance abuse (Moussawi et al., 2016).

These findings suggest that the globus pallidus is not only involved in pathological motivation towards binge drinking, but also appears to be necessary for its maintenance. Additionally, literature suggests that there is a dopaminergic role in this structure's functioning. These results are supportive of BDs reward-driven motivation via positive reinforcement. The smaller volume of the globus pallidus with BDs may be indicative of a positive reinforcement dysregulation in this group.

Results also showed that the ventral diencephalon volume was smaller in both BDs and HDs, in comparison to HCs. While past research has shown that this structure is associated with motivation and reward processing (Makris et al., 2008; Routtenberg & Huang, 1968) and is affected in alcohol use disorders (Bowirrat & Oscar-Berman, 2005; Makris et al., 2008), more specific conclusions, such as the ones presented for the globus pallidus, are difficult to make. The primary reason for lack of specificity is the broad array of structures that fall within the FreeSurfer's segmented Ventral Diencephalic structure (Neuromorphometrics, 2005), thus covering a large spectrum of cognitive correlates. Within the grey matter structures, ventral diencephalon includes the hypothalamus, mammillary body, subthalamic nuclei, substantia nigra, red nucleus, and the lateral and medal geniculate nuclei. Given the broad range of structures and associated functions, it not surprising that the ventral diencephalon is affected in both pathological drinking patterns. A narrower anatomical and functional discrimination might be necessary to detect group differences.

Aim 3: Cortical Thickness

Cortical thickness findings showed an area of thinner cortex in the left lateralized superior parietal region in BDs, overlapping primarily with the dorsal attention network, and a thicker cortex in the left medial occipito-parietal region in HDs overlapping primarily with the visual networks, but also impacts the volitional attention and the default mode networks. Two intriguing questions arise from these findings. First, what are the cognitive implications for the affected brain regions? Second, why are the cortical thickness results lateralized to the left side? Although definitive answers cannot be provided without additional experiments, empirically informed explanations are considered pertaining to each question.

The BD findings are best interpreted when taking the prefrontal cortices into account, given their involvement with respective ipsilateral network functions (Power et al., 2011). In this area of research, left PFC lesions were shown to be associated with impairments in inhibiting pre-potent responses (via Stroop task; (Cipolotti et al., 2016)). Right PFC lesions, on the other hand, were shown to be associated with impaired inhibition of dominant strategies, as measured by the Hayling sentence completion task (Cipolotti et al., 2016). Since right and left PFCs are involved with respective lateralized networks (Yeo et al., 2011), the left cortical thickness findings might point to network-wide attention problems with modulating previously learned information as well as impaired performance under higher demands (as measured by quicker mental fatigue onset). Since the left PFC is part of a fronto-parietal network (Yeo et al., 2011), this

serves as further evidence for a left attention impairment in BDs. In consideration of this interpretation, it is important to note that formal lateralization analyses have not been made, and are planned as part of follow-up work. Thus, while the left sided results are potentially indicative of lateralization, specific conclusions cannot yet be reached, and the discussion thus remains speculative.

One function ascribed to the PFC is that it mediates striatal activity that is often associated with craving (Grüsser et al., 2004; Heinz et al., 2014a; Kober et al., 2010). One way in which this is accomplished is through parietal mediation; the PFC works with the parietal cortex as part of a fronto-parietal attention network to shift attention towards or away from striatally amplified salient cues (Castellanos & Proal, 2012; Shulman et al., 2009). The PFC might fail to do this by being taken off-line either through a direct impairment or an indirect hindrance; an example of the latter impairment is one that affects the parietal lobe, which is crucial for accomplishing the PFC's function (Dodds, Morein-Zamir, & Robbins, 2010; Ptak, 2012). In this context, it is important to consider that the parietal region that is affected in BDs was recently found to be a task-positive "hot spot" (Glasser et al., 2016; Rushworth, Ellison, & Walsh, 2001). It is involved in a broad variety of attention and monitoring activities, including ones that regulate striatal function related to craving (Cona, Marino, & Bisiacchi, 2016; Do & Galván, 2016). Thus, not surprisingly, impulsive individuals such as BDs were shown to have a left PFC-striatal disconnect (with the PFC failing to properly activate during striatal regulatory function) that is mediated by the left superior parietal region (Premi et al., 2016). Additionally, evidence suggests that the task-positive left parietal component works

harder (via higher event-potential activation) with increasing mental fatigue (X. Liu et al., 2016). Future work linking cortical thickness findings to BOLD activity as well as attention processes, would be in line with prior findings indicating that BDs might not be as impaired in day-to-day functioning as HDs, but do show regulatory behavioral impairment during periods of binge drinking (Grzywacz & Almeida, 2008; Jennison, 2004; Lindsay M Squeglia, Schweinsburg, Pulido, & Tapert, 2011; Lindsay M Squeglia et al., 2012).

In order to properly interpret the occipital findings associated with the HD pattern, it is important to place them in the context of a plethora of studies reporting on the involvement of the occipital regions in AUD. For instance, a recent MRI study has found an occipital volumetric reduction within the AUD population, in comparison to healthy controls (Shimotsu, Chu, & Fein, 2009). Furthermore, a Positron Emission Tomography (PET) scan study has found a whole-brain decrease of the type 1 cannabinoid receptor (CB_1R), which was reduced at the highest extent within the parieto-occipital regions (Ceccarini et al., 2014). This receptor is known to reinforce the effects of GABA, and is thus believed to signal a neurochemical response to pathological drinking (Ceccarini et al., 2014). Interestingly, a study examining the acute effects of alcohol consumption in healthy individuals has reported a selective increase within the visual network connectivity (Esposito et al., 2010). The authors concluded that the visual network is a "selective and primary target of acute alcohol administration" (Esposito et al., 2010). Thus, the current findings are not only in line with the vast amount of literature pertaining to the occipital involvement in AUD, but also offer a new caveat: these regions

might be specific to the HD drinking pattern, rather than all AUDs.

A closer look at the receptor concentration in the occipital cortex suggests that HD might be associated with an alcohol-related neurochemical metabolic disruption within this region. In addition to the work discussed above, numerous studies have shown that the occipital cortex contains a selectively large concentration of GABA receptors ((Hill & Toffolon, 1990; Nicholson, Andre, Tyrrell, Wang, & Leibowitz, 1995; Pearson & Timney, 1998; Watten, Magnussen, & Greenlee, 1998). Furthermore, alcohol was shown to impact these neurochemicals as a result of acute, as well as long term, consumption (Volkow et al., 2008). It is thus not surprising that numerous PET studies have reported that alcohol has a potentiating effect on GABA (Davies, 2003), and selectively disrupts this metabolic activity within the occipital lobe (Volkow et al., 2008; Wang et al., 2000). In further support of these findings, a recent magnetic resonance spectroscopy study has shown a number of neurochemical metabolic alterations within AUD participants in comparison to healthy controls, all of which were specific to the primary visual cortex (Bagga et al., 2014). Amongst these findings, authors reported an AUD related decrease in levels of *N*-acetyl-aspartate/creatine (NAA/Cr) and glutamate–glutamine/creatine (Glu-Gln)/Cr ratios and an increase in choline/creatine (Cho/Cr) and myo-Inositol/creatine (mI/Cr) ratios (Bagga et al., 2014). While the nuances of these metabolic disruptions are beyond the scope of this discussion, it is relevant to note that the authors attributed the neurochemical dysregulation to regional neural loss as well neuroprotective adaptation in response to pathological drinking (Bagga et al., 2014).

In further consideration for the left occipital findings (as opposed to bilateral regions), it is important to consider recent cortical aging theory. This work suggests that the brain is more lateralized during the earlier stages of development and becomes more bilateral with age as a compensatory mechanism for neural decline (Agcaoglu, Miller, Mayer, Hugdahl, & Calhoun, 2015). According to this hypothesis, as cortical regions become less effective on one side, they begin to work bilaterally in order to keep accomplishing the previously unilateral function (Agcaoglu et al., 2015). Given that the examined sample is relatively young (mean age of 33), they are not likely to invoke these compensatory mechanisms as those who are aged in their late 60s (Cabeza, Anderson, Locantore, & McIntosh, 2002; Reuter-Lorenz et al., 2000).

In addition to the cortical aging theory, recent work has shown that the left hemisphere is significantly more sensitive to dopaminergic reward-related processing than the right side (Aberg, Doell, & Schwartz, 2016; Reuter-Lorenz et al., 2000; Tomer et al., 2014). Thus, while the occipital and parietal regions might be affected for different reasons, the common association with dopaminergically sensitive structures seems to persist in both drinking patterns, as exemplified by asymmetrical leftward findings. As mentioned earlier, formal asymmetry analyses will need to be conducted before specific lateralization conclusions can be reached.

Limitations and Future Directions

Among the limitations of this research is the lack of sufficient number of female participants to examine gender differences. Past studies have shown differential

neurological and behavioral findings for male and female pathological drinkers (Sawyer et al., 2016; Shokri-Kojori et al., 2016; E. Sullivan et al., 2000; E. V. Sullivan et al., 2002). For instance, cortical lateralization findings described above were shown to be less lateralized for females (Agcaoglu et al., 2015). Separate studies of neuropsychological findings indicate that visuospatial, working memory, and gait functions are affected in both genders (E. Sullivan et al., 2000; E. V. Sullivan et al., 2002), while men might be more impaired in their executive abilities (E. Sullivan et al., 2000). Given the recent rise of binge drinking among women (Dwyer-Lindgren et al., 2015), studies directly comparing differential effects of alcohol on gender are particularly important. Given that the current dataset consists of mostly males, it should be interpreted with caution for female participants until further analyses can be carried out.

Another limitation of this project pertains to the retrospective assessment of drinking. While the LDH questionnaire has been administered by trained staff and verified in a clinical consensus, it has two major shortfalls. First, it relies on participants' ability to recall their drinking history information. Such recollection might be flawed by poor memory (that could be exacerbated by a history of drinking) and is not as accurate as more on-line objective drinking tracking. Second, drinking patterns were estimated based on the general LDH measures, which are not specific enough to provide hour-by-hour drinking information. Since the LDH covers broader drinking stages, BD and HD patterns have been deduced via estimates. Although costly, an important future extension of this project would benefit from utilizing a real-time drinking tracker in order to

increase the accuracy of the rate and frequency of alcohol consumption without relying on self-report or mathematical approximations.

Finally, the cross-sectional nature of these analyses falls short of conclusions that could be reached by using a longitudinal design. Specifically, while significant group differences have been found, the design does not permit the conclusion that one drinking pattern is associated with a decrease in behavioral function or neurological structure in comparison to other groups. Additionally, this design does not lend itself to conclusions about whether the significant findings have preceded or resulted from each of the respective drinking patterns. A longitudinal design, tracking participants over time and beginning prior to the onset of pathological drinking, would provide evidence as to which changes precede alcohol consumption, which is caused by drinking, and how the brain and behavior changes over time with years of pathological drinking.

Conclusion

This project serves as a stepping-stone, amongst a series of recent advancements in alcohol research, for identifying two distinct alcohol disorder sub-types: Binge and Heaving Drinking. As discussed earlier, diagnostic criteria have evolved over the decades from a simple binary diagnosis (alcoholic or not) to more nuanced methods of identifying alcohol related disorders. Although data from these analyses needs to be replicated and extended in further research in order to address all of the limitations, it does provide the

first direct experimental comparison for the anatomical and cognitive correlates of common drinking patterns.

The current study contributes three major findings to the literature of AUD's drinking patterns. ***Aim 1*** results show that only HDs produce more errors on a task involving paying attention and stopping themselves from committing an action (i.e., pressing a button). Findings from ***Aim 2*** show that both pathological drinking patterns are associated with smaller volume of the bilateral ventral diencephalon, and only the binge drinking pattern is associated with a smaller volume of the globus pallidus. ***Aim 3*** results indicate that binge drinking is associated with a thinner superior parietal region and heavy drinking is associated with a thicker medial occipito-parietal area. Networks that are affected in binge drinking involve fronto-parietal components, and the heavy drinking pattern seems to primarily be linked with the impacted visual network, but also the fronto-parietal and the default mode network to a smaller extent.

Thus far, this project is hinting at a potential dissociation between the two drinking patterns, which might be indicative of their status as two differential AUD subtypes. Extending this work in the proposed directions will provide additional information about the motivational mechanisms in each of the drinking patterns and solidify the two forms of drinking as distinct AUD disorders with different symptomatology.

BIBLIOGRAPHY

Aberg, K. C., Doell, K. C., & Schwartz, S. (2016). The left hemisphere learns what is right: Hemispatial reward learning depends on reinforcement learning processes in the contralateral hemisphere. *Neuropsychologia, 89*, 1-13.

Adam, R., Leff, A., Sinha, N., Turner, C., Bays, P., Draganski, B., & Husain, M. (2013). Dopamine reverses reward insensitivity in apathy following globus pallidus lesions. *Cortex, 49*(5), 1292-1303.

