PREFRONTAL CORTICAL FUNCTION AS AN OBJECTIVE MARKER OF EARLY RELAPSE RISK
IN ALCOHOL-DEPENDENT PATIENTS FOLLOWING RESIDENTIAL TREATMENT:
A FUNCTIONAL NEAR-IR SPECTROSCOPY STUDY

A Dissertation in
Neuroscience
by
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Submitted in Partial Fulfillment
Of the Requirements
For the Degree of
Doctor of Philosophy

December 2016
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Alcohol dependence is a chronic relapsing disorder that has devastating effects on individuals, families, and society. Nearly half of alcohol-dependent patients relapse within three months of treatment. Recent neuroimaging research has provided evidence that the prefrontal cortex (PFC) plays a key role in substance use disorders. Studies suggest that PFC dysregulation, involving impairments in response inhibition and salience attribution (iRISA), may confer an increased risk for relapse following treatment for substance use disorders.

This investigation examined PFC function in alcohol-dependent patients in residential treatment using: (1) the color-word Stroop task as a measure of response inhibition, and (2) a visual cue reactivity paradigm as a measure of salience attribution to alcohol cues, as well as to natural reward stimuli. The objective of this research was to determine whether task-related PFC activity during treatment would be predictive of post-treatment relapse, using an innovative and clinically viable neuroimaging technology, functional near-infrared spectroscopy (fNIRS). Relative to abstainers, relapsers were expected to exhibit: (1) reduced inhibition-related PFC activity during the Stroop task, reflecting inhibitory control impairments, and (2) increased PFC activity to visual alcohol stimuli during the cue-reactivity paradigm, indicating heightened responsiveness to alcohol-related cues. Alcohol-dependent patients (n=50) were recruited from Caron Treatment Centers, Wernersville, PA, a residential drug and alcohol rehabilitation facility. Healthy control participants (n=20) were recruited from the local community. In the patient group, neuroimaging tasks were conducted using fNIRS 14-28 days after admission to treatment. Following discharge, patients were followed for prospective relapse on a weekly basis for 12 weeks, using web-based self-report queries.

In support of our hypothesis, relapsers exhibited reduced inhibition-related PFC activity during the Stroop task, relative to abstainers. Contrary to our hypothesis, however, these same
relapsers also exhibited blunted activity in the dorsolateral PFC (dlPFC) in response to alcohol stimuli during the cue-reactivity paradigm. This finding is consistent with recent fMRI research by Sinha and colleagues reporting PFC hypoactivity during alcohol-related cue exposure in subsequent relapsers (Seo et al., [JAMA Psychiatry, 70, 727 (2013)]). Rather than the attribution of salience to alcohol stimuli, blunted dlPFC activity may reflect deficits in self-regulation, leading to disinhibited behavior and increased risk for subsequent relapse. No significant correlations were found between fNIRS measures of prefrontal response to alcohol cues and self-reported craving.

In addition to neuroimaging variables, relapsers and abstainers were differentiated by two self-report measures: subjective craving ratings in response to alcohol cues and total scores on the Severity of Alcohol Dependence Questionnaire. A multivariate logistic regression analysis was used to determine the accuracy of neuroimaging variables to correctly classify patients as abstainers or relapsers. Neuroimaging measures alone correctly classified 80.6 percent of patients, and a model combining neuroimaging with self-report variables correctly classified relapsers versus abstainers with 93.8 percent accuracy. These data provide evidence for a brain-based metric which may be used to predict the likelihood of post-treatment relapse. Confirmation of these findings through further research is warranted, as this technique could provide clinicians with an objective measure to aid in treatment planning, aftercare recommendations, and pharmaceutical development.
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LIST OF ABBREVIATIONS

ACC  Anterior Cingulate Cortex  
ACQ  Alcohol Craving Questionnaire  
ANOVA Analysis of Variance  
AUD  Alcohol Use Disorder  
BIS  Barratt Impulsiveness Scale  
CNS  Central Nervous System  
dIPFC  Dorsolateral Prefrontal Cortex  
DSM  Diagnostic and Statistical Manual for Mental Disorders  
FHQ  Family History Questionnaire  
fMRI  Functional Magnetic Resonance Imaging  
fNIRS  Functional Near-Infrared Spectroscopy  
ICS  Impaired Control Scale  
ISI  Insomnia Severity Index  
LASSO  Least Absolute Shrinkage and Selection Operator  
mPFC  Medial Prefrontal Cortex  
OCDS  Obsessive Compulsive Drinking Scale  
PFC  Prefrontal Cortex  
SADQ  Severity of Alcohol Dependence Questionnaire  
SCID  Structured Clinical Interview for DSM-Diagnoses  
SUD  Substance Use Disorder  
TLFB  Timeline Followback  
vmPFC  Ventromedial Prefrontal Cortex  
vlPFC  Ventrolateral Prefrontal Cortex  
VTA  Ventral Tegmental Area
ACKNOWLEDGEMENTS

I would like to express my gratitude to the many individuals who have played an important role in my doctoral education and who supported the progress and completion of my dissertation research:

To my parents, Bob and Sharon Harris, who encouraged my commitment to education from an early age; to Scott Bunce, my adviser and mentor who I have had the fortune to work with closely over the past four years, learning the methods and marvels of affective neuroscience, as well as their exciting clinical implications for the field of psychiatry; to Roger Meyer, my mentor, who, as praised by George Koob, has “seen everything” and who has been gracious enough to share with me his wealth of knowledge on the history, complexity, and uniqueness of the addiction sciences; to Sue Grigson, my adviser and mentor who provided me with guidance and direction from the first of my graduate years and in whose lab I was first introduced to addiction-related animal models; to Kent Vrana, my MCDAP mentor for the CTSI, who is an exemplar of scientific professionalism and who has been influential in shaping my own professional development; to Andras Hajnal, whose rich intellect and background in alcohol addiction helped to broaden the scope of my research; to Erin Deneke and Caron Treatment Centers, who graciously agreed to have me conduct experiments with their patient population; to the Department of Psychiatry, which generously supported this research by funding my graduate assistantship; to Edward Bixler, who was a most reliable resource on matters concerning the protection of human subjects; to William Milchak, who was the key ingredient to our collaborative recipe with Caron, to Dean Stankoski, who shared with me the drudgery and long hours of data synthesis and technical troubleshooting; to Hasan Ayaz, who provided critical assistance with fNIRS data processing and analysis; to Lan Kong and Menghan Li, who helped with the advanced statistical methods involved in prediction modeling; to Larry Wyles, who listened without judgement to my truth about my work and supported me in my labors; to
Kathleen Brooks, who gave me wisdom and courage during my darker hours; to Toastmasters International, which provided me with a safe venue in which to become more comfortable speaking publically; to collaborative professors, Rajita Sinha, Tom Babor, Victor Hesselbrock, Henry Kranzler, Steven Wilson, Carmen Pulido, and Andrea King, with whom I consulted concerning the design and implementation of experimental methods; and to the Penn State Clinical and Translation Science Institute (CTSI), which supported this research via Grant UL1 TR000127 and TL1 TR000125 from the National Center for Advancing Translational Sciences (NCATS).
1.1 The Problem of Alcohol Use Disorders

Alcohol use disorders are a worldwide problem with enormous economic, medical, and social costs. In the United States alone, over 17 million people are known to abuse alcohol, and nearly 8 million of these individuals meet criteria for alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV; Grant et al., 2004). In 2006, US economic costs related to alcohol use disorders exceeded $225 billion (Bouchery, et al., 2011). Furthermore, individuals with alcohol dependence continue to drink despite recurrent physical, legal, and social problems (NIAAA, 2015).

A variety of therapeutic approaches and mutual support groups have been developed to treat individuals with alcohol use disorders. The most renowned of these organizations is Alcoholics Anonymous (AA), a twelve-step abstinence-based program established in 1935 and estimated to now include over 2.1 million members worldwide (www.aa.org). Interventions for alcohol use disorders also include psychosocial therapies such as cognitive behavioral therapy (CBT) and motivation enhancement therapy (MET), which have demonstrated equal efficacy (Glaser et al., 1999). In addition, pharmacotherapies such as disulfiram, naltrexone, and acamprosate have been approved by the FDA for the treatment of alcohol dependence (Williams, 2005).

Despite the efforts of these various treatments to reduce or eliminate drinking, relapse rates in alcohol-dependent individuals remain unacceptably high. A large proportion of patients fail to maintain abstinence following the completion of addiction treatment. Studies suggest that 50-85 percent of patients resume some level of drinking within three to six months (Boothby and Doering, 2005; Hunt, 1971; Kirchenbaum et al., 2009; Miller, Walters, and Bennet, 2001). Because of the
personal, social, and medical costs associated with relapse, it is critical for addiction treatment professionals to understand factors that influence early relapse in alcohol-dependent patients following discharge from treatment. The broad purpose of this study was to examine the putative variables which may best identify patients at an elevated risk for relapse. Aided by a measure of relapse liability, clinicians would then be better informed to deliver more targeted interventions and to recommend the most appropriate next level of patient care.

1.1.1 The Clinical Phenomenology of Alcohol Use Disorders

Formulations on the nature of alcohol use disorders have evolved extensively over the past 50 years, from Jellinek’s phenomenologically-based Disease Concept of Alcoholism (Jellinek, 1960) to the more recent neurobiological paradigm of alcohol dependence (Koob and Volkow, 2010; Weiss and Porrino, 2002). In the United States, the clinical description of alcohol use disorders has been based on the American Psychiatric Association’s development of the Diagnostic and Statistical Manual for Mental Disorders (DSM). The previous edition of the DSM, the DSM-IV-TR, categorized alcohol use disorders as either (1) alcohol abuse, or (2) alcohol dependence (APA, 2000). Alcohol abuse and dependence differed largely in that the latter manifested signs of tolerance and withdrawal symptoms. The current edition, DSM-5, eliminated the dichotomous categorization of abuse and dependence and introduced the diagnosis of alcohol use disorders along a severity continuum of mild to severe, based on the number of met qualifying criteria (APA, 2013). Additionally, the DSM-5 removed legal problems and added craving as criteria.

Despite these changes in clinical classification, the DSM criteria have been challenged due to its failure to consider disorder-specific pathophysiological and critical prognostic variables associated with alcohol dependence (Meyer, 2001). One model of alcohol use disorders without these limitations was the “provisional description” of alcohol dependence offered by Edwards and
Gross (1976). Their model, the “alcohol dependence syndrome”, was comprised of seven essential elements theoretically derived from the psychobiological and behavioral characteristics presented in patients with alcohol use disorders. These elements include: (1) a narrowing of drinking repertoire; (2) salience of drinking; (3) increased tolerance to alcohol; (4) withdrawal symptoms; (5) withdrawal relief by further drinking; (6) subjective awareness of the compulsion to drink; and (7) rapid reinstatement of the syndrome if drinking resumes. Importantly, each element presumably exists in varying degree, imbuing the dependence syndrome with a range of severity. One inventory developed to measure the essential features of the dependence syndrome, as they relate to a continuum of severity, was the Severity of Alcohol Dependence Questionnaire (SADQ; Stockwell et al., 1979). In contrast to DSM criteria, which are mainly based on the psychosocial consequences of heavy drinking, queries from the SADQ are based on the core clinical phenomenology of alcohol dependence, principally centered around “the ‘drive’ to consume alcohol” (Davidson, 1987; Stockwell, Murphy, and Hodgson, 1983).

1.1.2 Reward Comparison: Alcohol versus Natural Rewards

Concomitant with increases in motivation to obtain and consume alcohol is the devaluation of non-alcoholic, natural rewards (e.g., healthy foods, recreational activities, social bonding, etc.), which serve as behavioral reinforcers in non-addicted individuals (Grigson, 2008). Theories on sensitization of incentive salience posit that chronic alcohol consumption sensitizes the brain reward system to alcohol, which in turn fragments normal reward processes and intensifies the “wanting” (i.e., desire) for alcohol disproportionately to the motivation to engage with naturally occurring reinforcers (Kelley and Berridge, 2002; Robinson and Berridge, 2000).

There is evidence, however, that natural rewards may also confer defense against compulsive drinking behavior (Grigson, 2008). In animal models, the availability of alternative
natural rewards, such as enriched housing environments, has been demonstrated to facilitate extinction and reduced subsequent drug-induced reinstatement (Solinas et al., 2010; Stairs and Bardo, 2009). Likewise, sensitivity to the rewarding effects of natural reinforcers is thought to provide protection against relapse in clinical populations (Heinz et al., 2007; Kalivas and Volkow, 2005; Lubman et al., 2009).

1.2 The Neurobiology of Substance Use Disorders

In the 1950’s, Milner and Olds made the first discovery of the physiological mechanism of reward through electrical self-stimulation of the septal area and basal forebrain in rats (Olds and Milner, 1954). Over the ensuing decades, the neurobiological underpinnings of addiction have been explored using classical pharmacological and electrophysiological techniques in animal models, and, more recently, using methods in molecular biology, genetics, and human neuroimaging (Goldstein and Volkow, 2011; Meyer, 1996; 2001; Wilson, 2015). In this section, an overview of these findings, as they relate to alcohol use disorders, will be presented. First, the deleterious effect of chronic alcohol consumption on the brain will be discussed. Next, the conceptual framework of the underlying neurobiology of addiction will be outlined. Finally, motivational and inhibitory systems related to addiction will be reviewed.

1.2.1 Alcohol and the Brain

Due to its neurotoxic effects, chronic alcohol consumption promotes not only psychological dependence but also physiological injury to the brain (Oscar-Berman et al., 1997). The effects of alcohol-related brain damage include cognitive deficits and neuropsychological impairments, which are observed in approximately half of individuals in the United States with an alcohol use disorder.
Risk factors that influence alcohol-induced brain damage include the age of onset of heavy drinking, lifetime quantity of alcohol consumed, family history of alcoholism, genetic background, gender, and education (Parsons, 1996). Nearly ten percent of alcoholics eventually develop debilitating conditions such as Wernicke-Korsakoff syndrome and alcohol-induced dementia, which permanently impair memory, language, and reasoning functions (Rourke and Loberg, 1996).

Studies examining grey matter volumes in alcoholics have found significant cortical atrophy in frontal, limbic, and basal forebrain regions, which are hypothesized to be a consequence of the neurotoxic effects of alcohol (Lishman, 1990; Moselhy, Georgiou, and Kahn, 2001). Importantly, structural neuroimaging studies suggest that frontal regions are most susceptible to alcohol-related atrophy, and that damage to the frontal lobe, including the PFC, becomes most pronounced as alcoholics age (Pfefferbaum et al., 1997). However, alcohol-related reductions in frontal grey matter volumes and their associated neuropsychological impairments appear to be reversible with long-term abstinence in some patients (Moselhy, Georgiou, and Kahn, 2001). Most alcoholics with concomitant cognitive deficits show partial remediation of these symptoms within one year of abstinence, consistent with improvements in brain structure and function (Sullivan et al., 2000). Less is known, however, about the rate and extent to which the structure and function of frontal regions normalize as a function of abstinence duration (Oscar-Berman and Marinkovic, 2003).

1.2.2 The Conceptual Framework of Addiction

Addiction is characterized by compulsive consummatory behavior, loss of control over substance intake, and the emergence of withdrawal-associated negative affect (Koob and Volkow, 2010). Clinically, drug addiction is distinct from occasional, controlled drug use and abuse and is considered the end stage of a disease progression from drug use to abuse to dependence (Everitt
and Robbins, 2005). One of the main goals of neurobiological research in addiction, therefore, is to identify the neuroadaptive mechanisms that mediate the transition from the limited drug use to the emergence of compulsive drug-seeking and loss of behavioral control (Koob, 2011).

Current research has identified three main phases in the addiction cycle, each with discrete underlying neurocircuitry: (1) binging and intoxication, (2) withdrawal and negative affect, and (3) preoccupation and anticipation (Koob and Volkow, 2010). The binging and intoxication phase of addiction is largely mediated by brain-reward networks that subserve the reinforcing effects of drugs of abuse (Koob, 2004). These motivational networks, including mesocorticolimbic dopamine projections throughout the basal forebrain, respond to salient stimuli in the environment (Robinson and Berridge, 1993) and activate goal-directed behavior (Le Moal and Simon, 1991). While all drugs of abuse putatively activate the mesolimbic dopamine system, only psychostimulants, such as cocaine and methamphetamine, are directly reinforced by the release of dopamine in the nucleus accumbens (Nestler, 2005). Other drugs of abuse, such as alcohol, opioids, and marijuana, are thought to act indirectly on the mesolimbic dopamine system and to be mediated by additional neurotransmitters and neuromodulators, including γ-aminobutyric acid (GABA), opioid peptides, and endocannabinoids (Koob, 2011). Alcohol is thought to activate the mesolimbic dopamine system by promoting μ-opioid and GABA_A receptor function in the nucleus accumbens and, in particular, the central nucleus of the amygdala (Hyttia and Koob, 1995; Roberts et al., 2000; Volpicelli et al., 1992). Studies have consistently implicated the accumbens as a key nucleus in the processing of reward, whereby it receives input from the surrounding amygdala, frontal cortex, and hippocampus and putatively transforms this information into motivated behavior through its connections with the extrapyramidal motor system (Gilpin and Koob, 2008; Koob, 2011).

The withdrawal and negative affect phase of addiction occurs during periods of abstinence and is hypothesized to be mediated by the activation of brain stress systems (Koob and Volkow,
Activation of the brain stress system includes the release of corticotropin-releasing factor (CRF) from the paraventricular nucleus of the hypothalamus to the pituitary gland, where it promotes the synthesis of adrenocorticotrophic hormone (ACTH; Koob, 2008). ACTH is then transported by blood to the adrenal glands, where it stimulates the release of corticosteroids (e.g. glucocorticoid) into systemic circulation. These circulating corticosteroids provide negative feedback to the pituitary gland and hypothalamus to limit the stress response (Herman and Cullinan, 1997). This homeostatic process is known to be perturbed during acute and chronic alcohol administration, as well as withdrawal (Koob and Kreek, 2007).

Additional evidence suggests that glucocorticoids also sensitize CRF systems in the extended amygdala, which is known to mediate behavioral responses to stressors (Zorrilla, Logrip, and Koob, 2014). Therefore, while initial drug use involves activation the CRF-HPA axis, chronic drug administration also gives rise to subsequent activation of CRF-extended amygdala system (Koob, 2008). There is also evidence for withdrawal-related increases in vasopressin in the extended amygdala, suggesting that the vasopressin system may further mediate the aversive emotional consequences of stress (Zhou et al., 2008). Together, these HPA-axis and extended-amygdala brain stress systems are activated during withdrawal from chronic administration of all major drugs of abuse, which is believed to underlie the emotional dysregulation that drives the negative reinforcement mechanisms of addictive behavior (Koob and Kreek, 2007; Koob and Le Moal, 2005).