Agcaoglu, O., Miller, R., Mayer, A., Hugdahl, K., & Calhoun, V. (2015). Lateralization of resting state networks and relationship to age and gender. *Neuroimage, 104*, 310-325.

American Psychiatric Association. (1952). *Diagnostic and Statistical Manual of Mental Disorders, First Edition.* Washington, D.C.: American Psychiatric Pub.

American Psychiatric Association. (1968). *Diagnostic and Statistical Manual of Mental Disorders, Second Edition*. Washington, D.C.: American Psychiatric Pub.

American Psychiatric Association. (1980). *Diagnostic and Statistical Manual of Mental Disorders, Third Edition.* Washington, D.C.: American Psychiatric Pub.

American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised.* Washington, D.C.: American Psychiatric Pub.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.* Washington, D.C.: American Psychiatric Pub.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders DSM-IV-TR fourth edition (text revision).* Washington D.C.: American Psychiatric Pub.

American Psychiatric Association. (2003). *Diagnostic and Statistical Manual of Mental Disorders: 5th Edition: DSM-5*: American Psychiatric Pub.

Andersen, S. L., Thompson, A. T., Rutstein, M., Hostetter, J. C., & Teicher, M. H. (2000). Dopamine receptor pruning in prefrontal cortex during the periadolescent period in rats. *Synapse, 37*(2), 167-169.

Andrews-Hanna, J. R. (2012). The brain's default network and its adaptive role in internal mentation. *The Neuroscientist, 18*(3), 251-270.

Andrews-Hanna, J. R., Smallwood, J., & Spreng, R. N. (2014). The default network and self‐generated thought: component processes, dynamic control, and clinical relevance. *Annals of the New York Academy of Sciences, 1316*(1), 29-52.

Anokhin, A. P., Golosheykin, S., Grant, J. D., & Heath, A. C. (2011). Heritability of delay discounting in adolescence: a longitudinal twin study. *Behavior genetics, 41*(2), 175-183.

Anton, R. F. (2000). Obsessive–compulsive aspects of craving: development of the Obsessive Compulsive Drinking Scale. *Addiction, 95*(8s2), 211-217.

Anton, R. F., Moak, D. H., & Latham, P. (1995). The Obsessive Compulsive Drinking Scale: A self‐rated instrument for the quantification of thoughts about alcohol and drinking behavior. *Alcoholism: Clinical and Experimental Research, 19*(1), 92-99.

Arnett, J. J. (1999). Adolescent storm and stress, reconsidered. *American psychologist, 54*(5), 317.

Aron, A. R. (2007). The neural basis of inhibition in cognitive control. *The Neuroscientist, 13*(3), 214-228.

Aron, A. R., & Poldrack, R. A. (2006). Cortical and subcortical contributions to stop signal response inhibition: role of the subthalamic nucleus. *The Journal of Neuroscience, 26*(9), 2424-2433.

Aron, A. R., Robbins, T. W., & Poldrack, R. A. (2004). Inhibition and the right inferior frontal cortex. *Trends in cognitive sciences, 8*(4), 170-177.

Avila, C., & Parcet, M. A. (2001). Personality and inhibitory deficits in the stop-signal task: The mediating role of Gray's anxiety and impulsivity. *Personality and individual differences, 31*(6), 975-986.

Bagga, D., Khushu, S., Modi, S., Kaur, P., Bhattacharya, D., Garg, M., & Singh, N. (2014). Impaired visual information processing in alcohol-dependent subjects: a proton magnetic resonance spectroscopy study of the primary visual cortex. *Journal of studies on alcohol and drugs, 75*(5), 817-826.

Balodis, I. M., Potenza, M. N., & Olmstead, M. C. (2009). Binge drinking in undergraduates: Relationships with gender, drinking behaviors, impulsivity and the perceived effects of alcohol. *Behavioural pharmacology, 20*(5-6), 518.

Balogh, K. N., Mayes, L. C., & Potenza, M. N. (2013). Risk-taking and decision-making in youth: Relationships to addiction vulnerability. *Journal of behavioral addictions, 2*(1), 1-9.

Banca, P., Harrison, N. A., & Voon, V. (2016). Compulsivity across the pathological misuse of drug and non-drug rewards. *Frontiers in Behavioral Neuroscience, 10*.

Banca, P., Lange, I., Worbe, Y., Howell, N. A., Irvine, M., Harrison, N. A., . . . Voon, V. (2015). Reflection impulsivity in binge drinking: behavioural and volumetric correlates. *Addiction biology*.

Barbaccia, M. L., Affricano, D., Trabucchi, M., Purdy, R. H., Colombo, G., Agabio, R., & Gessa, G. L. (1999). Ethanol markedly increases "GABAergic" neurosteroids in alcohol-preferring rats. *European journal of pharmacology, 384*(2), R1-R2.

Barbaccia, M. L., Serra, M., Purdy, R. H., & Biggio, G. (2001). Stress and neuroactive steroids. *International Review of Neurobiology, 46*, 243-272.

Barrett, L. F. (1998). Discrete emotions or dimensions? The role of valence focus and arousal focus. *Cognition & Emotion, 12*(4), 579-599.

Bauer, A. M., Quas, J. A., & Boyce, W. T. (2002). Associations between physiological reactivity and children's behavior: Advantages of a multisystem approach. *Journal of Developmental & Behavioral Pediatrics, 23*(2), 102-113.

Beattie, M. C., Longabaugh, R., Elliott, G., Stout, R. L., Fava, J., & Noel, N. E. (1993). Effect of the social environment on alcohol involvement and subjective well-being prior to alcoholism treatment. *Journal of Studies on Alcohol, 54*(3), 283-296.

Beaunieux, H., Eustache, F., & Pitel, A.-L. (2014). The relation of alcohol-induced brain changes to cognitive function. In J. Svanberg, A. Withall, B. Draper, & S. Bowden (Eds.), *Alcohol and the Adult Brain*. New York: Psychology Press.

Beck, A. T., & Clark, D. A. (1988). Anxiety and depression: An information processing perspective. *Anxiety research, 1*(1), 23-36.

Beck, A. T., & Clark, D. A. (1997). An information processing model of anxiety: Automatic and strategic processes. *Behaviour research and therapy, 35*(1), 49-58.

Becker, H. C. (1998). Kindling in alcohol withdrawal. *Alcohol Research and Health, 22*(1), 25.

Berridge, K. C. (2007). The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology, 191*(3), 391-431.

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research Reviews, 28*(3), 309-369.

Bezdjian, S., Baker, L. A., Lozano, D. I., & Raine, A. (2009). Assessing inattention and impulsivity in children during the Go/NoGo task. *British Journal of Developmental Psychology, 27*(2), 365-383.

Bickel, W. K., Jarmolowicz, D. P., Mueller, E. T., Gatchalian, K. M., & McClure, S. M. (2012). Are executive function and impulsivity antipodes? A conceptual reconstruction with special reference to addiction. *Psychopharmacology, 221*(3), 361-387.

Bisley, J. W., & Goldberg, M. E. (2010a). Attention, intention, and priority in the parietal lobe. *Annual review of neuroscience, 33*, 1-21.

Bisley, J. W., & Goldberg, M. E. (2010b). Attention, intention, and priority in the parietal lobe. *Annual review of neuroscience, 33*, 1.

Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Gusman, F. D., Charney, D. S., & Keane, T. M. (1995). The development of a clinician-administered PTSD scale. *Journal of traumatic stress, 8*(1), 75-90.

Blakemore, S.-J., & Robbins, T. W. (2012). Decision-making in the adolescent brain. *Nature neuroscience, 15*(9), 1184-1191.

Boksem, M. A., & Tops, M. (2008). Mental fatigue: costs and benefits. *Brain Research Reviews, 59*(1), 125-139.

Borsari, B. E., & Carey, K. B. (1999). Understanding fraternity drinking: Five recurring themes in the literature, 1980–1998. *Journal of American College Health, 48*(1), 30-37.

Bowirrat, A., & Oscar‐Berman, M. (2005). Relationship between dopaminergic neurotransmission, alcoholism, and reward deficiency syndrome. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 132*(1), 29-37.

Brady, K. T., & Sonne, S. C. (1999). The role of stress in alcohol use, alcoholism treatment, and relapse. *Alcohol Research & Health, 23*(4), 263-263.

Braver, T. S., Krug, M. K., Chiew, K. S., Kool, W., Westbrook, J. A., Clement, N. J., . . . Carver, C. S. (2014). Mechanisms of motivation–cognition interaction: challenges and opportunities. *Cognitive, Affective, & Behavioral Neuroscience, 14*(2), 443-472.

Brown, J., Bullock, D., & Grossberg, S. (1999). How the basal ganglia use parallel excitatory and inhibitory learning pathways to selectively respond to unexpected rewarding cues. *The Journal of Neuroscience, 19*(23), 10502-10511.

Brown, S. A., Vik, P. W., Patterson, T. L., Grant, I., & Schuckit, M. A. (1995). Stress, vulnerability and adult alcohol relapse. *Journal of Studies on Alcohol, 56*(5), 538-545.

Buckner, R., Andrews-Hanna, J., & Schacter, D. (2008). The brain's default network: anatomy, function, and relevance to disease Ann NY Acad Sci 2008; 1124: 1-38.

Buckner, R. L., Head, D., Parker, J., Fotenos, A. F., Marcus, D., Morris, J. C., & Snyder, A. Z. (2004). A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. *Neuroimage, 23*(2), 724-738.

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage, 17*(3), 1394-1402.

Cala, L., Jones, B., Mastaglia, F., & Wiley, B. (1978). Brain atrophy and intellectual impairment in heavy drinkers—a clinical, psychometric and computerized tomography study. *Internal Medicine Journal, 8*(2), 147-153.

Campanella, S., Absil, J., Sinde, C. C., Schroder, E., Peigneux, P., Bourguignon, M., . . . Goldman, S. (2016). Neural correlates of correct and failed response inhibition in heavy versus light social drinkers: an fMRI study during a go/no-go task by healthy participants. *Brain Imaging and Behavior*, 1-16.

Carlen, P. L., Wortzman, G., Holgate, R., Wilkinson, D., & Rankin, J. (1978). Reversible cerebral atrophy in recently abstinent chronic alcoholics measured by computed tomography scans. *Science, 200*(4345), 1076-1078.

Carretié, L., Ríos, M., De La Gandara, B., Tapia, M., Albert, J., López-Martín, S., & Álvarez-Linera, J. (2009). The striatum beyond reward: caudate responds intensely to unpleasant pictures. *Neuroscience, 164*(4), 1615-1622.

Carta, M., Mameli, M., & Valenzuela, C. F. (2004). Alcohol enhances GABAergic transmission to cerebellar granule cells via an increase in Golgi cell excitability. *The Journal of Neuroscience, 24*(15), 3746-3751.

Casey, B. J., Jones, R. M., & Hare, T. A. (2008). The adolescent brain. *Annals of the New York Academy of Sciences, 1124*(1), 111-126.

Castellanos, F. X., & Proal, E. (2012). Large-scale brain systems in ADHD: beyond the prefrontal–striatal model. *Trends in cognitive sciences, 16*(1), 17-26.

Ceccarini, J., Hompes, T., Verhaeghen, A., Casteels, C., Peuskens, H., Bormans, G., . . . Van Laere, K. (2014). Changes in cerebral CB1 receptor availability after acute and chronic alcohol abuse and monitored abstinence. *The Journal of Neuroscience, 34*(8), 2822-2831.

Chambers, R. A., Taylor, J. R., & Potenza, M. N. (2003). Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. *American Journal of Psychiatry, 160*(6), 1041-1052.

Chanraud, S., Pitel, A.-L., Pfefferbaum, A., & Sullivan, E. V. (2011). Disruption of functional connectivity of the default-mode network in alcoholism. *Cerebral Cortex*, bhq297.

Chassin, L., Pitts, S. C., & Prost, J. (2002). Binge drinking trajectories from adolescence to emerging adulthood in a high-risk sample: predictors and substance abuse outcomes. *Journal of Consulting and Clinical Psychology, 70*(1), 67.

Chen, A. C., Porjesz, B., Rangaswamy, M., Kamarajan, C., Tang, Y., Jones, K. A., . . . Begleiter, H. (2007). Reduced frontal lobe activity in subjects with high impulsivity and alcoholism. *Alcoholism: Clinical and Experimental Research, 31*(1), 156-165.

Cipolotti, L., Spanò, B., Healy, C., Tudor-Sfetea, C., Chan, E., White, M., . . . Bozzali, M. (2016). Inhibition processes are dissociable and lateralized in human prefrontal cortex. *Neuropsychologia, 93*, 1-12.

Clark, D. B., Lesnick, L., & Hegedus, A. M. (1997). Traumas and other adverse life events in adolescents with alcohol abuse and dependence. *Journal of the American Academy of Child & Adolescent Psychiatry, 36*(12), 1744-1751.

Claus, E. D., Kiehl, K. A., & Hutchison, K. E. (2011). Neural and behavioral mechanisms of impulsive choice in alcohol use disorder. *Alcoholism: Clinical and Experimental Research, 35*(7), 1209-1219.

Clerkin, E. M., Magee, J. C., Wells, T. T., Beard, C., & Barnett, N. P. (2016). Randomized controlled trial of attention bias modification in a racially diverse, socially anxious, alcohol dependent sample. *Behaviour research and therapy, 87*, 58-69.

Colder, C. R. (2001). Life stress, physiological and subjective indexes of negative emotionality, and coping reasons for drinking: Is there evidence for a self-medication model of alcohol use? *Psychology of Addictive Behaviors, 15*(3), 237.

Colder, C. R., & Chassin, L. (1993). The stress and negative affect model of adolescent alcohol use and the moderating effects of behavioral undercontrol. *Journal of Studies on Alcohol, 54*(3), 326-333.

Colder, C. R., & Chassin, L. (1997). Affectivity and impulsivity: Temperament risk for adolescent alcohol involvement. *Psychology of Addictive Behaviors, 11*(2), 83.

Colder, C. R., & O'Connor, R. (2002). Attention bias and disinhibited behavior as predictors of alcohol use and enhancement reasons for drinking. *Psychology of Addictive Behaviors, 16*(4), 325.

Compton, W. M., Conway, K. P., Stinson, F. S., Colliver, J. D., & Grant, B. F. (2005). Prevalence, correlates, and comorbidity of DSM-IV antisocial personality syndromes and alcohol and specific drug use disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. *The Journal of clinical psychiatry, 66*(6), 677-685.

Cona, G., Marino, G., & Bisiacchi, P. S. (2016). Superior parietal cortex and the attention to delayed intention: An rTMS study. *Neuropsychologia, 95*, 130-135.

Connor, J. P., Feeney, G., & Young, R. M. (2004). A comparison of the Yale-Brown Obsessive Compulsive Scale for" heavy drinking" with a single item craving measure: construct validity and clinical utility. *Substance use & misuse, 40*(4), 551-561.

Cooper, A. J., Duke, É., Pickering, A. D., & Smillie, L. D. (2015). Individual differences in reward prediction error: contrasting relations between feedback-related negativity and trait measures of reward sensitivity, impulsivity and extraversion. *Dopaminergic Foundations of Personality and Individual Differences*.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience, 3*(3), 201-215.

Cox, W. M., Hogan, L. M., Kristian, M. R., & Race, J. H. (2002). Alcohol attentional bias as a predictor of alcohol abusers' treatment outcome. *Drug and alcohol dependence, 68*(3), 237-243.

Crawford, J. R., & Henry, J. D. (2003). The Depression Anxiety Stress Scales (DASS): Normative data and latent structure in a large non‐clinical sample. *British Journal of Clinical Psychology, 42*(2), 111-131.

Crego, A., Holguín, S. R., Parada, M., Mota, N., Corral, M., & Cadaveira, F. (2009). Binge drinking affects attentional and visual working memory processing in young university students. *Alcoholism: Clinical and Experimental Research, 33*(11), 1870-1879.

Crews, F., He, J., & Hodge, C. (2007). Adolescent cortical development: a critical period of vulnerability for addiction. *Pharmacology Biochemistry and Behavior, 86*(2), 189-199.

Crews, F. T., & Boettiger, C. A. (2009). Impulsivity, frontal lobes and risk for addiction. *Pharmacology Biochemistry and Behavior, 93*(3), 237-247.

Crews, F. T., Buckley, T., Dodd, P. R., Ende, G., Foley, N., Harper, C., . . . Pfefferbaum, A. (2005). Alcoholic neurobiology: changes in dependence and recovery. *Alcoholism: Clinical and Experimental Research, 29*(8), 1504-1513.

Crum, R. M., Muntaner, C., Eaton, W. W., & Anthony, J. C. (1995). Occupational stress and the risk of alcohol abuse and dependence. *Alcoholism: Clinical and Experimental Research, 19*(3), 647-655.

Cryan, J. F., & Kaupmann, K. (2005). Don't worry 'B'happy!: a role for GABA B receptors in anxiety and depression. *Trends in Pharmacological Sciences, 26*(1), 36-43.

Davies, M. (2003). The role of GABAA receptors in mediating the effects of alcohol in the central nervous system. *Journal of Psychiatry & Neuroscience*.

Dawe, S., Gullo, M. J., & Loxton, N. J. (2004). Reward drive and rash impulsiveness as dimensions of impulsivity: implications for substance misuse. *Addictive behaviors, 29*(7), 1389-1405.

Dawe, S., & Loxton, N. J. (2004). The role of impulsivity in the development of substance use and eating disorders. *Neuroscience & Biobehavioral Reviews, 28*(3), 343-351.

De Wit, H. (2009). Impulsivity as a determinant and consequence of drug use: a review of underlying processes. *Addiction biology, 14*(1), 22-31.

Degnan, K. A., & Fox, N. A. (2007). Behavioral inhibition and anxiety disorders: Multiple levels of a resilience process. *Development and psychopathology, 19*(03), 729-746.

Denys, D. (2014). Compulsivity and free will. *CNS spectrums, 19*(01), 8-9.

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., . . . Hyman, B. T. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage, 31*(3), 968-980.

Dick, D. M., Smith, G., Olausson, P., Mitchell, S. H., Leeman, R. F., O'Malley, S. S., & Sher, K. (2010). Review: understanding the construct of impulsivity and its relationship to alcohol use disorders. *Addiction biology, 15*(2), 217-226.

Do, K. T., & Galván, A. (2016). Neural Sensitivity to Smoking Stimuli Is Associated With Cigarette Craving in Adolescent Smokers. *Journal of adolescent health, 58*(2), 186-194.

Dodds, C. M., Morein-Zamir, S., & Robbins, T. W. (2010). Dissociating inhibition, attention, and response control in the frontoparietal network using functional magnetic resonance imaging. *Cerebral Cortex, 21*(5), 10.

Dolcos, F., LaBar, K. S., & Cabeza, R. (2004). Dissociable effects of arousal and valence on prefrontal activity indexing emotional evaluation and subsequent memory: an event-related fMRI study. *Neuroimage, 23*(1), 64-74.

Donovan, J. E. (2004). Adolescent alcohol initiation: a review of psychosocial risk factors. *Journal of adolescent health, 35*(6), 529-e527.

Dubowski, K. M. (1957). Stages of acute alcoholic influence/intoxication. *POLICE, 1*(3), 32.

Duckworth, A. L., Tsukayama, E., & Kirby, T. A. (2013). Is it really self-control? Examining the predictive power of the delay of gratification task. *Personality and Social Psychology Bulletin*, 843-855.

Durana, J., Barnes, P., Johnson, J., & Shure, M. (1993). A neurodevelopmental view of impulsivity and its relationship to the superfactors of personality. *The impulsive client*, 23-37.

Dwyer-Lindgren, L., Flaxman, A. D., Ng, M., Hansen, G. M., Murray, C. J., & Mokdad, A. H. (2015). Drinking patterns in US counties from 2002 to 2012. *American journal of public health, 105*(6), 1120-1127.

Economidou, D., Cippitelli, A., Stopponi, S., Braconi, S., Clementi, S., Ubaldi, M., . . . Ciccocioppo, R. (2011). Activation of brain NOP receptors attenuates acute and protracted alcohol withdrawal symptoms in the rat. *Alcoholism: Clinical and Experimental Research, 35*(4), 747-755.

Elliott, R., Ogilvie, A., Rubinsztein, J. S., Calderon, G., Dolan, R. J., & Sahakian, B. J. (2004). Abnormal ventral frontal response during performance of an affective go/no go task in patients with mania. *Biological psychiatry, 55*(12), 1163-1170.

Enoch, M.-A. (2006). Genetic and environmental influences on the development of alcoholism. *Annals of the New York Academy of Sciences, 1094*(1), 193-201.

Enoch, M.-A. (2008). The role of GABA A receptors in the development of alcoholism. *Pharmacology Biochemistry and Behavior, 90*(1), 95-104.

Erickson, K., Drevets, W. C., Clark, L., Cannon, D. M., Bain, E. E., Zarate Jr, C. A., . . . Sahakian, B. J. (2005). Mood-congruent bias in affective go/no-go performance of unmedicated patients with major depressive disorder. *American Journal of Psychiatry, 162*(11), 2171-2173.

Esposito, F., Pignataro, G., Di Renzo, G., Spinali, A., Paccone, A., Tedeschi, G., & Annunziato, L. (2010). Alcohol increases spontaneous BOLD signal fluctuations in the visual network. *Neuroimage, 53*(2), 534-543.

Esterman, M., Liu, G., Okabe, H., Reagan, A., Thai, M., & DeGutis, J. (2015). Frontal eye field involvement in sustaining visual attention: Evidence from transcranial magnetic stimulation. *Neuroimage, 111*, 542-548.

Esterman, M., Noonan, S. K., Rosenberg, M., & DeGutis, J. (2012). In the zone or zoning out? Tracking behavioral and neural fluctuations during sustained attention. *Cerebral Cortex, 23*(11).

Esterman, M., Poole, V., Liu, G., & DeGutis, J. (2016). Modulating Reward Induces Differential Neurocognitive Approaches to Sustained Attention. *Cerebral Cortex*, 1-11.

Esterman, M., Tamber-Rosenau, B. J., Chiu, Y.-C., & Yantis, S. (2010). Avoiding non-independence in fMRI data analysis: leave one subject out. *Neuroimage, 50*(2), 572-576.

Euser, A. M., Oosterhoff, M., & van Balkom, I. (2016). Stuck song syndrome: musical obsessions—when to look for OCD. *Br J Gen Pract, 66*(643), 90-90.

Evenden, J. L. (1999). Varieties of impulsivity. *Psychopharmacology, 146*(4), 348-361.

Fadardi, J. S., & Cox, W. M. (2009). Reversing the sequence: reducing alcohol consumption by overcoming alcohol attentional bias. *Drug and alcohol dependence, 101*(3), 137-145.

Farooqi, I. S., & O'Rahilly, S. (2007). Genetic factors in human obesity. *Obesity Reviews, 8*(s1), 37-40.

Fein, G., Sclafani, V., Cardenas, V., Goldmann, H., Tolou‐Shams, M., & Meyerhoff, D. J. (2002). Cortical gray matter loss in treatment‐naive alcohol dependent individuals. *Alcoholism: Clinical and Experimental Research, 26*(4), 558-564.

Fein, G., Shimotsu, R., & Barakos, J. (2010). Age‐Related Gray Matter Shrinkage in a Treatment Naïve Actively Drinking Alcohol‐Dependent Sample. *Alcoholism: Clinical and Experimental Research, 34*(1), 175-182.

Field, M., Wiers, R. W., Christiansen, P., Fillmore, M. T., & Verster, J. C. (2010). Acute alcohol effects on inhibitory control and implicit cognition: implications for loss of control over drinking. *Alcoholism: Clinical and Experimental Research, 34*(8), 1346-1352.

Finn, P. R., Earleywine, M., & Pihl, R. O. (1992). Sensation seeking, stress reactivity, and alcohol dampening discriminate the density of a family history of alcoholism. *Alcoholism: Clinical and Experimental Research, 16*(3), 585-590.

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences, 97*(20), 11050-11055.

Fischl, B., Liu, A., & Dale, A. M. (2001). Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE transactions on medical imaging, 20*(1), 70-80.

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., . . . Dale, A. M. (2002). Whole Brain Segmentation. *Neuron, 33*(3), 341-355.

Fischl, B., Sereno, M. I., Tootell, R. B., & Dale, A. M. (1999). High-resolution intersubject averaging and a coordinate system for the cortical surface. *Human brain mapping, 8*(4), 272-284.

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D. H., . . . Kennedy, D. (2004). Automatically parcellating the human cerebral cortex. *Cerebral Cortex, 14*(1), 11-22.

Flannery, B., Volpicelli, J., & Pettinati, H. (1999). Psychometric properties of the Penn alcohol craving scale. *Alcoholism: Clinical and Experimental Research, 23*(8), 1289-1295.

Fliessbach, K., Weber, B., Trautner, P., Dohmen, T., Sunde, U., Elger, C. E., & Falk, A. (2007). Social comparison affects reward-related brain activity in the human ventral striatum. *Science, 318*(5854), 1305-1308.

Fortier, C. B., Leritz, E. C., Salat, D. H., Venne, J. R., Maksimovskiy, A. L., Williams, V., . . . McGlinchey, R. E. (2011). Reduced Cortical Thickness in Abstinent Alcoholics and Association with Alcoholic Behavior. *Alcoholism: Clinical ..., 35*(12), 2193-2201.