Furthermore, as a consequence of this chronic perturbation brain reward and stress systems, brain reward function eventually fails to return within the normal homeostatic range. This perturbation results in a new homeostatic set point, the allostatic state, which represents the transition from alcohol abuse to dependence (Koob, 2013). Moreover, this allostatic state is thought to persist beyond detoxification (i.e., protracted abstinence), during which time the reward system
still bears an allostatic load, promoting compulsive drinking behavior (Koob and Le Moal, 2008; McEwen, 2000).

The preoccupation and anticipatory phase of addiction is largely characterized by drug craving and is brought about by negative affect and stress states as well as increased sensitivity to drug-related stimuli (Koob and Volkow, 2010). Because this anticipatory state is also capable of being evoked by conditioned cues long after acute withdrawal symptoms have abated (i.e., cue-elicited craving; see section 1.4.1), the enduring propensity to enter this state, and subsequently relapse, is one of the major challenges in treating patients with substance dependence (Langleben et al, 2008; Sinha and Li, 2007). Stress is known to play an important role in anticipatory craving and relapse in patients with alcohol use disorders (Breese, Sinha, and Heilig, 2011), while also moderating the salience of, and appetitive responsiveness to, conditioned alcohol cues (Sinha and Li, 2007). These stress- and craving-related constructs have been modeled in laboratory settings using the cue-reactivity paradigm (Drummond, 2000; Sinha, 2009). Findings from this paradigm in addiction research will be discussed in more detail in a later section (see Section 1.4: Cue Reactivity).

1.2.3 Addiction as Pathology of Motivation and Choice

The previous section outlined the motivational networks involved in reinforcement learning, including the positive reinforcement of drug administration subserved by the mesolimbic dopamine system (brain reward network) and negative reinforcement of withdrawal relief subserved by CRF-HPA axis and CRF-amygdala systems (brain stress networks). More recently, however, clinical research, aided by the advances in human neuroimaging, has provided evidence for the involvement of frontal brain regions in addiction (Goldstein and Volkow, 2002; 2011; Perry et al., 2011; Garavan et al., 2013). In particular, the PFC has been implicated as a key neurobiological substrate in
addictive behaviors, through its regulation of subcortical reward networks and its role in inhibitory control processes (Goldstein and Volkow, 2011).

Because of the neurobiological disturbances in both subcortical reward areas and cortical regulatory regions, addiction has been described as “a pathology of motivation and choice” (Kalivas and Volkow, 2005). While acknowledging the significance of the motivational networks in the reinforcement of addictive behavior, the role of PFC dysfunction in addiction and its relationship with relapse in treatment-seeking alcoholics will be the focus of the remainder of this dissertation.

1.3 Inhibitory Control

Inhibition and inhibitory-related processes have been investigated since the writings of William James and his nineteenth-century discourse on the Principles of Psychology (James, 1890). In particular, the construct of inhibitory control has been conceptualized as the ability to control or suppress a prepotent response or impulse and is thought to serve as the basis of volition and goal-directed behavior (Bari and Robbins, 2013; Dalley, Everitt, and Robbins, 2011). Furthermore, inhibitory control failures, resulting in disinhibited behavior, represent a broad range of clinical and non-clinical phenomena, including risk taking, attentional deficits, perseveration, inflexibility, compulsivity, and, in particular, impulsivity (Bari and Robbins, 2013; Jones et al., 2013).

1.3.1 Impulsivity and Inhibition

Impulsivity refers to a multidimensional construct comprised of a number of underlying psychobiological processes that together contribute to poor behavioral control and impaired decision making (de Wit, 2008). Although the field of psychiatry has reached no consensus as to its exact definition, impulsivity is generally regarded as action without adequate thought or planning
Clinically, impulsivity is most commonly associated with certain personality disorders, attentional and hyperactivity disorders, and substance use disorders. Neurobiologically, impulsivity has been associated with functional impairment of and structural insult to the frontal lobe (Crews and Boettiger, 2009; Jentsch and Taylor, 1999).

As a function of disinhibition, impulsivity has been associated with several additional constructs such as executive function, self-regulation, response inhibition, cognitive control, and, ultimately, inhibitory control (Bari and Robbins, 2013). As an overarching construct, inhibitory control includes cognitive inhibition (i.e., control over attention and perceptions) and behavioral inhibition (i.e., control over motor processes and responses). Although elements of cognitive inhibition and cognitive control are expressed in impulsive individuals, impulsivity is regarded more as a disorder of behavioral disinhibition than of cognitive disinhibition (Bari and Robbins, 2013; Fillmore and Weafer, 2011).

Importantly, impulsivity and its related constructs, including executive function, self-regulation, and inhibitory control, are mediated by the functions of the PFC (Crews and Boettiger 2009; Chambers, Garavan, and Bellgrove, 2009; Fuster, 2008). As the most anterior region of the frontal lobe, the PFC is thought to subserve the central executive processes in the generation of action and behavior (Fuster, 2008). As such, the PFC is essential to self-regulation through inhibitory and executive functions, processes commonly impaired in substance-abusing populations (Baler and Volkow, 2006; Bickel et al., 2012; Feil et al., 2010; Goldstein and Volkow, 2002; 2011).

1.3.2 Self-Report Measures of Inhibitory Control and Impulsivity

Impulsivity and its related construct, inhibitory control, are often measured using one or more of three main modalities: self-report, behavioral, and neuroimaging (Bari and Robbins, 2013; Dalley, Everitt, and Robbins, 2011; Moeller et al., 2001). Self-report measures, including validated
inventories and questionnaires such as the Barratt Impulsiveness Scale (BIS; Patton et al., 1995) and the Eysenck Impulsiveness Questionnaire (EIQ; Eysenck and Eysenck, 1977), provide a subjective assessment of behavioral inclinations in a variety of contexts. Examples of such self-report items include “I plan trips well ahead of time” and “I buy things on impulse” (Patton et al., 1995). Although these measures are easy to administer, they are limited by the awareness and veracity of study participants (Moeller et al., 2001). These response biases are accentuated in substance-dependent populations (Sher and Epler, 2004).

1.3.3 Behavioral Measures of Inhibitory Control and Impulsivity

Often used in conjunction with self-report scales are objective laboratory measures which assess task-related behavioral performance. These tasks typically include measures of behavioral response time and accuracy, that confer protection from the subjective response biases of self-report measures (Moeller et al., 2001; Perry and Carroll, 2008). Three of these performance-based paradigms used to assess inhibitory control are the go/no-go paradigm (GNG; Yechiam et al., 2006), the stop-signal reaction time task (SSRT; Logan, Cowan, and Davis, 1984), and the word-color Stroop task (Stroop, 1935).

The go/no-go (GNG) task is a laboratory paradigm in which participant responses are based on a target cue indicating whether to subsequently respond or inhibit the response (i.e., activate motor response following GO stimulus and withhold motor response following NO-GO stimulus; Yechiam et al., 2006). On a minority of trials, however, the cue predicting a GO stimulus is instead followed by a NO-GO stimulus. It is during this condition that participants tend to fail to withhold the prepotent GO response. In this way, the GNG task is hypothesized to measure inhibitory control (Fillmore, 2003).
The stop-signal reaction time task (SSRT) is another laboratory measure of inhibitory control and response inhibition (Logan, Cowan, and Davis, 1984; Smith et al., 2014). In this paradigm, participants are instructed to engage in a primary task, such as responding to a target stimulus as quickly as possible. On a minority of trials, a stop signal is presented after a short, varying interval following the primary target, which indicates that the participant is to countermand or withhold his or her response. The length of delay at which participants successfully inhibit their response on 50 percent of the stop trials indicates the stop-signal reaction time. As an objective measure of response inhibition, the SSRT is regarded as a valid paradigm of inhibitory and behavioral control (Chambers, Garavan, and Bellgrove, 2009).

A third and widely used inhibitory paradigm is the Stroop interference task (MacLeod, 1991; Stroop, 1935). In the classic color-word version of the Stroop task, participants are shown a color word (e.g., “RED”) that is presented in an incongruent font color (e.g., “RED” presented in blue text). Participants are instructed to suppress the semantic meaning of the word and, instead, report the font color. This interference condition reliably leads to increased reaction time and decreased response accuracy (i.e., the Stroop Effect) and serves as a well validated laboratory measure of cognitive and inhibitory control (Herd, Banich, and O’Rielly, 2006; MacLeod, 1991).

1.3.4 Inhibitory Control and Impulsivity in Addiction

In addictive disorders, the shift in consummatory behavior, from controlled use to compulsive abuse, is a hallmark sign of disease progression (Everitt and Robbins, 2005; Koob and Le Moal, 2005). Indeed, “loss of control” has been suggested to be an outcome of approximately ten years of heavy drinking in alcohol-dependent men (Meyer, 1994), and is also one of the criteria for alcohol use disorders in DSM-5 (American Psychiatric Association, 2013). Current neurobiological models of addiction implicate not only alcohol-related sensitization of the brain reward system but
also exacerbated impairment of inhibitory control mechanisms in the development toward uncontrolled addictive behavior (Bechara, 2005; Feil et al., 2010; Goldstein and Volkow, 2002, 2011; Lubman, Yucel, and Pantelis, 2004).