Foundation for a Drug-Free World. (2016). Alcohol: A Short History. Retrieved from http://www.drugfreeworld.org/drugfacts/alcohol/a-short-history.html

Franklin, T. B., Saab, B. J., & Mansuy, I. M. (2012). Neural mechanisms of stress resilience and vulnerability. *Neuron, 75*(5), 747-761.

Frone, M. R., Barnes, G. M., & Farrell, M. P. (1994). Relationship of work-family conflict to substance use among employed mothers: The role of negative affect. *Journal of Marriage and the Family*, 1019-1030.

Furl, N., & Averbeck, B. B. (2011). Parietal cortex and insula relate to evidence seeking relevant to reward-related decisions. *Journal of neuroscience, 31*(48), 17572-17582.

Galarreta, M., & Hestrin, S. (1998). Frequency-dependent synaptic depression and the balance of excitation and inhibition in the neocortex. *Nature neuroscience, 1*(7), 587-594.

Galvan, A. (2010). Adolescent development of the reward system. *Frontiers in human neuroscience, 4*, 116-124.

Galvan, A., Hare, T., Voss, H., Glover, G., & Casey, B. (2007). Risk‐taking and the adolescent brain: who is at risk? *Developmental science, 10*(2), F8-F14.

Garland, E. L., Franken, I. H., & Howard, M. O. (2012). Cue-elicited heart rate variability and attentional bias predict alcohol relapse following treatment. *Psychopharmacology, 222*(1), 17-26.

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., . . . Rapoport, J. L. (1999). Brain development during childhood and adolescence: a longitudinal MRI study. *Nature neuroscience, 2*(10), 861-863.

Gil-Hernandez, S., & Garcia-Moreno, L. M. (2016). Executive performance and dysexecutive symptoms in binge drinking adolescents. *Alcohol, 51*, 79-87.

Glasser, M. F., Smith, S. M., Marcus, D. S., Andersson, J. L., Auerbach, E. J., Behrens, T. E., . . . Moeller, S. (2016). The human connectome project's neuroimaging approach. *Nature neuroscience, 19*(9), 1175-1187.

Gmeindl, L., Chiu, Y.-C., Esterman, M. S., Greenberg, A. S., Courtney, S. M., & Yantis, S. (2016). Tracking the will to attend: Cortical activity indexes self-generated, voluntary shifts of attention. *Attention, Perception, & Psychophysics, 78*(7), 1-9.

Goeleven, E., De Raedt, R., Baert, S., & Koster, E. H. (2006). Deficient inhibition of emotional information in depression. *Journal of affective disorders, 93*(1), 149-157.

Goldin, P. R., McRae, K., Ramel, W., & Gross, J. J. (2008). The neural bases of emotion regulation: reappraisal and suppression of negative emotion. *Biological psychiatry, 63*(6), 577-586.

Goleman, D. J., & Schwartz, G. E. (1976). Meditation as an intervention in stress reactivity. *Journal of Consulting and Clinical Psychology, 44*(3), 456.

Gonçalves, Ó. F., Carvalho, S., Leite, J., Fernandes-Gonçalves, A., Carracedo, A., & Sampaio, A. (2016). Gray Matter Morphological Alteration in Obsessive Compulsive Disorder: Evidence for an Inhibitory Control and Emotional Regulation Disorder. *Principles and Practice of Clinical Research, 2*(2).

Gorwood, P., Schumann, G., Treutlein, J., & Adès, J. (2006). Pharmacogenetics of alcohol-dependence *Psychopharmacogenetics* (pp. 177-201): Springer.

Grandy, D. K., Litt, M., Allen, L., Bunzow, J., Marchionni, M., Makam, H., . . . Civelli, O. (1989). The human dopamine D2 receptor gene is located on chromosome 11 at q22-q23 and identifies a TaqI RFLP. *American journal of human genetics, 45*(5), 778.

Grant, B. F., & Harford, T. C. (1995). Comorbidity between DSM-IV alcohol use disorders and major depression: results of a national survey. *Drug and alcohol dependence, 39*(3), 197-206.

Gray, M. J., Litz, B. T., Hsu, J. L., & Lombardo, T. W. (2004). Psychometric properties of the life events checklist. *Assessment, 11*(4), 330-341.

Greenberg, A. S., Esterman, M., Wilson, D., Serences, J. T., & Yantis, S. (2010). Control of spatial and feature-based attention in frontoparietal cortex. *The Journal of Neuroscience, 30*(43), 14330-14339.

Grier, R. A., Warm, J. S., Dember, W. N., Matthews, G., Galinsky, T. L., Szalma, J. L., & Parasuraman, R. (2003). The vigilance decrement reflects limitations in effortful attention, not mindlessness. *Human Factors: The Journal of the Human Factors and Ergonomics Society, 45*(3), 349-359.

Griffiths, K., Lagopoulos, J., Hermens, D., Hickie, I., & Balleine, B. (2015). Right external globus pallidus changes are associated with altered causal awareness in youth with depression. *Translational psychiatry, 5*(10).

Groenewegen, H. J. (2003). The basal ganglia and motor control. *Neural plasticity, 10*(1-2), 107-120.

Grüsser, S. M., Wrase, J., Klein, S., Hermann, D., Smolka, M. N., Ruf, M., . . . Braus, D. F. (2004). Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology, 175*(3), 296-302.

Grzywacz, J. G., & Almeida, D. M. (2008). Stress and binge drinking: A daily process examination of stressor pile-up and socioeconomic status in affect regulation. *International Journal of Stress Management, 15*(4), 364.

Gujar, N., Yoo, S.-S., Hu, P., & Walker, M. P. (2011). Sleep deprivation amplifies reactivity of brain reward networks, biasing the appraisal of positive emotional experiences. *The Journal of Neuroscience, 31*(12), 4466-4474.

Hamilton, J. P., & Gotlib, I. H. (2008). Neural substrates of increased memory sensitivity for negative stimuli in major depression. *Biological psychiatry, 63*(12), 1155-1162.

Hampshire, A., Chamberlain, S. R., Monti, M. M., Duncan, J., & Owen, A. M. (2010). The role of the right inferior frontal gyrus: inhibition and attentional control. *Neuroimage, 50*(3), 1313-1319.

Harding, A., Halliday, G., Caine, D., & Kril, J. (2000). Degeneration of anterior thalamic nuclei differentiates alcoholics with amnesia. *Brain, 123*(1), 141-154.

Harding, A., Wong, A., Svoboda, M., Kril, J., & Halliday, G. (1997). Chronic alcohol consumption does not cause hippocampal neuron loss in humans. *Hippocampus, 7*(1), 78-87.

Hariri, A. R., Bookheimer, S. Y., & Mazziotta, J. C. (2000). Modulating emotional responses: effects of a neocortical network on the limbic system. *Neuroreport, 11*(1), 43-48.

Harper, C. (1998). The neuropathology of alcohol-specific brain damage, or does alcohol damage the brain? *Journal of Neuropathology & Experimental Neurology, 57*(2), 101-110.

Harper, C., & Kril, J. (1989). Patterns of neuronal loss in the cerebral cortex in chronic alcoholic patients. *Journal of the neurological sciences, 92*(1), 81-89.

Harper, C., Kril, J., & Daly, J. (1987). Are we drinking our neurones away? *Br Med J (Clin Res Ed), 294*(6571), 534-536.

Harper, C., & Matsumoto, I. (2005). Ethanol and brain damage. *Current opinion in pharmacology, 5*(1), 73-78.

Hazeltine, E., Grafton, S. T., & Ivry, R. (1997). Attention and stimulus characteristics determine the locus of motor-sequence encoding. A PET study. *Brain, 120*(1), 123-140.

Heinz, A., Siessmeier, T., Wrase, J., Hermann, D., Klein, S., Grüsser-Sinopoli, S. M., . . . Gründer, G. (2014a). Correlation between dopamine D2 receptors in the ventral striatum

and central processing of alcohol cues and craving. *American Journal of Psychiatry, 161*(10).

Heinz, A., Siessmeier, T., Wrase, J., Hermann, D., Klein, S., Grüsser-Sinopoli, S. M., . . . Gründer, G. (2014b). Correlation between dopamine D2 receptors in the ventral striatum and central processing of alcohol cues and craving. *American Journal of Psychiatry*.

Hellemans, K. G., Verma, P., Yoon, E., Yu, W., & Weinberg, J. (2008). Prenatal alcohol exposure increases vulnerability to stress and anxiety‐like disorders in adulthood. *Annals of the New York Academy of Sciences, 1144*(1), 154-175.

Hendershot, C. S., Wardell, J. D., McPhee, M. D., & Ramchandani, V. A. (2016). A prospective study of genetic factors, human laboratory phenotypes, and heavy drinking in late adolescence. *Addiction biology*, n/a-n/a.

Herman, J. P., & Cullinan, W. E. (1997). Neurocircuitry of stress: central control of the hypothalamo–pituitary–adrenocortical axis. *Trends in neurosciences, 20*(2), 78-84.

Higley, J., Hasert, M., Suomi, S., & Linnoila, M. (1991). Nonhuman primate model of alcohol abuse: effects of early experience, personality, and stress on alcohol consumption. *Proceedings of the National Academy of Sciences, 88*(16), 7261-7265.

Hill, J. C., & Toffolon, G. (1990). Effect of alcohol on sensory and sensorimotor visual functions. *Journal of Studies on Alcohol, 51*(2), 108-113.

Holmes, A. J., Hollinshead, M. O., Roffman, J. L., Smoller, J. W., & Buckner, R. L. (2016). Individual Differences in Cognitive Control Circuit Anatomy Link Sensation Seeking, Impulsivity, and Substance Use. *The Journal of Neuroscience, 36*(14), 4038-4049.

Hommer, D. W., Momenan, R., Kaiser, E., & Rawlings, R. R. (2001). Evidence for a gender-related effect of alcoholism on brain volumes. *American Journal of Psychiatry, 158*(2), 198-204.

Houben, K., Havermans, R. C., Nederkoorn, C., & Jansen, A. (2012). Beer à No‐Go: Learning to stop responding to alcohol cues reduces alcohol intake via reduced affective associations rather than increased response inhibition. *Addiction, 107*(7), 1280-1287.

Houben, K., Nederkoorn, C., Wiers, R. W., & Jansen, A. (2011). Resisting temptation: decreasing alcohol-related affect and drinking behavior by training response inhibition. *Drug and alcohol dependence, 116*(1), 132-136.

Houghton, G., & Tipper, S. P. (1996). Inhibitory mechanisms of neural and cognitive control: Applications to selective attention and sequential action. *Brain and cognition, 30*(1), 20-43.

Howell, N. A., Prescott, I. A., Lozano, A. M., Hodaie, M., Voon, V., & Hutchison, W. D. (2016). Preliminary evidence for human globus pallidus pars interna neurons signaling reward and sensory stimuli. *Neuroscience, 328*, 30-39.

Hussong, A. M., & Chassin, L. (1994). The stress-negative affect model of adolescent alcohol use: disaggregating negative affect. *Journal of Studies on Alcohol, 55*(6), 707-718.

Ito, T. A., Larsen, J. T., Smith, N. K., & Cacioppo, J. T. (1998). Negative information weighs more heavily on the brain: the negativity bias in evaluative categorizations. *Journal of Personality and Social Psychology, 75*(4), 887.

Jacobs, S. C., Friedman, R., Parker, J. D., Tofler, G. H., Jimenez, A. H., Muller, J. E., . . . Stone, P. H. (1994). Use of skin conductance changes during mental stress testing as an index of autonomic arousal in cardiovascular research. *American heart journal, 128*(6), 1170-1177.

Jellinek, E. M. (1960). *The disease concept of alcoholism*. New Haven, Connecticut: Hillhouse Press.

Jennison, K. M. (2004). The short‐term effects and unintended long‐term consequences of binge drinking in college: a 10‐year follow‐up study. *The American journal of drug and alcohol abuse, 30*(3), 659-684.

Jones, K. L. (2011). The effects of alcohol on fetal development. *Birth Defects Research Part C: Embryo Today: Reviews, 93*(1), 3-11.

Jones, S. A., Cservenka, A., & Nagel, B. J. (2016). Binge drinking impacts dorsal striatal response during decision making in adolescents. *Neuroimage, 129*, 378-388.

Joormann, J. (2006). Differential effects of rumination and dysphoria on the inhibition of irrelevant emotional material: Evidence from a negative priming task. *Cognitive therapy and research, 30*(2), 149-160.

Kagan, J., Reznick, J. S., & Snidman, N. (1987). The physiology and psychology of behavioral inhibition in children. *Child development*, 1459-1473.

Kamarajan, C., Porjesz, B., Jones, K. A., Choi, K., Chorlian, D. B., Padmanabhapillai, A., . . . Begleiter, H. (2005). Alcoholism is a disinhibitory disorder: neurophysiological evidence from a Go/No-Go task. *Biological Psychology, 69*(3), 353-373.

Karen, S. A. M. J. L., & Sasmita, S. (2016). Rewards Boost Sustained Attention through Higher. *Nature, 216*, 515-516.

Karreman, M., & Moghaddam, B. (1996). The prefrontal cortex regulates the basal release of dopamine in the limbic striatum: an effect mediated by ventral tegmental area. *Journal of neurochemistry, 66*(2), 589-598.

Keller, J., Young, C. B., Kelley, E., Prater, K., Levitin, D. J., & Menon, V. (2013). Trait anhedonia is associated with reduced reactivity and connectivity of mesolimbic and paralimbic reward pathways. *Journal of psychiatric research, 47*(10), 1319-1328.

Kelley, T. A., Serences, J. T., Giesbrecht, B., & Yantis, S. (2008). Cortical mechanisms for shifting and holding visuospatial attention. *Cerebral Cortex, 18*(1), 114-125.

Kennerley, S. W., Dahmubed, A. F., Lara, A. H., & Wallis, J. D. (2009). Neurons in the frontal lobe encode the value of multiple decision variables. *Journal of cognitive neuroscience, 21*(6), 1162-1178.

Ketchesin, K. D., Stinnett, G. S., & Seasholtz, A. F. (2016). Binge Drinking Decreases Corticotropin‐Releasing Factor‐Binding Protein Expression in the Medial Prefrontal Cortex of Mice. *Alcoholism: Clinical and Experimental Research, 40*(8), 1641-1650.

Khantzian, E. J. (1997). The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. *Harvard review of psychiatry, 4*(5), 231-244.

Kim, H., Somerville, L. H., Johnstone, T., Alexander, A. L., & Whalen, P. J. (2003). Inverse amygdala and medial prefrontal cortex responses to surprised faces. *Neuroreport, 14*(18), 2317-2322.

King, A. C., De Wit, H., McNamara, P. J., & Cao, D. (2011). Rewarding, stimulant, and sedative alcohol responses and relationship to future binge drinking. *Archives of general psychiatry, 68*(4), 389-399.

King, A. C., McNamara, P. J., Hasin, D. S., & Cao, D. (2014). Alcohol challenge responses predict future alcohol use disorder symptoms: a 6-year prospective study. *Biological psychiatry, 75*(10), 798-806.

King, D., King, L., & Vogt, D. (2003). Manual for the Deployment Risk and Resilience Inventory (DRRI): A collection of measures for studying deployment-related experiences of military veterans. *Boston, MA: National Center for PTSD*.

Klatsky, A. L., Friedman, G. D., Siegelaub, A. B., & Gérard, M. J. (1977). Alcohol consumption and blood pressure: Kaiser-Permanente multiphasic health examination data. *New England Journal of Medicine, 296*(21), 1194-1200.

Klooster, A., Larkin, J. R., Wiersema-Buist, J., Gans, R. O., Thornalley, P. J., Navis, G., . . . Bakker, S. J. (2013). Are brain and heart tissue prone to the development of thiamine deficiency? *Alcohol, 47*(3), 215-221.

Knight, R. T., Staines, W. R., Swick, D., & Chao, L. L. (1999). Prefrontal cortex regulates inhibition and excitation in distributed neural networks. *Acta psychologica, 101*(2), 159-178.

Kober, H., Mende-Siedlecki, P., Kross, E. F., Weber, J., Mischel, W., Hart, C. L., & Ochsner, K. N. (2010). Prefrontal–striatal pathway underlies cognitive regulation of craving. *Proceedings of the National Academy of Sciences, 107*(33), 14811-14816.

Koob, G. F. (2003a). Alcoholism: Allostasis and Beyond. *Alcoholism: Clinical and Experimental Research, 27*(2), 232-243.

Koob, G. F. (2003b). Alcoholism: Allostasis and Beyond. Figure 1. In F. 1. (Ed.). Alcoholism: Clinical and Experimental Research: John Wiley and Sons.

Koob, G. F. (2004). A role for GABA mechanisms in the motivational effects of alcohol. *Biochemical pharmacology, 68*(8), 1515-1525.

Koob, G. F., & Le Moal, M. (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology, 24*(2), 97-129.

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology, 35*(1), 217-238.

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: a neurocircuitry analysis. *The Lancet Psychiatry, 3*(8), 760-773.

Koster, E. H., De Raedt, R., Goeleven, E., Franck, E., & Crombez, G. (2005). Mood-congruent attentional bias in dysphoria: maintained attention to and impaired disengagement from negative information. *Emotion, 5*(4), 446.

Kreek, M. J., Nielsen, D. A., Butelman, E. R., & LaForge, K. S. (2005). Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. *Nature neuroscience, 8*(11), 1450-1457.

Kuffler, S. W., Nicholls, J. G., & Martin, A. (1976). A cellular approach to the function of the nervous system. *Massachusetts: Sinauer Assoc*.

Kühn, S., Schubert, F., & Gallinat, J. (2011). Structural correlates of trait anxiety: reduced thickness in medial orbitofrontal cortex accompanied by volume increase in nucleus accumbens. *Journal of affective disorders, 134*(1), 315-319.

Kumar, S., Porcu, P., Werner, D. F., Matthews, D. B., Diaz-Granados, J. L., Helfand, R. S., & Morrow, A. L. (2009). The role of GABAA receptors in the acute and chronic effects of ethanol: a decade of progress. *Psychopharmacology, 205*(4), 529-564.

Kumpfer, K. L., & Bluth, B. (2004). Parent/child transactional processes predictive of resilience or vulnerability to "substance abuse disorders". *Substance use & misuse, 39*(5), 671-698.

Kuperberg, G. R., Broome, M. R., McGuire, P. K., David, A. S., Eddy, M., Ozawa, F., . . . van der Kouwe, A. J. (2003). Regionally localized thinning of the cerebral cortex in schizophrenia. *Archives of general psychiatry, 60*(9), 878-888.

Kurzban, R., Duckworth, A., Kable, J. W., & Myers, J. (2013). An opportunity cost model of subjective effort and task performance. *Behavioral and Brain Sciences, 36*(06), 661-679.

Lamm, C., Benson, B., Guyer, A., Perez-Edgar, K., Fox, N., Pine, D., & Ernst, M. (2014). Longitudinal study of striatal activation to reward and loss anticipation from mid-adolescence into late adolescence/early adulthood. *Brain and cognition, 89*, 51-60.

Larimer, M. E., Turner, A. P., Anderson, B. K., Fader, J. S., Kilmer, J. R., Palmer, R. S., & Cronce, J. M. (2001). Evaluating a brief alcohol intervention with fraternities. *Journal of Studies on Alcohol, 62*(3), 370-380.

Lau-Barraco, C., Linden-Carmichael, A. N., Hequembourg, A., & Pribesh, S. (2016). Motivations and Consequences of Alcohol Use Among Heavy Drinking Nonstudent Emerging Adults. *Journal of Adolescent Research*, 1-29.

Le Pelley, M., Beesley, T., & Griffiths, O. (2016). Associative learning and derived attention in humans. *The Wiley Handbook on the Cognitive Neuroscience of Learning*, 114-135.

Le Pelley, M., Mitchell, C., Beesley, T., George, D., & Wills, A. (2016). Attention and associative learning in humans: An integrative review. *Psychological Bulletin, 142*(10), 1111.

Levine, D. S. (2000). *Introduction to neural and cognitive modeling* (2 ed.). Mahwah, NJ: Lawrence Erlbaum Associates.

Lewis, D. A. (1997). Development of the prefrontal cortex during adolescence: insights into vulnerable neural circuits in schizophrenia. *Neuropsychopharmacology, 16*(6), 385-398.

Lisdahl, K. M., Thayer, R., Squeglia, L. M., McQueeny, T. M., & Tapert, S. F. (2013). Recent binge drinking predicts smaller cerebellar volumes in adolescents. *Psychiatry Research: Neuroimaging, 211*(1), 17-23.

Lishman, W. (1990). Alcohol and the brain. *The British Journal of Psychiatry, 156*(5), 635-644.

Liu, T., Slotnick, S. D., Serences, J. T., & Yantis, S. (2003). Cortical mechanisms of feature-based attentional control. *Cerebral Cortex, 13*(12), 1334-1343.

Liu, X., Liu, J., Gai, S., Meyer, K., Xu, S., & Cai, X. (2016). Time–frequency distribution properties of event-related potentials in mental fatigue induced by visual memory tasks. *Neuroreport, 27*(14), 1031-1036.

Lowe, C., & Rabbitt, P. (1998). Test\ re-test reliability of the CANTAB and ISPOCD neuropsychological batteries: theoretical and practical issues. *Neuropsychologia, 36*(9), 915-923.

MacKillop, J., Amlung, M. T., Few, L. R., Ray, L. A., Sweet, L. H., & Munafò, M. R. (2011). Delayed reward discounting and addictive behavior: a meta-analysis. *Psychopharmacology, 216*(3), 305-321.

Makris, N., Oscar-Berman, M., Jaffin, S. K., Hodge, S. M., Kennedy, D. N., Caviness, V. S., . . . Harris, G. J. (2008). Decreased volume of the brain reward system in alcoholism. *Biological psychiatry, 64*(3), 192-202.

Mangione, T. W., Howland, J., Amick, B., Cote, J., Lee, M., Bell, N., & Levine, S. (1999). Employee drinking practices and work performance. *Journal of Studies on Alcohol, 60*(2), 261-270.

Manly, T., Robertson, I. H., Galloway, M., & Hawkins, K. (1999). The absent mind: further investigations of sustained attention to response. *Neuropsychologia, 37*(6), 661-670.

Marchitti, S. A., Brocker, C., Stagos, D., & Vasiliou, V. (2008). Non-P450 aldehyde oxidizing enzymes: the aldehyde dehydrogenase superfamily. *Expert opinion on drug metabolism & toxicology, 4*(6), 697-720.

Marczinski, C. A., Fillmore, M. T., Henges, A. L., Ramsey, M. A., & Young, C. R. (2013). Mixing an energy drink with an alcoholic beverage increases motivation for more alcohol in college students. *Alcoholism: Clinical and Experimental Research, 37*(2), 276-283.

Markus, C. R., & De Raedt, R. (2011). Differential effects of 5-HTTLPR genotypes on inhibition of negative emotional information following acute stress exposure and tryptophan challenge. *Neuropsychopharmacology, 36*(4), 819-826.

Marlatt, G. A. (1976). Alcohol, stress, and cognitive control. In I. G. Sarason & C. D. Spielberger (Eds.), *Stress and Anxiety*. University of Michigan: John Wiley & Sons, Incorporated.

Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering minds: the default network and stimulus-independent thought. *Science, 315*(5810), 393-395.

Massar, S., Lim, J., Sasmita, K., & Chee, M. (2016). Rewards boost sustained attention through higher effort: A value-based decision making approach. *Biological Psychology, 120*, 21-27.

Masten, A. S., Best, K. M., & Garmezy, N. (1990). Resilience and development: Contributions from the study of children who overcome adversity. *Development and psychopathology, 2*(04), 425-444.

Mathews, A., & MacLeod, C. (2002). Induced processing biases have causal effects on anxiety. *Cognition & Emotion, 16*(3), 331-354.

McAteer, A. M., Curran, D., & Hanna, D. (2015). Alcohol attention bias in adolescent social drinkers: an eye tracking study. *Psychopharmacology, 232*(17), 3183-3191.

McCabe, S. E. (2002). Gender differences in collegiate risk factors for heavy episodic drinking. *Journal of Studies on Alcohol, 63*(1), 49-56.

McClure, S. M., Daw, N. D., & Montague, P. R. (2003). A computational substrate for incentive salience. *Trends in neurosciences, 26*(8), 423-428.

McGlinchey, R. E., Milberg, W. P., Fonda, J. R., & Fortier, C. B. (2017). A methodology for assessing deployment trauma and its consequences in OEF/OIF/OND veterans: The TRACTS longitudinal prospective cohort study. *International journal of methods in psychiatric research*.

McGlinchey, R. E., Milberg, W. P., Fonda, J. R., & Fortier, C. B. (In press). A methodology for assessing deployment trauma and its consequences in OEF/OIF/OND Veterans: the TRACTS longitudinal prospective cohort study. *International Journal of Methods in Psychiatric Research.*

McGlinchey‐Berroth, R., Cermak, L. S., Carrillo, M. C., Armfield, S., Gabrieli, J. D., & Disterhoft, J. F. (1995). Impaired delay eyeblink conditioning in amnesic Korsakoff s patients and recovered alcoholics. *Alcoholism: Clinical and Experimental Research, 19*(5), 1127-1132.

McGovern, T. F., & White, W. L. (2002). *Alcohol Problems in the United States: Twenty Years of Treatment Perspective*: Haworth Press.

Meaney, M. J. (2001). Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annual review of neuroscience, 24*(1), 1161-1192.

Mellos, E. (2009). Comorbidity in alcohol-use disorders. *Encephalos, 46*(2), 72-78.