As described previously, impulsivity has been conceptualized as a function of inhibitory control failure with particular relevance to drug and alcohol abuse and dependence (Fillmore and Weafer, 2011; Potenza and de Wit, 2010). Data from cross-sectional studies support the hypothesis that substance use disorder populations are more impulsive than healthy control populations on a variety of impulsivity measures, including self-report scales and inhibitory behavioral tasks (Dick et al., 2010; Noel, Van Der Linden, and Bechara, 2005; Perry and Carroll, 2008; Sher and Trull, 1994). Evidence for a causal relationship between substance dependence and impulsivity, however, is less clear (Dick et al., 2010; Perry and Carroll, 2008). Some studies suggest that impulsivity is a trait-like risk factor which predisposes individuals to the development of substance dependence (Ersche et al., 2010; Ersche et al., 2012). Other studies highlight the emergence of impulsivity as a result of chronic, excessive drug and alcohol consumption (Fillmore, 2003; Weafer and Fillmore, 2008). Considered together, the collective breadth of research indicates that impulsivity likely serves as both determinant and consequence of addiction (de Wit, 2008).

1.3.5 The Neural Basis of Inhibitory Control

Studies on the neural basis of inhibition have made important advances with the aid of modern neuroimaging techniques, including functional magnetic resonance imaging (fMRI), functional near-infrared spectroscopy (fNIRS), and electroencephalography (EEG). From the wealth of findings that these methods have yielded, the field has reached a general consensus that inhibitory processes are largely mediated by the PFC (Aron, 2007; Banich and Depue, 2014; Fuster,
In particular, the PFC is hypothesized to provide “top-down” regulation over subcortical motivational networks through frontostriatal inhibitory pathways (Feil et al., 2010; Jentsch and Taylor, 1999; Morein-Zamir and Robbins, 2015). The precise localization of the origin of these functions within the PFC, however, is less clear. Aron and colleagues have argued that the right inferior frontal cortex (rIFC) plays a central and exclusive role in inhibition, acting as a brake over subcortical activity via fronto-basal-ganglia networks (Aron, Robbins, and Poldrack, 2004, 2014). This model of inhibition, however, remains controversial (Hampshire et al., 2010; Swick and Chatham, 2014).

Mounting evidence suggests that the PFC in general, and the lateral PFC (lPFC) in particular, works in concert with the basal ganglia to subserve inhibitory control functions (Banich and Depue, 2015; Chambers et al., 2009; Morein-Zamir and Robbins, 2015; Nee and D’Esposito 2016). Furthermore, disruption of PFC functioning is strongly associated impairments in inhibitory control, an increase in impulsive behavior, and the presentation of clinical disorders, including substance use disorders (Dalley, Everitt, and Robbins, 2011; Feil et al 2010; Jentsch and Taylor, 1999; Moeller et al., 2001).

Because of the strong relationship between impulsive disorders and substance use disorders, and the neural mechanisms of the PFC implicated in inhibitory control, the study of the relationship between PFC dysfunction and addiction has gained considerable attention in recent years (Crews and Boettiger, 2009; Feil et al., 2010). Accumulating research implicates the addiction-related impairment of PFC function as a key mediator of compulsive drug use and recurrent relapse (Jentsch and Taylor, 1999; Goldstein and Volkow, 2002, 2011).
1.4 Cue Reactivity

As discussed in Section 1.2 (The Neurobiology of Substance Use Disorders), craving during preoccupation/anticipation stage of addiction is believed to be triggered in part by conditioned cues associated with drug use and is thought to reflect an important factor for relapsing to compulsive drug taking, even after withdrawal symptoms have subsided (Koob and Volkow, 2010). These conditioned cues, which provoke the emergence of latent preoccupation/anticipation, may be interoceptive (i.e., stress states) as well as exteroceptive (i.e., geographical proximity to a favorite bar). The study of the responsiveness to exteroceptive cues in a controlled laboratory setting has been developed using the cue-reactivity paradigm. The section below discusses the cue-reactivity paradigm and its relation to craving. Also discussed are the methods used to measure cue reactivity, including the self-report scales and neuroimaging techniques, as well as findings from these methods in studies with alcohol-dependent populations. Finally, findings on the relationship between cue reactivity and treatment outcome (i.e., relapse) are reviewed.

1.4.1 Cue Reactivity and Cue-Elicited Craving

Craving has long been identified as an essential feature of addiction to alcohol and other drugs of abuse (Anton, 1999; Drummond, 2000; Jellinek et al., 1955 Ludwig and Wikler, 1974). Despite the recognition of craving as an important construct in addiction, however, the definition, measurement, and interpretation of craving has been heatedly debated by researchers in the field (Meyer, 2000; Pickens and Johanson, 1992; Tiffany, Carter, and Singleton, 2000). One notable line of inquiry yet to reach consensus in the alcohol field is the relationship between self-reported craving and subsequent relapse to alcohol use in treatment-seeking alcoholics (Drummond, 2000; Meyer, 2000). While some evidence supports the association between alcohol craving and prospective
drinking (Marlatt, 1978), in general, studies have shown subjective craving, in general, to be a poor predictor of relapse (Tiffany and Conklin, 2000; Grusser et al., 2004).

Discrepancies in clinical descriptions and experimental findings related to craving may, in part, be explained by the difference between two types of craving: (1) ambient or “tonic” craving, which persists during acute withdrawal and decays throughout prolonged periods of abstinence, and (2) situational or “cue-elicited” craving, which occurs in response to environmental cues, such as alcohol or alcohol-related stimuli (Drummond, 2000; Meyer, 2000). Tonic craving is hypothesized to be an unconditioned physiological response related to the time-course and severity of withdrawal (Drummond, 2000). On the other hand, acute craving is thought to arise from the conditioned response to alcohol-related cues (e.g., the sight of a favorite bottle of wine) that have been closely associated in time and space with the reinforcing effects of alcohol intoxication (Anton, 1999; Everitt and Robbins, 2005). Therefore, exposure to alcohol-related cues which have become imbued with personal salience (i.e., conditioned stimuli) is reported to induce acute craving (i.e., conditioned response), even in the absence of the opportunity to drink (Carter and Tiffany, 1999). Importantly, this cue-elicited craving is thought to persist despite prolonged periods of abstinence, conferring a sustained propensity for relapse even after withdrawal symptoms have abated (Drummond, 2000).

The investigation of cue-induced craving allows for the development of testable hypotheses and the manipulation of cue reactivity in controlled clinical and laboratory environments (Drummond, 2000). In most cue reactivity paradigms, stimuli of one or more sensory modalities (i.e., visual, olfactory, etc.) are presented to the research participant during an experimental presentation. In addiction research, the visual cue reactivity paradigm commonly includes images depicting alcohol and alcohol-related scenes presented on a screen or computer monitor for the participant to passively observe. Because visual stimuli are chosen based on craving-related salience,
the participant is hypothesized to react to these cues (e.g., experience craving), and this reaction is believed to be associated with relapse risk in real-world situations (Drummond, 2000).

1.4.2. Alcohol Cue Reactivity and Neuroimaging

Traditionally, the cue reactivity paradigm includes the presentation of stimuli relevant to craving, followed by single-item ratings of subjective craving along a visual-analog scale (Rosenberg, 2009). In order to relate self-reported craving with concurrent objective, physiological responses, this paradigm has been modified to allow simultaneous recording of data using a variety of psychophysiological modalities, including skin conductance response (Kaplan et al., 1985), heart rate variability (Ingjalldsson, Laberg, and Thayer, 2003), and event-related potentials (Herrmann et al., 2000). With recent advances in neuroimaging, including positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and functional near-infrared spectroscopy (fNIRS), a large body of research has been conducted in effort to identify the neural correlates of cue-induced craving (Filbey, Claus, and Hutchison, 2011; Jasinska et al., 2014; Schacht, Anton, and Myrick, 2012).

In one of the first functional imaging studies examining the neural correlates of alcohol-related cue exposure, ten non-treatment seeking alcoholics were compared with ten age-matched healthy control social drinkers in an fMRI cue-reactivity paradigm involving the presentation of visual alcohol stimuli immediately following a sip of alcohol (George et al., 2001). The investigators compared the subjective craving rating before and after the sip of alcohol as well as before and after exposure to alcohol stimuli presented in block design tailored for fMRI image acquisition. As hypothesized, subjective craving for alcohol was higher in the alcoholic group after the sip and after the presentation of alcohol stimuli, as compared with the social drinking control group. Additionally, exposure to alcohol stimuli in social drinkers was not associated with an increase brain activity in any regions the investigators measured. In contrast, the alcoholic participants exhibited an increase
in activity in the left medial frontal cortex and the anterior thalamus. The authors did not report on any correlations between cue-related activations and subjective craving ratings.

In a follow up study, the investigators replicated their findings in a group of ten additional non-treatment seeking alcoholics and ten age-matched healthy social drinking controls (Myrick et al., 2004). Using a similar block-design cue-reactivity paradigm, they found activations in the prefrontal cortex, cingulate cortex, nucleus accumbens, and insula during alcohol-related stimuli exposure in the alcoholic, but not control, group. Also, alcoholics, but not social drinkers, reported increased craving resulting from exposure to alcohol stimuli. Importantly, in this investigation, the authors reported on the correlation of subjective craving with task-related activations. In the alcoholic group, subjective craving was correlated with activity in the nucleus accumbens, anterior cingulate, and orbitofrontal cortex. Such correlations provided preliminary evidence for changes in regional brain activity that accompany subjective craving evoked by the cue-reactivity paradigm.

A host of investigations have further examined brain-related activations during alcohol cue reactivity and compared groups including alcoholics and controls, treatment and non-treatment seekers, and relapsers and abstainers, as well as the effects of pharmacotherapies on cue-induced craving (e.g., Langosch et al., 2012; Myrick et al., 2008; Myrick et al., 2010). These studies have also included behavioral and self-report data, including psychometrically-validated measures of craving, self-control, and alcohol-dependence severity.