Migliaccio, R., Gallea, C., Kas, A., Perlbarg, V., Samri, D., Trotta, L., . . . Lehericy, S. (2016). Functional Connectivity of Ventral and Dorsal Visual Streams in Posterior Cortical Atrophy. *Journal of Alzheimer's Disease*(Preprint), 1-12.

Mitchell, J. M., O'Neil, J. P., Janabi, M., Marks, S. M., Jagust, W. J., & Fields, H. L. (2012). Alcohol consumption induces endogenous opioid release in the human orbitofrontal cortex and nucleus accumbens. *Science translational medicine, 4*(116).

Modell, J. G., Glaser, F. B., Cyr, L., & Mountz, J. M. (1992). Obsessive and compulsive characteristics of craving for alcohol in alcohol abuse and dependence. *Alcoholism: Clinical and Experimental Research, 16*(2), 272-274.

Monk, C. S., McClure, E. B., Nelson, E. E., Zarahn, E., Bilder, R. M., Leibenluft, E., . . . Pine, D. S. (2003). Adolescent immaturity in attention-related brain engagement to emotional facial expressions. *Neuroimage, 20*(1), 420-428.

Moussawi, K., Kalivas, P. W., & Lee, J. W. (2016). Abstinence from drug dependence after bilateral Globus Pallidus hypoxic ischemic injury. *Biological psychiatry*.

Müller-Oehring, E., Jung, Y., Sullivan, E., Hawkes, W., Pfefferbaum, A., & Schulte, T. (2013). Midbrain-driven emotion and reward processing in alcoholism. *Neuropsychopharmacology, 38*(10), 1844-1853.

Murphy, F., Sahakian, B., Rubinsztein, J., Michael, A., Rogers, R., Robbins, T., & Paykel, E. (1999). Emotional bias and inhibitory control processes in mania and depression. *Psychological Medicine, 29*(06), 1307-1321.

N.I.A.A.A. (2016a, June 2016). Alcohol Facts and Statistics. Retrieved from https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/alcohol-facts-and-statistics

N.I.A.A.A. (2016b). Drinking Levels Defined. Retrieved from https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking

Neuromorphometrics, I. (2005). Segmentation: Ventral Diencephalon. Retrieved from http://www.neuromorphometrics.org:8080/seg/html/segmentation/ventral diencephalon.html

Nicholls, M. E., Loveless, K. M., Thomas, N. A., Loetscher, T., & Churches, O. (2015). Some participants may be better than others: sustained attention and motivation are higher early in semester. *The Quarterly Journal of Experimental Psychology, 68*(1), 10-18.

Nicholson, M. E., Andre, J. T., Tyrrell, R. A., Wang, M., & Leibowitz, H. W. (1995). Effects of moderate dose alcohol on visual contrast sensitivity for stationary and moving targets. *Journal of Studies on Alcohol, 56*(3), 261-266.

Nicola, S. M. (2007). The nucleus accumbens as part of a basal ganglia action selection circuit. *Psychopharmacology, 191*(3), 521-550.

Niv, Y., Daw, N. D., Joel, D., & Dayan, P. (2007). Tonic dopamine: opportunity costs and the control of response vigor. *Psychopharmacology, 191*(3), 507-520.

Noble, E., Jeor, S. S., Ritchie, T., Syndulko, K., Jeor, S. S., Fitch, R., . . . Sparkes, R. (1994). D2 dopamine receptor gene and cigarette smoking: a reward gene? *Medical hypotheses, 42*(4), 257-260.

Notarius, C. I., & Levenson, R. W. (1979). Expressive tendencies and physiological response to stress. *Journal of Personality and Social Psychology, 37*(7), 1204.

Ockenfels, M. C., Porter, L., Smyth, J., Kirschbaum, C., Hellhammer, D. H., & Stone, A. A. (1995). Effect of chronic stress associated with unemployment on salivary cortisol: overall cortisol levels, diurnal rhythm, and acute stress reactivity. *Psychosomatic Medicine, 57*(5), 460-467.

Okun, M., & Lampl, I. (2008). Instantaneous correlation of excitation and inhibition during ongoing and sensory-evoked activities. *Nature neuroscience, 11*(5), 535-537.

Olzak, M., Laskowska, I., Jelonek, J., Michalak, M., Szolna, A., Gryz, J., . . . Gorzelanczyk, E. J. (2006). Psychomotor and executive functioning after unilateral posteroventral pallidotomy in patients with Parkinson's disease. *Journal of the neurological sciences, 248*(1), 97-103.

Oscar Berman, M., Kirkley, S. M., Gansler, D. A., & Couture, A. (2004). Comparisons of Korsakoff and Non‐Korsakoff Alcoholics on Neuropsychological Tests of Prefrontal Brain Functioning. *Alcoholism: Clinical and Experimental Research, 28*(4), 667-675.

Oscar Berman, M., Valmas, M. M., Sawyer, K. S., Ruiz, S. M., Luhar, R. B., & Gravitz, Z. R. (2014). Profiles of impaired, spared, and recovered neuropsychological processes in alcoholism. In A. Pfefferbaum & E. V. Sullivan (Eds.), *Handbook of Clinical Neurology: Alcohol and the Nervous System.* (Vol. 125, pp. 183-210). Edinburgh: Elsevier.

Oslin, D., Atkinson, R. M., Smith, D. M., & Hendrie, H. (1998). Alcohol related dementia: proposed clinical criteria. *International journal of geriatric psychiatry, 13*(4), 203-212.

Parada, M., Corral, M., Mota, N., Crego, A., Holguín, S. R., & Cadaveira, F. (2012). Executive functioning and alcohol binge drinking in university students. *Addictive behaviors, 37*(2), 167-172.

Pardini, D., Lochman, J., & Wells, K. (2004). Negative emotions and alcohol use initiation in high-risk boys: The moderating effect of good inhibitory control. *Journal of abnormal child psychology, 32*(5), 505-518.

Patrick, C. H. (1952). *Alcohol, culture, and society.* Durham, N.C.: Duke Univ. Pres.

Paus, T. (2010). Growth of white matter in the adolescent brain: myelin or axon? *Brain and cognition, 72*(1), 26-35.

Pearson, P., & Timney, B. (1998). Effects of moderate blood alcohol concentrations on spatial and temporal contrast sensitivity. *Journal of Studies on Alcohol, 59*(2), 163-173.

Petit, G., Kornreich, C., Maurage, P., Noël, X., Letesson, C., Verbanck, P., & Campanella, S. (2012). Early attentional modulation by alcohol-related cues in young binge drinkers: an event-related potentials study. *Clinical neurophysiology, 123*(5), 925-936.

Petry, N. M. (2001). Pathological gamblers, with and without substance abuse disorders, discount delayed rewards at high rates. *Journal of Abnormal Psychology, 110*(3), 482.

Pfefferbaum, A., Lim, K. O., Desmond, J. E., & Sullivan, E. V. (1996). Thinning of the corpus callosum in older alcoholic men: a magnetic resonance imaging study. *Alcoholism: Clinical and Experimental Research, 20*(4), 752-757.

Pfefferbaum, A., Lim, K. O., Zipursky, R. B., Mathalon, D. H., Rosenbloom, M. J., Lane, B., . . . Sullivan, E. V. (1992). Brain gray and white matter volume loss accelerates with aging in chronic alcoholics: a quantitative MRI study. *Alcoholism: Clinical and Experimental Research, 16*(6), 1078-1089.

Pirkola, S. P., Isometsä, E., Suvisaari, J., Aro, H., Joukamaa, M., Poikolainen, K., . . . Lönnqvist, J. K. (2005). DSM-IV mood-, anxiety-and alcohol use disorders and their comorbidity in the Finnish general population. *Social psychiatry and psychiatric epidemiology, 40*(1), 1-10.

Piron, C., Kase, D., Topalidou, M., Goillandeau, M., Orignac, H., N'Guyen, T. H., . . . Boraud, T. (2016). The globus pallidus pars interna in goal‐oriented and routine behaviors: Resolving a long‐standing paradox. *Movement Disorders*.

Pitel, A. L., Rivier, J., Beaunieux, H., Vabret, F., Desgranges, B., & Eustache, F. (2009). Changes in the Episodic Memory and Executive Functions of Abstinent and Relapsed Alcoholics Over a 6‐Month Period. *Alcoholism: Clinical and Experimental Research, 33*(3), 490-498.

Porges, S. W., & Byrne, E. A. (1992). Research methods for measurement of heart rate and respiration. *Biological Psychology, 34*(2-3), 93-130.

Poulton, A., Mackenzie, C., Harrington, K., Borg, S., & Hester, R. (2016). Cognitive control over immediate reward in binge alcohol drinkers. *Alcoholism: Clinical and Experimental Research, 40*(2), 429-437.

Power, J. D., Cohen, A. L., Nelson, S. M., Wig, G. S., Barnes, K. A., Church, J. A., . . . Schlaggar, B. L. (2011). Functional network organization of the human brain. *Neuron, 72*(4), 665-678.

Premi, E., Pilotto, A., Garibotto, V., Bigni, B., Turrone, R., Alberici, A., . . . Formenti, A. (2016). Impulse control disorder in PD: A lateralized monoaminergic frontostriatal disconnection syndrome? *Parkinsonism & Related Disorders, 30*, 62-66.

Ptak, R. (2012). The frontoparietal attention network of the human brain action, saliency, and a priority map of the environment. *The Neuroscientist, 18*(5), 502-515.

Quay, H. C. (1988). The behavioral reward and inhibition system in childhood behavior disorder. In L. M. Bloomingdale (Ed.), *New research in attention, treatment, and psychopharmacology* (pp. 176-186). Elmsford, NY: Pergamon Press.

Rajkowska, G., Miguel-Hidalgo, J. J., Wei, J., Dilley, G., Pittman, S. D., Meltzer, H. Y., . . . Stockmeier, C. A. (1999). Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biological psychiatry, 45*(9), 1085-1098.

Repetti, R. L., Taylor, S. E., & Seeman, T. E. (2002). Risky families: family social environments and the mental and physical health of offspring. *Psychological Bulletin, 128*(2), 330.

Reuter-Lorenz, P. A., Jonides, J., Smith, E. E., Hartley, A., Miller, A., Marshuetz, C., & Koeppe, R. A. (2000). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. *Journal of cognitive neuroscience, 12*(1), 174-187.

Ridderinkhof, K. R., Van Den Wildenberg, W. P., Segalowitz, S. J., & Carter, C. S. (2004). Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain and cognition, 56*(2), 129-140.

Roberts, J. S., Anton, R. F., Latham, P. K., & Moak, D. H. (1999). Factor structure and predictive validity of the Obsessive Compulsive Drinking Scale. *Alcoholism: Clinical and Experimental Research, 23*(9), 1484-1491.

Robertson, I. H., Manly, T., Andrade, J., Baddeley, B. T., & Yiend, J. (1997). Oops!': performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia, 35*(6), 747-758.

Romeo, R. D., & McEwen, B. S. (2006). Stress and the adolescent brain. *Annals of the New York Academy of Sciences, 1094*(1), 202-214.

Romer, D. (2010). Adolescent risk taking, impulsivity, and brain development: Implications for prevention. *Developmental psychobiology, 52*(3), 263-276.

Ron, M. A. (1983). The alcoholic brain: CT scan and psychological findings. *Psychological Medicine Monograph Supplement, 3*, 1-33.

Rosas, H., Liu, A., Hersch, S., Glessner, M., Ferrante, R., Salat, D., . . . Fischl, B. (2002). Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology, 58*(5), 695-701.

Rosett, H. L., Weiner, L., Lee, A., Zuckerman, B., Dooling, E., & Oppenheimer, E. (1983). Patterns of alcohol consumption and fetal development. *Obstetrics & Gynecology, 61*(5), 539-546.

Routtenberg, A., & Huang, Y. H. (1968). Reticular formation and brainstem unitary activity: effects of posterior hypothalamic and septal-limbic stimulation at reward loci. *Physiology & Behavior, 3*(5), 611-617.

Rushworth, M. F., Ellison, A., & Walsh, V. (2001). Complementary localization and lateralization of orienting and motor attention. *Nature neuroscience, 4*(6), 656-661.

Rutter, M. (1987). Psychosocial resilience and protective mechanisms. *American journal of orthopsychiatry, 57*(3), 316.

Sacks, J. J., Gonzales, K. R., Bouchery, E. E., Tomedi, L. E., & Brewer, R. D. (2015). 2010 National and State Costs of Excessive Alcohol Consumption. *American Journal of Preventive Medicine, 49*(5), e73-e79.

Salat, D. H., Buckner, R. L., Snyder, A. Z., Greve, D. N., Desikan, R. S., Busa, E., . . . Fischl, B. (2004). Thinning of the cerebral cortex in aging. *Cerebral Cortex, 14*(7), 721-730.

Salat, D. H., Lee, S. Y., Van der Kouwe, A., Greve, D. N., Fischl, B., & Rosas, H. D. (2009). Age-associated alterations in cortical gray and white matter signal intensity and gray to white matter contrast. *Neuroimage, 48*(1), 21-28.

Sałat, K., Więckowska, A., Więckowski, K., Höfner, G. C., Kamiński, J., Wanner, K. T., . . . Kulig, K. (2012). Synthesis and pharmacological properties of new GABA uptake inhibitors. *Pharmacological Reports, 64*(4), 817-833.

Samejima, K., Ueda, Y., Doya, K., & Kimura, M. (2005). Representation of action-specific reward values in the striatum. *Science, 310*(5752), 1337-1340.

Santhakumar, V., Wallner, M., & Otis, T. S. (2007). Ethanol acts directly on extrasynaptic subtypes of GABA A receptors to increase tonic inhibition. *Alcohol, 41*(3), 211-221.

SAS Institute Inc. (1989-2016.). JMP®, Version 12. Cary, NC.

Savage, L. (2014). Alcohol-Related Brain Damage And Neuropathology. In J. Svanberg, A. Withall, B. Draper, & S. Bowden (Eds.), *Alcohol and the Adult Brain* (Kindle Edition. ed., pp. 107-125): Taylor and Francis.

Sawyer, K. S., Oscar‐Berman, M., Mosher Ruiz, S., Gálvez, D. A., Makris, N., Harris, G. J., & Valera, E. M. (2016). Associations Between Cerebellar Subregional Morphometry and Alcoholism History in Men and Women. *Alcoholism: Clinical and Experimental Research, 40*(6), 1262-1272.

Schacht, J. P., Anton, R. F., Randall, P. K., Li, X., Henderson, S., & Myrick, H. (2011). Stability of fMRI striatal response to alcohol cues: a hierarchical linear modeling approach. *Neuroimage, 56*(1), 61-68.

Schilling, C., Kühn, S., Romanowski, A., Banaschewski, T., Barbot, A., Barker, G. J., . . . Conrod, P. J. (2013). Common structural correlates of trait impulsiveness and perceptual reasoning in adolescence. *Human brain mapping, 34*(2), 374-383.

Schlam, T. R., Wilson, N. L., Shoda, Y., Mischel, W., & Ayduk, O. (2013). Preschoolers' delay of gratification predicts their body mass 30 years later. *The Journal of pediatrics, 162*(1), 90-93.

Schoenmakers, T., Wiers, R. W., & Field, M. (2008). Effects of a low dose of alcohol on cognitive biases and craving in heavy drinkers. *Psychopharmacology, 197*(1), 169-178.

Schuckit, M. A. (1994). Low level of response to alcohol as a predictor of future alcoholism. *American Journal of Psychiatry, 151*(2), 184-189.

Schuckit, M. A., & Smith, T. L. (2000). The relationships of a family history of alcohol dependence, a low level of response to alcohol and six domains of life functioning to the development of alcohol use disorders. *Journal of Studies on Alcohol, 61*(6), 827-835.

Schulenberg, J. E., & Maggs, J. L. (2002). A developmental perspective on alcohol use and heavy drinking during adolescence and the transition to young adulthood. *Journal of Studies on Alcohol, Supplement*(14), 54-70.

Schultz, W. (2000). Multiple reward signals in the brain. *Nature Reviews Neuroscience, 1*(3), 199-207.

Schultz, W., Apicella, P., Scarnati, E., & Ljungberg, T. (1992). Neuronal activity in monkey ventral striatum related to the expectation of reward. *Journal of neuroscience, 12*(12), 4595-4610.

Scott, R. B., Harrison, J., Boulton, C., Wilson, J., Gregory, R., Parkin, S., . . . Aziz, T. Z. (2002). Global attentional–executive sequelae following surgical lesions to globus pallidus interna. *Brain, 125*(3), 562-574.

Ségonne, F., Pacheco, J., & Fischl, B. (2007). Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. *IEEE transactions on medical imaging, 26*(4), 518-529.

Serences, J. T., Schwarzbach, J., Courtney, S. M., Golay, X., & Yantis, S. (2004). Control of object-based attention in human cortex. *Cerebral Cortex, 14*(12), 1346-1357.

Shaw, P., Greenstein, D., Lerch, J., Clasen, L., Lenroot, R., Gogtay, N., . . . Giedd, J. (2006). Intellectual ability and cortical development in children and adolescents. *Nature, 440*(7084), 676-679.

Shaw, P., Kabani, N. J., Lerch, J. P., Eckstrand, K., Lenroot, R., Gogtay, N., . . . Wise, S. P. (2008a). Neurodevelopmental Trajectories of the Human Cerebral Cortex. *The Journal of Neuroscience, 28*(14), 3586-3594.

Shaw, P., Kabani, N. J., Lerch, J. P., Eckstrand, K., Lenroot, R., Gogtay, N., . . . Wise, S. P. (2008b). Neurodevelopmental Trajectories of the Human Cerebral Cortex: Figure 2. In F. 2. (Ed.), (pp. Figure 2. Complexity of developmental trajectories throughout the cerebral cortex. Obtained from Vol. 28, Issue 14. Permission has been granted on 10/13/16.). The Journal of Neuroscience: Society for Neuroscience.

Sher, K. J., Grekin, E. R., & Williams, N. A. (2005). The development of alcohol use disorders. *Annu. Rev. Clin. Psychol., 1*, 493-523.

Sher, K. J., & Levenson, R. W. (1982). Risk for alcoholism and individual differences in the stress-response-dampening effect of alcohol. *Journal of Abnormal Psychology, 91*(5), 350.

Shimamura, A. P. (2000). The role of the prefrontal cortex in dynamic filtering. *Psychobiology, 28*(2), 207-218.

Shimotsu, R., Chu, R., & Fein, G. (2009). *Reduced Cortical Gray Matter in Long-Term Abstinent Alcoholics.* Paper presented at the International Society for Magnetic Resonance in Medicine, Honolulu, Hawai'i.

Shokri-Kojori, E., Tomasi, D., Wiers, C., Wang, G., & Volkow, N. (2016). Alcohol affects brain functional connectivity and its coupling with behavior: greater effects in male heavy drinkers. *Molecular psychiatry*, 1-11.

Shomstein, S., & Yantis, S. (2004). Control of attention shifts between vision and audition in human cortex. *The Journal of Neuroscience, 24*(47), 10702-10706.

Shulman, G. L., Astafiev, S. V., Franke, D., Pope, D. L., Snyder, A. Z., McAvoy, M. P., & Corbetta, M. (2009). Interaction of stimulus-driven reorienting and expectation in ventral and dorsal frontoparietal and basal ganglia-cortical networks. *The Journal of Neuroscience, 29*(14), 4392-4407.

Siegle, G. J., Steinhauer, S. R., Thase, M. E., Stenger, V. A., & Carter, C. S. (2002). Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biological psychiatry, 51*(9), 693-707.

Silberman, Y., Bajo, M., Chappell, A. M., Christian, D. T., Cruz, M., Diaz, M. R., . . . Siggins, G. R. (2009). Neurobiological mechanisms contributing to alcohol–stress–anxiety interactions. *Alcohol, 43*(7), 509-519.

Sinha, R. (2001). How does stress increase risk of drug abuse and relapse? *Psychopharmacology, 158*(4), 343-359.

Sinha, R. (2008). Chronic stress, drug use, and vulnerability to addiction. *Annals of the New York Academy of Sciences, 1141*(1), 105-130.

Skinner, H. A., Holt, S., Schuller, R., Roy, J., & Israel, Y. (1984). Identification of alcohol abuse using laboratory tests and a history of trauma. *Annals of Internal Medicine, 101*(6), 847-851.

Smeets, A., Duits, A., Plantinga, B., Leentjens, A., Oosterloo, M., Visser-Vandewalle, V., . . . Ackermans, L. (2016). Deep Brain Stimulation of the internal globus pallidus in refractory Tourette Syndrome. *Clinical neurology and neurosurgery, 142*, 54-59.

Smith, E. E., & Jonides, J. (1999). Storage and executive processes in the frontal lobes. *Science, 283*(5408), 1657-1661.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., . . . Flitney, D. E. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23*, S208-S219.

Sokol, R. J., Delaney-Black, V., & Nordstrom, B. (2003). Fetal alcohol spectrum disorder. *Jama, 290*(22), 2996-2999.

Southwick, S. M., & Charney, D. S. (2012). The science of resilience: implications for the prevention and treatment of depression. *Science, 338*(6103), 79-82.

Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience & Biobehavioral Reviews, 24*(4), 417-463.

Spear, L. P. (2009). Heightened stress responsivity and emotional reactivity during pubertal maturation: Implications for psychopathology. *Development and psychopathology, 21*(01), 87-97.

Spechler, P. A., Chaarani, B., Hudson, K. E., Potter, A., Foxe, J. J., & Garavan, H. (2016). Response inhibition and addiction medicine: from use to abstinence. *Progress in brain research, 223*, 143-164.

Spivak, B., Maayan, R., Kotler, M., Mester, R., Gil-Ad, I., Shtaif, B., & Weizman, A. (2000). Elevated circulatory level of GABA A–antagonistic neurosteroids in patients with combat-related post-traumatic stress disorder. *Psychological Medicine, 30*(05), 1227-1231.

Spoelder, M., Hesseling, P., Styles, M., Baars, A. M., Lozeman‐van‘t Klooster, J. G., Lesscher, H., & Vanderschuren, L. J. (2017). Dopaminergic neurotransmission in ventral and dorsal striatum differentially modulates alcohol reinforcement. *European Journal of Neuroscience, 45*(1), 147-158.

Spreng, R. N., Mar, R. A., & Kim, A. S. (2009). The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. *Journal of cognitive neuroscience, 21*(3), 489-510.

Squeglia, L. M., & Gray, K. M. (2016). Alcohol and Drug Use and the Developing Brain. *Current Psychiatry Reports, 18*(5), 46-10.

Squeglia, L. M., Schweinsburg, A. D., Pulido, C., & Tapert, S. F. (2011). Adolescent binge drinking linked to abnormal spatial working memory brain activation: differential gender effects. *Alcoholism: Clinical and Experimental Research, 35*(10), 1831-1841.

Squeglia, L. M., Sorg, S. F., Schweinsburg, A. D., Wetherill, R. R., Pulido, C., & Tapert, S. F. (2012). Binge drinking differentially affects adolescent male and female brain morphometry. *Psychopharmacology, 220*(3), 529-539.

Stahre, M., Roeber, J., Kanny, D., Brewer, R. D., & Zhang, X. (2014). Contribution of Excessive Alcohol Consumption to Deaths and Years of Potential Life Lost in the United States. *Preventing chronic disease, 11*, 130293. doi:papers3://publication/doi/10.5888/pcd11.130293

Stern, E. R., Muratore, A. F., Taylor, S. F., Abelson, J. L., Hof, P. R., & Goodman, W. K. (2016). Switching between internally and externally focused attention in obsessive-compulsive disorder: Abnormal visual cortex activation and connectivity. *Psychiatry Research: Neuroimaging, 0*(0).

Stern, E. R., & Taylor, S. F. (2014). Cognitive neuroscience of obsessive-compulsive disorder. *Psychiatric Clinics of North America, 37*(3), 337-352.

Stewart, S. H. (1996). Alcohol abuse in individuals exposed to trauma: a critical review. *Psychological Bulletin, 120*(1), 83.

Stock, A.-K., Riegler, L., Chmielewski, W. X., & Beste, C. (2016). Paradox effects of binge drinking on response inhibition processes depending on mental workload. *Archives of toxicology, 90*(6), 1429-1436.

Streissguth, A. P., Bookstein, F. L., Barr, H. M., Sampson, P. D., O'Malley, K., & Young, J. K. (2004). Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. *Journal of Developmental & Behavioral Pediatrics, 25*(4), 228-238.

Substance Abuse and Mental Health Services Administration. (2014). *014 National Survey on Drug Use and Health (NSDUH). Table 2.46B—Alcohol use, binge alcohol use, and heavy alcohol use in the past month among persons aged 18 or older, by demographic characteristics: Percentages, 2013 and 2014.* Retrieved from http://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs2014/NSDUH-DetTabs2014.htm - tab2-46b

Sullivan, E., Rosenbloom, M., & Pfefferbaum, A. (2000). Pattern of motor and cognitive deficits in detoxified alcoholic men. *Alcoholism: Clinical and Experimental Research, 24*(5), 611-621.

Sullivan, E. V., Fama, R., Rosenbloom, M. J., & Pfefferbaum, A. (2002). A profile of neuropsychological deficits in alcoholic women. *Neuropsychology, 16*(1), 74.

Sullivan, E. V., & Marsh, L. (2003). Hippocampal volume deficits in alcoholic Korsakoff's syndrome. *Neurology, 61*(12), 1716-1719.