In a systematic review, Schacht and colleagues performed activation likelihood estimations for within-subjects (across different experimental conditions) and between-subjects (cases versus controls) comparisons (Schacht, Anton, and Myrick, 2013). In AUD participants, alcohol cues elicited activations in the ventral striatum and anterior cingulate cortex, with additional clusters of activation in the ventromedial prefrontal cortex (vmPFC), insula, precuneus, and parahippocampal gyrus. Interestingly, when comparing AUD participants with healthy control participants, regions of
alcohol cue-elicited activation included only the precuneus, posterior cingulate, and superior temporal gyrus. No between-group differences were found in regions most related to craving and reward anticipation, including the ventral striatum and amygdala. These results suggest that alcoholics may not be reliably differentiated from healthy control subjects by cue-elicited activations in regions typically associated with addiction-related processes, including the brain reward system. Possible explanations for these unexpected findings are discussed below.

Additional analyses showed these activations did, however, correlate with a number of self-report and behavioral measures in treatment- and nontreatment-seeking AUD subjects. Inventories on severity of dependence, craving, and impaired control were correlated positively and most consistently with activity in the ventral striatum. In particular, scores on the Failed Control subscale of Impaired Control Scale (ICSFC; Heather et al. 1993), the Obsessive Compulsive Drinking Scale (OCDS; Anton, Moak, and Latham, 1996), Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993), Alcohol Dependence Scale (ADS; Skinner and Allen, 1982), and in-scanner craving were positively correlated with cue-elicited ventral striatum activity, as well as activity in amygdala, insula, anterior cingulate, and orbital and lateral prefrontal cortical regions. Although the direction of most of these brain-behavior correlations were positive, one study (Vollstad-Klein et al., 2010) reported a negative correlation between scores on the OCDS and ventral striatal activity in heavy drinkers, illustrating a level of inconsistency in findings across the cue-reactivity studies.

Additional inconsistencies have been found in neuroimaging studies on alcohol cue reactivity. Robust activation of the ventral striatum, vmPFC, and anterior cingulate, regions associated with reward processing, have been elicited among light social drinkers in response to alcohol cues (Seo et al., 2011). Another study found that social drinking control subjects exhibited greater activity in the ventral striatum and vmPFC than did heavy drinkers (Vollsadt-Klein et al.,
a finding which directly counters the hypothesis that exposure to alcohol stimuli is associated with greater activation in reward-related regions in subjects with AUD disorders.

These findings, and the lack of consistencies among studies, exemplify the complexity of neuroimaging studies in cue reactivity. There are several possible reasons why cue-related brain activity in patients with alcohol use disorders, and their comparisons with healthy control subjects, remains unclear. Differences in methodological procedures likely account for the majority of the discrepancies among studies. For instance, in some studies, but not all, participants are given an alcohol taste cue before the presentation of visual alcohol stimuli. While it is likely this priming effect may elicit greater cue reactivity and may better correlate with prospective drinking behavior than visual stimuli alone (Meyer 2001), regulations in many clinical treatment settings preclude the availability to administer alcohol to alcohol-dependent patients. Also, differences in neuroimaging technologies and analytic techniques following data acquisition may be responsible for additional variation in study findings. Importantly, the characteristics of patient samples, including treatment seeking status, treatment program, and abstinent duration often vary among studies. Moreover, the degree of severity of alcohol dependence (i.e., differences among severely, moderately, and non-dependent drinkers) has also been associated with subjective and physiological responses to alcohol stimuli (Laberg, 1986). Neglecting to account for the heterogeneity of patients with alcohol use disorders, research will likely continue to yield inconsistent outcomes in studies on cue reactivity.

1.4.3 Cue Reactivity as a Predictor of Relapse

The propensity to react to conditioned stimuli associated with alcohol and alcohol-related activities, resulting in cue-induced craving, is thought to represent an enduring vulnerability to relapse during short- and long-term abstinence (Langleben et al, 2008; Sinha and Li, 2007). For this reason, the manipulation of craving in the laboratory environment, via the cue reactivity paradigm
and cue-elicited craving, has been explored as a predictor of relapse in patients with alcohol use disorders. Studies on the relationship between subjective craving and relapse, however, have found conflicting results (Drummond, 2000; McHugh et al., 2016). Importantly, self-reported craving for alcohol is subject to response bias (i.e., poor awareness and denial; Rosenberg, 2009), resulting in unreliable laboratory measurement. Studies examining the relationship between conditioned physiological responses to alcohol cues and relapse, however, have demonstrated that physiological responses may predict subsequent relapse even in the absence of subjective craving (Rohsenow et al., 1994; Witteman et al., 2015). Due to the limitations of self-report measures, researchers have argued that physiological measures of cue-reactivity may be better predictors of relapse than self-reported craving alone (Carter and Tiffany, 1999).

To date, four studies have examined the relationship between neural activations during alcohol cue exposure and prospective relapse (Beck et al., 2010; Grusser et al., 2004; Heinz et al., 2007; Seo et al., 2013). Grusser and colleagues were the first to associate neural responses to visual alcohol stimuli in treatment-seeking alcoholics (n = 10) with three-month post-treatment relapse (Grusser et al., 2004). Patients who later relapsed showed increased activity in the anterior cingulate cortex (ACC) and adjacent medial prefrontal cortex (mPFC) in response to alcohol vs. neutral stimuli. This frontal activity did not correlate with subjective alcohol craving. It was, however, associated with the amount of subsequent alcohol intake. Grusser and colleagues interpreted this activity as the attribution of salience to alcohol-related stimuli. This study first demonstrated how objective brain activity, and not subjective craving ratings, could be used to help identify patients at an elevated risk of relapse.

In a follow-up study, Heinz and colleagues further explored the relationship between cue exposure and six-month relapse in twelve treatment-seeking alcoholics (Heinz et al., 2007). Contrary to their hypothesis, the authors found no significant relationship between alcohol cue exposure and
subsequent relapse. They did, however, report a negative correlation between PFC activity in response to affectively positive (i.e., natural reward) visual stimuli and subsequent drinking days (i.e., increased PFC activity to natural reward stimuli was associated with abstinence). The authors interpreted the observed increase in PFC response to positive stimuli to represent greater sensitivity to natural rewards, therefore serving as a protective factor in maintaining abstinence.

Further examining the relationship between cue response and prospective relapse, Beck and colleagues followed a larger cohort of alcohol-dependent patients (n = 46) to measure drinking intake for three months following treatment (Beck et al., 2012). The authors found that subsequent relapse was associated with increased medial PFC (mPFC) activity in response to alcohol stimuli, and, counter-intuitively, decreased responses in the ventral tegmental area (VTA) and ventral striatum to these same alcohol cues. Increased mPFC activity in response to alcohol cue exposure was interpreted as attentional bias and the attribution of salience to alcohol-related stimuli.

In a study by Sinha and colleagues, activity in the ventromedial prefrontal cortex (vmPFC) was also associated with three-month relapse in alcohol-dependent patients during personalized neutral, stress, and alcohol-related scripts (Seo et al., 2013). Hyperactivity in the vmPFC during neutral scripts correlated with alcohol cue-induced and stress-induced craving in patients compared to controls. This vmPFC hyperactivity also predicted subsequent relapse. However, reduced vmPFC activity in response to alcohol vs. neutral scripts was associated with higher craving and shorter time to relapse. Sinha and colleagues hypothesized that this hypoactivity represented a deficit in self-regulation, leading to increased risk for subsequent relapse.

Together, these studies highlight the promise and complexity of neuroimaging measures during alcohol cue exposure in the prediction of relapse risk. Although the consistency of findings in recent studies is lacking, such as the relationship between neural responses and subjective craving ratings, these findings demonstrate the value of neural signatures of prospective relapse in the
absence of reliable self-report measures. Improved standards for cue-reactivity design as well as studies with larger sample sizes will be advantageous in future investigations (Pulido et al., 2010; Jasinska et al., 2014).

1.5 The Prefrontal Cortex in Addiction

Over the past several decades, research on the neurobiological basis of addictive disorders has largely focused on the subcortical, motivational networks involved in the processing of reward and stress (Koob and Volkow, 2010). In addition to these subcortical systems, however, a burgeoning body of research has more recently examined the role of the prefrontal cortical mechanisms involved in the development and maintenance of addiction (Bechara, 2005; Everitt and Robbins, 2005; Goldstein and Volkow, 2002, 2011; Lubman, Yucel, and Pantelis, 2004). As a center of regulatory and executive functions, the PFC plays a critical role in cognitive and behavioral control and in salience and attentional processing (Heatherton and Wagner, 2011; Ochsner and Gross, 2005; Mansouri, Tanaka, and Buckley, 2009; Miller and Cohen, 2001). Therefore, PFC disruption in addiction is believed to be a key mediator of compulsive drug use, a hallmark feature of substance use disorders. The following section presents a unified model which explains the putative role of PFC dysfunction in addiction (Goldstein and Volkow, 2011) and its relevance to treating addictive disorders.