Sullivan, E. V., & Pfefferbaum, A. (2009). Neuroimaging of the Wernicke–Korsakoff syndrome. *Alcohol and Alcoholism, 44*(2), 155-165.

Svanberg, J., Withall, A., Draper, B., & Bowden, S. (2014). *Alcohol and the Adult Brain*: Psychology Press.

Swift, R., & Davidson, D. (1998). Alcohol hangover. *Alcohol Health Res World, 22*, 54-60.

Tabakoff, B., Saba, L., Printz, M., Flodman, P., Hodgkinson, C., Goldman, D., . . . Bell, R. L. (2009). Genetical genomic determinants of alcohol consumption in rats and humans. *BMC biology, 7*(1), 1.

Takahashi, Y. K., Langdon, A. J., Niv, Y., & Schoenbaum, G. (2016). Temporal specificity of reward prediction errors signaled by putative dopamine neurons in rat VTA depends on ventral striatum. *Neuron, 91*(1), 182-193.

Tamber-Rosenau, B. J., Esterman, M., Chiu, Y.-C., & Yantis, S. (2011). Cortical mechanisms of cognitive control for shifting attention in vision and working memory. *Journal of cognitive neuroscience, 23*(10), 2905-2919.

Tawa, E. A., Hall, S. D., & Lohoff, F. W. (2016). Overview of the Genetics of Alcohol Use Disorder: Table 1. *Alcohol and Alcoholism, 51*(5), 507-514.

Telzer, E. H. (2016). Dopaminergic reward sensitivity can promote adolescent health: A new perspective on the mechanism of ventral striatum activation. *Developmental cognitive neuroscience, 17*, 57-67.

Thayer, R. E., Hagerty, S. L., Sabbineni, A., Claus, E. D., Hutchison, K. E., & Weiland, B. J. (2016). Negative and interactive effects of sex, aging, and alcohol abuse on gray matter morphometry. *Human brain ..., 37*(6), 2276-2292.

Thomson, D. R., Besner, D., & Smilek, D. (2015). A resource-control account of sustained attention evidence from mind-wandering and vigilance paradigms. *Perspectives on Psychological Science, 10*(1), 82-96.

Tomaka, J., Blascovich, J., Kelsey, R. M., & Leitten, C. L. (1993). Subjective, physiological, and behavioral effects of threat and challenge appraisal. *Journal of Personality and Social Psychology, 65*(2), 248.

Tomer, R., Slagter, H. A., Christian, B. T., Fox, A. S., King, C. R., Murali, D., . . . Davidson, R. J. (2014). Love to win or hate to lose? Asymmetry of dopamine D2 receptor binding predicts sensitivity to reward versus punishment. *Journal of cognitive neuroscience, 26*(5), 1039-1048.

Townshend, J., & Duka, T. (2001). Attentional bias associated with alcohol cues: differences between heavy and occasional social drinkers. *Psychopharmacology, 157*(1), 67-74.

Townshend, J. M., & Duka, T. (2005). Binge drinking, cognitive performance and mood in a population of young social drinkers. *Alcoholism: Clinical and Experimental Research, 29*(3), 317-325.

Travis, F. (2001). Autonomic and EEG patterns distinguish transcending from other experiences during Transcendental Meditation practice. *International Journal of Psychophysiology, 42*(1), 1-9.

Tsuang, M. T., Bar, J. L., Stone, W. S., & Faraone, S. V. (2004). Gene-environment interactions in mental disorders. *World Psychiatry, 3*(2), 73-83.

C. L. Productions, H. Matsos, N. d. Tyson, L. Walker, & J. Bontemps (Producer). (2016, November 4, 2016). *"Is Our Universe a Simulation?" with Brian Greene* [Retrieved from https://www.startalkradio.net/show/universe-simulation-brian-greene/]

Van Leijenhorst, L., Zanolie, K., Van Meel, C. S., Westenberg, P. M., Rombouts, S. A., & Crone, E. A. (2010). What motivates the adolescent? Brain regions mediating reward sensitivity across adolescence. *Cerebral Cortex, 20*(1), 61-69.

Vandenberghe, R., Gitelman, D., Parrish, T., & Mesulam, M. (2001). Functional specificity of superior parietal mediation of spatial shifting. *Neuroimage, 14*(3), 661-673.

Verbruggen, F., & Logan, G. D. (2008). Response inhibition in the stop-signal paradigm. *Trends in cognitive sciences, 12*(11), 418-424.

Verdejo-García, A., Lawrence, A. J., & Clark, L. (2008). Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk research, problem gamblers and genetic association studies. *Neuroscience & Biobehavioral Reviews, 32*(4), 777-810.

Victor, M., Adams, R. D., & Collins, G. H. (1971). The Wernicke-Korsakoff syndrome. A clinical and pathological study of 245 patients, 82 with post-mortem examinations. *Contemporary neurology series, 7*, 1.

Volkow, N. D., Koob, G. F., & McLellan, A. T. (2016). Neurobiologic advances from the brain disease model of addiction. *New England Journal of Medicine, 374*(4), 363-371.

Volkow, N. D., Ma, Y., Zhu, W., Fowler, J. S., Li, J., Rao, M., . . . Wang, G.-J. (2008). Moderate doses of alcohol disrupt the functional organization of the human brain. *Psychiatry Research: Neuroimaging, 162*(3), 205-213.

Volkow, N. D., & Wise, R. A. (2005). How can drug addiction help us understand obesity? *Nature neuroscience, 8*(5), 555-560.

Voon, V., & Dalley, J. W. (2015). Translatable and back-translatable measurement of impulsivity and compulsivity: convergent and divergent processes. In T. W. Robbins & B. J. Sahakian (Eds.), *Translational Neuropsychopharmacology* (Vol. 28, pp. 53-91): Springer International Publishing.

Voon, V., Pessiglione, M., Brezing, C., Gallea, C., Fernandez, H. H., Dolan, R. J., & Hallett, M. (2010). Mechanisms underlying dopamine-mediated reward bias in compulsive behaviors. *Neuron, 65*(1), 135-142.

Vossel, S., Geng, J. J., & Fink, G. R. (2014). Dorsal and Ventral Attention Systems: Distinct Neural Circuits but Collaborative Roles. *The Neuroscientist, 20*(2), 150-159.

W.H.O. (1967). *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Eighth Revision.* Geneva: World Health Organization.

W.H.O. (1977). *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Ninth Revision. Vol. 1.* Geneva: World Health Organization.

W.H.O. (1978). *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Ninth Revision. Vol. 2.* Geneva: World Health Organization.

W.H.O. (1992). *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Tenth Revision.* Geneva: World Health Organization.

W.H.O. (2016, October 26, 2016). ICD-11 Beta Draft (Joint Linearization for Mortality and Morbidity Statistics). Retrieved from http://apps.who.int/classifications/icd11/browse/l-m/en -/http%3a%2f%2fid.who.int%2ficd%2fentity%2f1580466198

Wall, T. L., Luczak, S. E., & Hiller-Sturmhöfel, S. (2016). Biology, Genetics, and Environment: Underlying Factors Influencing Alcohol Metabolism. *Alcohol research: current reviews, 38*(1), 59.

Wang, G. J., Volkow, N. D., Franceschi, D., Fowler, J. S., Thanos, P. K., Scherbaum, N., . . . Felder, C. A. (2000). Regional brain metabolism during alcohol intoxication. *Alcoholism: Clinical and Experimental Research, 24*(6), 822-829.

Warm, J. S., Parasuraman, R., & Matthews, G. (2008). Vigilance requires hard mental work and is stressful. *Human Factors: The Journal of the Human Factors and Ergonomics Society, 50*(3), 433-441.

Watson, T. D., Newton-Mora, M., & Pirkle, J. (2016). Event-related potential correlates of processing alcohol-related pictures in young adult binge drinkers. *The American journal of drug and alcohol abuse, 42*(1), 77-87.

Watten, R. G., Magnussen, S., & Greenlee, M. W. (1998). Spatial-frequency discrimination, brain lateralisation, and acute intake of alcohol. *Perception, 27*(6), 729-736.

Waugh, C. E., Panage, S., Mendes, W. B., & Gotlib, I. H. (2010). Cardiovascular and affective recovery from anticipatory threat. *Biological Psychology, 84*(2), 169-175.

Weafer, J., & Fillmore, M. T. (2008). Individual differences in acute alcohol impairment of inhibitory control predict ad libitum alcohol consumption. *Psychopharmacology, 201*(3), 315-324.

Weathers, F. W., Keane, T. M., & Davidson, J. R. (2001). Clinician‐Administered PTSD Scale: A review of the first ten years of research. *Depression and anxiety, 13*(3), 132-156.

Weathers, F. W., Ruscio, A. M., & Keane, T. M. (1999). Psychometric properties of nine scoring rules for the Clinician-Administered Posttraumatic Stress Disorder Scale. *Psychological Assessment, 11*(2), 124.

Wechsler, D. (2001). *Wechsler Test of Adult Reading: WTAR*: Psychological Corporation.

Weiland, B. J., Heitzeg, M. M., Zald, D., Cummiford, C., Love, T., Zucker, R. A., & Zubieta, J.-K. (2014). Relationship between impulsivity, prefrontal anticipatory activation, and striatal dopamine release during rewarded task performance. *Psychiatry Research: Neuroimaging, 223*(3), 244-252.

Wentura, D. (1999). Activation and inhibition of affective information: For negative priming in the evaluation task. *Cognition & Emotion, 13*(1), 65-91.

Werner, E. E. (2000). Protective factors and individual resilience. *Handbook of early childhood intervention, 2*, 115-132.

Whelan, R., Conrod, P. J., Poline, J.-B., Lourdusamy, A., Banaschewski, T., Barker, G. J., . . . Cummins, T. D. (2012). Adolescent impulsivity phenotypes characterized by distinct brain networks. *Nature neuroscience, 15*(6), 920-925.

Whitmer, A. J., & Banich, M. T. (2007). Inhibition versus switching deficits in different forms of rumination. *Psychological science, 18*(6), 546-553.

Williams, S. W. (1913). *The Middle Kingdom*. New York: Charles Scribner's Sons.

Wilsnack, S. C., Vogeltanz, N. D., Klassen, A. D., & Harris, T. R. (1997). Childhood sexual abuse and women's substance abuse: national survey findings. *Journal of Studies on Alcohol, 58*(3), 264-271.

Wilson, S., Malone, S. M., Thomas, K. M., & Iacono, W. G. (2015). Adolescent drinking and brain morphometry: A co-twin control analysis. *Developmental cognitive neuroscience, 16*, 130-138.

Wood, S. K., Walker, H. E., Valentino, R. J., & Bhatnagar, S. (2010). Individual differences in reactivity to social stress predict susceptibility and resilience to a depressive phenotype: role of corticotropin-releasing factor. *Endocrinology, 151*(4), 1795-1805.

Woolrich, M. W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., . . . Smith, S. M. (2009). Bayesian analysis of neuroimaging data in FSL. *Neuroimage, 45*(1), S173-S186.

Wrase, J., Grüsser, S., Klein, S., Diener, C., Hermann, D., Flor, H. e., . . . Heinz, A. (2002). Development of alcohol-associated cues and cue-induced brain activation in alcoholics. *European Psychiatry, 17*(5), 287-291.

Wrase, J., Schlagenhauf, F., Kienast, T., Wüstenberg, T., Bermpohl, F., Kahnt, T., . . . Knutson, B. (2007). Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. *Neuroimage, 35*(2), 787-794.

Yantis, S., Schwarzbach, J., Serences, J. T., Carlson, R. L., Steinmetz, M. A., Pekar, J. J., & Courtney, S. M. (2002). Transient neural activity in human parietal cortex during spatial attention shifts. *Nature neuroscience, 5*(10), 995-1002.

Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., . . . Polimeni, J. R. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of neurophysiology, 106*(3), 1125-1165.

Yoshimoto, K., McBride, W. J., Lumeng, L., & Li, T.-K. (1992). Alcohol stimulates the release of dopamine and serotonin in the nucleus accumbens. *Alcohol, 9*(1), 17-22.

Zahr, N. M., Kaufman, K. L., & Harper, C. G. (2011). Clinical and pathological features of alcohol-related brain damage. *Nature Reviews Neurology, 7*(5), 284-294.

Zelazo, P. D., & Carlson, S. M. (2012). Hot and cool executive function in childhood and adolescence: Development and plasticity. *Child Development Perspectives, 6*(4), 354-360.

Zetsche, U., D'Avanzato, C., & Joormann, J. (2012). Depression and rumination: Relation to components of inhibition. *Cognition & Emotion, 26*(4), 758-767.

Zhou, Y., Colombo, G., Gessa, G. L., & Kreek, M. J. (2013). Effects of voluntary alcohol drinking on corticotropin-releasing factor and preprodynorphin mRNA levels in the central amygdala of Sardinian alcohol-preferring rats. *Neuroscience letters, 554*, 110-114.

CURRICULUM VITAE