1.5.1 The Impaired Response Inhibition and Salience Attribution (iRISA) Model

Ongoing research has supported the hypothesis that the PFC, the cerebral region most developed in the human primate (Goldman-Rakic, 1995), is devoted to the processing of the mental representation (i.e., planning) and material production (i.e., acting) of goal-directed behavior
(Fuster, 2008; Miller and Cohen, 2001). However, because of its architectural complexity and functional heterogeneity, as well as the breadth of addiction research focused instead on subcortical reward and stress systems, the role of the PFC in addiction has remained unclear. Mounting clinical evidence, however, has demonstrated that addicted individuals exhibit disruptions in prefrontally-mediated executive functions, and that these prefrontal disruptions underlie compulsive drug-taking behavior. In their two reviews, Goldstein and Volkow have posited a model that explains the roles of the various subregions of the PFC in the relapse cycle of addiction: The impaired response inhibition and salience attribution (iRISA) syndrome (2002; 2011).

The iRISA model describes how disruptions in dorsal and ventral prefrontal activity relate to the core clinical phenomenology of addictive disorders (Goldstein and Volkow, 2002; 2011). In particular, Goldstein and Volkow posit that dorsal PFC activity subserves “cold” cognitive processes, such as inhibitory and executive functions, while the ventral PFC activity subserves “hot” affective functions, such as value- and salience-attribution processing. During anticipatory or craving-related states, “cold” cognitive processes become compromised, leading to impaired inhibitory control, and “hot” affective processes are accentuated, leading to heightened salience of alcohol stimuli and motivation toward alcohol consumption.

Included in their model is a comprehensive inventory of impaired affective and cognitive processes and implicated PFC subregions. These include addiction-related disruptions in: (1) self-control and behavioral monitoring, subserved by the dorsolateral PFC (dLPFC), inferior frontal gyrus (IFG), and ventrolateral PFC (vLPFC); (2) awareness and interoception, subserved by the dorsal anterior cingulate cortex (dACC), medial PFC (mPFC), and vLPFC; (3) attention and flexibility, subserved by the dLPFC, ACC, IFG, and vLPFC; and (4) salience attribution and attentional bias, subserved by the vmlPFC and dLPFC.
Importantly, because of the neuroanatomical complexity of frontal regions, precise structure-function relationships within the PFC have not yet been determined. As described above, many distinct PFC subregions mediate a single cognitive or affective process (a neurocomputational concept known as degeneracy; Pessoa, 2008). Likewise, any single PFC subregion likely mediates a number of different cognitive processes (i.e., pluripotentiality). Moreover, prefrontal areas have a greater degree of functional flexibility than other primary somatosensory cortices (Fuster, 2008; Goldstein and Volkow, 2011). This difficulty in mapping these structure-function relationships may explain why findings in PFC studies on addiction have remained unclear. For example, the authors ask rhetorically: “Are the dorsal anterior cingulate cortex (dACC) and dorsolateral prefrontal cortex (dLPFC) involved in the craving response or in control over craving, or in both?” Although conclusive answers remain elusive, Goldstein and Volkow propose a simple set of hypotheses in the iRISA model which highlight the role of the PFC in responses to alcohol cue exposure and behavioral control over alcohol consumption.

In particular, PFC responses to alcohol-related stimuli are thought be heightened in addicted individuals and that this response would be reduced as an effect of treatment. Furthermore, Goldstein and Volkow propose that addicted individuals have concomitant decreases in response to positive, non-drug stimuli, reflecting diminished sensitivity to “natural rewards”. Finally, the authors hypothesize that cognitive and behavioral deficits in inhibitory control are incurred by hypoactivity in frontal regions. Consequently, the authors recommend that the normalization of these functions, using targeted interventions, be a prospective goal in the treatment of addiction (Goldstein and Volkow, 2011).
1.5.2 General Findings on PFC Function in Addiction Studies

In addition to fMRI studies, previous studies have examined the PFC substrates of cue reactivity using functional near-infrared spectroscopy (fNIRS; see section 1.6). Bunce and colleagues examined the prefrontal cortical responses to alcohol and natural reward stimuli in non-treatment seeking (actively drinking) alcoholics, treatment seeking alcoholics (90-180 days abstinent), and social drinking control participants (Bunce et al., 2012). In response to alcohol cues, differential activations were found between treatment and non-treatment seeking alcoholics in the right dorsolateral PFC (dIPFC), in general, and the right middle frontal gyrus (Brodmann Area 10/46), in particular (Figure 1). Group-differences in PFC activity in response to natural rewards were also found in the right lateral PFC, although more ventral to activations to alcohol cues (i.e., Brodmann Area 44/46), and the direction of these activations were opposite to those of alcohol cues. This study demonstrated cue-related activations of the prefrontal cortex in response to visual alcohol and natural reward stimuli, and the differential activation of the right dIPFC as a function of treatment-seeking status.

**Figure 1.** PFC responses to alcohol and natural-reward cues in non-treatment seeking alcoholics, treatment seeking alcoholics, and social drinking healthy control participants.

A, Current alcoholics show increased PFC responses to alcohol cues, relative to recovering alcoholics (90-180 days abstinent) and control participants. B, Current alcoholics show blunted PFC responses to natural rewards, relative to recovering alcoholics and controls.
These findings were echoed in a subsequent investigation with prescription opioid-dependent patients, in which Bunce and colleagues investigated cue reactivity in recently withdrawn patients (7-10 days abstinent), extended-care patients (60-90 days abstinent), and healthy controls (Bunce et al., 2015). Differential activity in the right dlPFC were found between recently withdrawn and extended care patients in response to visual prescription opioid stimuli (e.g., photographic images of pills and pharmacy bottles). In this same region, differential responses to natural reward cues were also found between these two groups. Across these two studies examining PFC function during cue reactivity using fNIRS, results showed a common region of interest in the right dlPFC in response to drug stimuli. Furthermore, these results support the findings of Wilson and colleagues, which suggest that group-related differences (e.g., treatment status, motivation for abstinence, perceived opportunity to drink, etc.) may help explain the inconsistent findings among studies examining prefrontal cortical responses to drug and alcohol cues (Wilson, Sayette, and Fiez, 2004).

1.6 Introduction to Functional Near-Infrared Spectroscopy (fNIRS)

Near-infrared spectroscopy has been used in the clinical monitoring of tissue oxygenation, such as pulse oximetry, for over 30 years (Neuman, 1987; Wahr et al., 1996). The experimental application of near-infrared to the monitoring of cerebral metabolism, however, has become popular within the past 20 years (Villinger and Chance, 1997; Hoshi, 2007) and has since been demonstrated as a valid and reliable tool in the study of functional brain imaging (Boas et al., 2014; Plichta et al., 2006; Schecklmann et al., 2008). The application of fNIRS to laboratory paradigms offers a cost-effective and clinic-friendly alternative to fMRI imaging methods used in psychiatric research (Ehlis et al., 2014).
1.6.1 *Principles of Functional Near-Infrared Spectroscopy*

Like other neuroimaging methods, such as functional magnetic resonance imaging, functional near-infrared spectroscopy is a non-invasive imaging technology that monitors cerebral blood oxygen levels during metabolically demanding tasks (Cui et al., 2011). This blood-oxygen-level dependent (BOLD) signal is thought to represent the local processing of neural information within a given brain region (Logothetis, 2002). Consequent to an increase in task-related cerebral workload, oxygen and glucose is consumed in the capillary bed innervating the local brain region of the underlying task-related neural computation, which results in an initial decrease in local oxygenated hemoglobin in that region (Buxton et al., 2004). To compensate for this hypooxygenated state, cerebral blood flood to this same region is subsequently increased through neurovascular coupling (Girouard and Iadecola, 1985). This adjustment of local cerebral blood flood and corresponding increase in oxygenated hemoglobin is known as the hemodynamic response (Lindquist et al., 2011). The hemodynamic response serves as the basis for the neural signal obtained in both fMRI and fNIRS (Cui et al., 2011).

The capacity of fNIRS to monitor the hemodynamic response emerges from the differential optical properties of oxygenated and deoxygenated hemoglobin (Figure 2A; Bunce et al., 2006). In addition to cytochrome oxidase and water, hemoglobin is a predominant chromophore, or light-absorbing molecule, of the cerebral cortex (Hoshi, 2003). Within the near-infrared spectral range of 700-900 nm, deoxygenated hemoglobin absorbs light maximally at 760 nm (Mancini et al., 1994), whereas oxygenated hemoglobin absorbs light maximally above 800 nm, the isosbestic point of oxygenated and deoxygenated hemoglobin (Wray et al., 1988). Measurements obtained from two wavelengths, one above and one below the isosbestic point, allows for the investigation of the selective changes in oxygenated and deoxygenated hemoglobin.
**Figure 2.** Functional NIRS Photon Path and Wavelength Absorption Characteristics

**A**, Wavelength absorption characteristics of oxygenated hemoglobin (HbO₂), deoxygenated hemoglobin (Hb), and water. **B**, Photon path (banana-shaped) from light emitting diode (LED) to light detector.

Most biological tissue is relatively transparent to light in the near-infrared spectral band; however, some photons emitted within this optical window are either absorbed or scattered as they pass through the skull, meninges, cerebrospinal fluid, and the cerebral cortex and are then reflected back to the surface of the scalp (Figure 2B; Bunce et al., 2006). A relatively predictable amount of photons will travel this banana-shaped path in the adult head, and the light intensity at the adjacent photodetector can be measured (Gratton et al., 1994). Using the intensities of the light emitted from the source and the light measured by the photodetector, the relative change in concentration of chromophore in the measured region can be calculated using a modification of the Beer-Lambert law (Boas et al., 2001). Thus, by emitting light at wavelengths above and below the 800 nm isosbestic point, the relative change in concentration of oxygenated and deoxygenated hemoglobin can be monitored. In experimental paradigms, increases in cognitive workload results in a compensatory rise in oxygenated hemoglobin and concurrent decrease in deoxygenated hemoglobin. The monitoring of these task-related metabolic changes thus serves as the basis for the measurement of cortical activity in fNIRS studies (Ehlis et al., 2014).
1.6.2 Validity of fNIRS as a Neuroimaging Methodology

Recent studies have found strong temporal correlations ($r = 0.77 – 0.94$) between the hemodynamic signals obtained from fNIRS and fMRI in the primary motor cortex during simple motor tasks (Cui et al., 2011; Noah et al., 2015; Okamoto et al., 2004). Strong correlations between these imaging methods have also been demonstrated in the PFC during cognitive and decision-making tasks (Heinzel et al., 2013; Sato et al., 2013), in widespread cortices during resting-state functional connectivity (Duan, Zang, and Zhu, 2012; Sasai et al., 2012), and during respiration challenge (Alderliesten et al., 2014). These results provide strong evidence for the validity of fNIRS as an optical brain imaging technology comparable to fMRI measures across spatial and temporal parameters.

1.7 Rationale for Study

The overall purpose of this study was to identify functional PFC signatures of prospective relapse in residential patients with severe alcohol use disorders (AUD). In particular, this study sought to measure prefrontal cortical activity subserving inhibitory control and alcohol cue reactivity as a predictive biomarker of treatment outcome, based on the impaired response inhibition and salience attribution (iRISA) model posited by Goldstein and Volkow (2002; 2011). Although the current gold-standard technology for measuring brain activations in laboratory tasks is functional magnetic resonance imaging (fMRI), this study employed functional near-infrared spectroscopy (fNIRS) due to (1) its clinical relevance and (2) its capacity to monitor activity in PFC, the brain region of interest in this study. Treatment outcome was defined as any return to heavy drinking (i.e., 5 or more drinks per day for men; 4 or more drinks per day for women) within 12 weeks following discharge. Weekly follow-up drinking data was obtained using web-based self-report questionnaires.
Pre-discharge task-related PFC activations were then associated with post-treatment outcome data to determine the utility of neuroimaging measures in the prediction of relapse.

1.7.1 Clinical Utility of Neuroimaging Predictors of Relapse

Managing the chronic and relapsing nature of substance use disorders is one of the major challenges for addiction treatment professionals (McLellan, 2002; Volkow and Baler, 2013). A number of factors have previously been associated with alcohol treatment outcomes, including dependence severity, socioeconomic status, employment, living environment, neuropsychological functioning, negative mood, stress, and craving (Adamson et al., 2009; Marlatt and George, 1984; Witkiewitz, 2011). With the exception of dependence severity, the reliability of variables predicting outcome, however, has been poor across studies (Adamson et al., 2009). Furthermore, many of these variables are obtained using self-report methods. Importantly, self-report measures are subject to response biases (i.e., tendencies of participants to answer items misleadingly or untruthfully) and are, therefore, generally unreliable (Nisbett and Wilson, 1977). This methodological limitation is accentuated in addiction populations, where denial and lack of awareness are key features of the disease (Goldstein et al., 2009). This limitation highlights the field’s need for objective markers of relapse risk (Volkow and Baler, 2013). Given the key role of brain-related disturbances in addictive disorders, investigators have begun to evaluate the promise of neuroimaging measures as indices relapse liability (Courtney et al., 2015).

Despite ongoing investigations on the neurobiology of addiction, only recently has clinical research been conducted around the neurobiology of relapse vulnerability (Garavan et al., 2013; Heinz et al., 2008; Sinha, 2011). Recent investigations which characterize the functional state of the addicted brain have shown promise toward developing a reliable approach to identify individuals at greater risk for relapse (Garrison and Potenza, 2014; Volkow and Baler, 2013). These studies have
employed fMRI paradigms to examine clinically relevant addiction-related alterations of motivational and inhibitory networks (Goldstein and Volkow, 2011; Thayer and Hutchison, 2013). In particular, neuroimaging cue-reactivity paradigms probing the motivational responses to drug-related stimuli offer a potential translational mechanism by which treatment interventions may be better targeted and treatment outcomes may be better predicted (Courtney et al., 2015). Additionally, PFC-mediated inhibitory control processes are also considered an important target for cognitive and behavioral intervention (Garavan et al., 2013). Moreover, by examining the relevant neurobiological changes underlying the clinical phenomenology of addictive disorders, the development of prognostic neuroimaging paradigms may yield objective biomarkers with greater clinical utility than self-report, cognitive, or behavioral measures alone (Courtney et al., 2015; Garavan et al., 2013; Menossi et al., 2013).

Because of the mounting evidence implicating PFC dysfunction in addiction, including impairments in response inhibition and the salience attributed to drug-related stimuli (i.e., the iRISA model; Goldstein and Volkow, 2011), we sought to combine these two processes in a unified study design, examining the prefrontal activity subserving each process and relating these PFC activations with prospective relapse. Furthermore, a common barrier to implementing clinical neuroimaging technologies in addiction treatment practice is the geographical distance between treatment centers and neuroimaging facilities. What has been needed is a technology that can bring the insights of brain imaging and clinical neuroscience to the prediction of treatment outcomes in real-world environments. This study offered noteworthy translational value by utilizing a cost-effective neuroimaging technology readily deployable in the clinical setting (i.e., fNIRS). Therefore, the results of this study would not only provide further evidence for prefrontal indicators of relapse risk, but its methodology would also be relevant to addiction treatment professionals. Treatment providers could then be equipped with better tools to inform clinical decision making, identify more effective
targets for treatment, and reduce relapse rates. Optimally, the development of prognostic PFC signatures could also provide markers of efficacy in early pharmacotherapy trials.

1.7.2 Selection of Study Tasks

The objective of this study was to identify task-related PFC activity predictive of post-treatment relapse. We examined task-related PFC function across two main cognitive domains: (1) salience and (2) inhibition. PFC activations putatively subserving the salience, or perceived reward value, of alcohol and alcohol-related stimuli was measured using the visual cue-reactivity paradigm (Courtney et al., 2015; Drummond, 2000; Jasinska et al., 2014). In the present study, we employed a block-design visual cue-reactivity paradigm, tailored to fNIRS data acquisition. Included in this paradigm were photographic images depicting alcohol and alcohol-related scenarios (e.g., beer being poured from a tap, wine being swirled in a glass, whiskey being purchased at a liquor store, etc.). During this task, we monitored changes in PFC activity underlying the processing of salience and craving elicited from the visual alcohol stimuli. Also measured were PFC activations in response to images depicting natural rewards (e.g., cute puppies, children playing, a beautiful sunset, etc.).

In addition to the cue-reactivity paradigm, the color-word Stroop task was selected as the inhibitory paradigm. A number of paradigms were suitable for inhibition-related measurement, including the go/no-go paradigm (GNG; Yechiam et al., 2006), the stop-signal reaction time task (SSRT; Logan, Cowan, and Davis, 1984), and the word-word Stroop task (Stroop, 1935). (For a description of each of these tasks, see section 1.3.3). The word-color Stroop task was selected our measure of inhibition for several reasons. First, originally studied in the early twentieth century, the Stroop task is one of the most extensively investigated and widely used cognitive paradigms in psychological research (MacLeod, 1991; Stroop, 1935). Second, it is considered a well-validated measure of inhibitory control in neuroimaging paradigms (Egner and Hirsch, 2005; Goldstein and
Finally, it has been used in a number of previous neuroimaging studies in addiction (Nestor et al., 2011; Potenza, et al., 2003; Silveri et al., 2011) and has also been used as a predictive measure of treatment outcomes (Brewer et al., 2008).

1.7.3 Research Hypotheses

The central hypotheses concerned the prediction of treatment outcome at three-months post-discharge and the variable which best predicted relapse in our patient sample. We first hypothesized that neuroimaging variables would be superior outcome predictors to behavioral or self-report predictor variables. Additionally, based on the findings of our previous fNIRS cue-reactivity studies (Bunce et al., 2012; 2015) and from fMRI studies of cue reactivity and treatment outcome by other investigators (Grusser et al., 2004; Heinz et al., 2007), we hypothesized that, relative to abstainers, relapsers would show increased regional PFC activity in response to alcohol stimuli and decreased response to natural reward stimuli. We also expected that PFC responses to alcohol stimuli would be associated with cue-elicited subjective craving ratings. Furthermore, we also hypothesized that inhibition-related activity in the word-color Stroop task would be reduced in relapsers relative to abstainers, indicating impairments in inhibitory control processing (Nestor et al., 2011). Moreover, we hypothesized that poorer performance measures during the Stroop, including longer reaction time and reduced accuracy, would predict relapse, although less robustly than neuroimaging measures.

Finally, using our neuroimaging variables as predictors, we sought to estimate an optimal model of prediction based on multivariate logistic regression. To control for family-wise error, the least absolute shrinkage and selector operator (LASSO) method was used for variables selection (Tibshirani, 1996). Using this approach, we hypothesized that prospective relapse would be
predicted with maximal accuracy from a combination of (a) severity scores on the SADQ, and (b) PFC activity in response to the Stroop effect, alcohol cues, and natural reward cues.


CHAPTER TWO
METHODS

2.1 Participants

Seventy treatment-seeking AUD participants (ages 25-65) were recruited from Caron Treatment Centers, Wernersville, PA, a 12-step residential addiction treatment facility. Of these 70 patients, 14 patients remained at Caron for extended care and were not included in the final analysis. An additional 6 patients withdrew from the study or were lost to follow up. The final alcohol-dependent patient sample (n = 50) remained for 28-day treatment and were followed for relapse for 12 weeks after discharge. For group comparison, healthy control participants (n = 20) with no lifetime history of a substance use disorder were recruited from the local community in Hershey, PA. All participants provided written consent before participation in accordance with protocol endorsed by the Pennsylvania State University Institutional Review Board. All AUD participants met criteria for alcohol dependence on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID; First et al., 2002).

Participant exclusion criteria were as follows: Current DSM-IV criteria for dependence on any substance other than alcohol, caffeine, or nicotine; current pharmacotherapy for alcohol dependence; DSM-IV criteria for major Axis I disorders other than depression and anxiety. The principal inclusion criterion for patient selection was a primary diagnosis of alcohol dependence. Control participants were screened using the same exclusion criteria as the alcohol-dependent participants in addition to exclusion due to history of drug or alcohol abuse or dependence. Alcohol-dependent participants were recruited into the study 7-14 days following admission to treatment and participated in the fNIRS scanning session 14-28 days following admission.
2.2 Experimental Procedures

2.2.1 Study Design

Experimental procedures for alcohol-dependent patients, including functional neuroimaging, were conducted onsite at Caron Treatment Centers. Prospective outcome measures were collected from patients after discharge from Caron. All experimental procedures for healthy control participants were conducted at the Penn State College of Medicine, Hershey, PA. Potential patient candidates were first identified by the investigator using Caron’s electronic medical records. Qualifying candidates were then scheduled to meet with the investigator for study recruitment, 7-14 days following admission to treatment. Those who elected to participate were informed of the experimental tasks and study purpose before signing informed consent. The first session with the investigator included a Structured Clinical Interview for DSM-IV Diagnoses (SCID; First et al., 2002) and several inventory assessments (see Section 2.2.2). Following this session, patients were scheduled for fNIRS scanning session, including a 20-minute word-color Stroop task and a 25-minute visual cue-reactivity paradigm, 14-28 days following admission to treatment. Following discharge, patients were followed for relapse to any heavy drinking using web-based self-report queries distributed weekly for 12 weeks (Figure 3).

**Figure 3. Study Design**

Alcohol-dependent patients were recruited 7-14 post-admission and participated in fNIRS measures 14-28 days post-admission. Following discharge, patients participated in weekly online self-report questionnaires to determine relapse status by 12 weeks post-discharge.
2.2.2 Inventories and Self-Report Scales

During the interview, participants completed several inventories in addition to the SCID. Demographic information, including income and education, was obtained using the Demographic Interview screening form (version 2.2; CASAA, 1997). Additionally, alcohol use during the 90 days prior to abstinence was assessed using the Form 90-AI, a standard inventory for retrospective estimates of alcohol intake (Miller, 1996).

The construct of severity of dependence was assessed using the Severity of Alcohol Dependence Questionnaire (SADQ; Stockwell et al., 1979). The SADQ is a 20-item scale formulated from the elements of the alcohol dependence syndrome (Edwards and Gross, 1976), and is comprised of five subscales: Physical Withdrawal (PHYS), Affective Withdrawal (AFFECT), Withdrawal Relief Drinking (COMP), Recent Alcohol Consumption (ALCOHOL), and Predictive Rapidity of Reinstatement (POST). Psychometric studies have demonstrated test–rest reliability as well as content and construct validity (Davidson, 1987; Stockwell, Murphy, Hodgson, 1983). This questionnaire was selected as a measure of severity because of its putative operational measurement of the core clinical phenomenology of alcohol dependence (Edwards, 1986), and because it has been associated with alcohol treatment outcomes in previous investigations (Adamson et al., 2009).

Self-reported impulsivity was assessed using the Barratt Impulsiveness Scale (BIS; Patton, Stanford, and Barratt, 1995). This inventory was included due to the well-known relationships among inhibitory control measures (e.g., the Stroop task), impulsive disorders, and alcohol use disorders (Courtney et al., 2012; Houben and Wiers, 2009; Moeller and Dougherty, 2002). The BIS is a 30-item scale measuring self-reported impulsivity along three dimensions: (1) ATTENTION impulsivity, involving quick decisions and poor sustained attention; (2) MOTOR impulsivity, involving spontaneous disinhibited behavior; and (3) NON-PLANNING impulsivity, involving acting without
forethought or consideration to possible outcomes (Patton, Stanford, and Barratt, 1995). The BIS was also selected due to its strong psychometric properties and its extensive use and development over the past 50 years (Moeller et al., 2001; Spinella, 2007; Stanford et al., 2009).

Following the interview, participants returned for a second session to complete neuroimaging procedures. Prior to scanning, participants completed the Insomnia Severity Index (ISI), the Obsessive Compulsive Drinking Scale (OCDS), and the Alcohol Craving Questionnaire (ACQ). Self-report measures of subjective sleep disturbances were obtained using the Insomnia Severity Index (ISI; Morin, 1993), a brief, validated, 7-item assessment of recent insomnia-related complaints (Bastien, Vallieres, and Morin, 2001). The OCDS, a widely used and well validated 14-item self-report scale quantifying thoughts and compulsions to drinking (Anton et al., 1996; Roberts et al., 1999; Bohn et al., 1996), was used as a measure of tonic craving (Meyer, 2001; Moak et al., 1998). Right handedness was verified using the Edinburgh Handedness Inventory (Oldfield, 1971). Cue-related craving was assessed using a (0-100) visual-analogue scale. Because this single-item scale has been questioned as a valid measure of acute craving (Rosenberg, 2009), the ACQ was also administered (Singleton, Tiffany, and Henningfield, 1995). The ACQ is a 12-item scale of situational craving that has demonstrated internal consistency and construct validity (Singleton, Tiffany, and Henningfield, 2000). Visual-analogue and ACQ measures of acute craving were administered before and after the cue-reactivity paradigm.

Prior to scanning, participants were seated at a desk and positioned to view a 19-inch computer monitor (4:3 aspect ratio) from a distance of 24 inches. The fNIRS sensor was then positioned in alignment with the International 10-20 site F7, FP1, FP2, F8 measurements. The order of the two fNIRS paradigms was chosen to circumvent the potentially impairing effects of, and variability in, craving response to alcohol stimuli during the cue reactivity paradigm on cognitive performance during the Stroop task (Gauggel et al., 2010; Noel et al., 2007; Wilson et al., 2007).
2.2.3 Color-Word Stroop Task

The color-word Stroop task consisted of a sequence of three 110-second epochs. Each epoch contained three 30-second blocks, including one block of each of the following stimulus types: congruent, incongruent, and neutral. Each 30s block was comprised of a series of 15 stimuli. Each stimulus was presented for 1300ms, preceded by a 700ms fixation point. Block order was randomized with a 10s interblock rest period. Prior to the experimental epochs, participants completed a practice block consisting of one block of each stimulus type.

Stimuli were presented using E-Prime 2.0 Professional software (Psychology Software Tools, Pittsburgh, PA). Participants responded to stimuli vocally, and responses were recorded using a Serial Response Box (Psychology Software Tools) to measure response time. Accuracy of responses to incongruent stimuli was coded manually by the investigator.

2.2.4 Visual Cue-Reactivity Paradigm

The visual cue-reactivity paradigm (Figure 4) included photographic images selected from the International Affective Picture System (IAPS; Lang, Oehman, and Taitl, 1988) and the Normative Affective Picture System (NAPS; Breiner et al., 1995). Alcohol and non-alcoholic beverage cues were supplemented with a stimulus set developed by Pulido and colleagues (Pulido et al., 2010). Prior to cue presentation, participants were asked to self-rate their (1) “craving for alcohol” and (2) perceived “control over drinking” on a 100-point visual analogue scale. Participants also completed the ACQ.

Part 1 of the stimulus presentation series consisted of six 140-second epochs. Each epoch included one 25-second block of each of the following four stimulus types: Alcohol, Non-Alcoholic Beverage, Natural Reward, and Neutral. Blocks were separated by a 10-second fixation period, during which a crosshair was displayed. Each block contained five photographic images, and each
image was displayed for 5 seconds. Alcohol-stimulus blocks were separated by type (beer, wine, and liquor), with two blocks per type. To control for order effects and attentional fatigue, epoch sequence, within-epoch block sequence, and within-block image sequence were randomized for each participant. Epochs were separated by a 20-second fixation period. Part 2 of the stimulus presentation series repeated identical alcohol and non-alcoholic beverage stimuli from Part 1.

**Figure 4. Cue Reactivity Experimental Design**

Stimuli were comprised on photographic images representing natural rewards (affectively positive), neutral (control), non-alcoholic beverage (control) and alcohol-related scenes and were selected from the International Affective Picture System (IAPS; Lang, Oehman, and Taitl, 1988), the Normative Affective Picture System (NAPS; Breiner et al., 1995), and supplemented with stimuli from Pulido et al. (2010). Inter-block intervals consisted of a blank screen with crosshair.
Alcohol and non-alcoholic beverage order was alternated across the 12 repeated blocks. Following the presentation series, participants again rated their subjective craving for alcohol use on a 100-point visual analogue scale and completed a follow-up ACQ inventory to measure changes in subjective craving due to alcohol cue exposure.

2.3 Functional NIRS Acquisition and Processing

Continuous-wave fNIRS data were obtained using an fNIR Imager 1100 with a 16-channel sensor (fNIR Devices, LLC). Functional NIRS data was recorded in Cognitive Optical Brain Imaging (COBI) Studio, a hardware-integrated software platform designed to acquire and visualize fNIRS signals (fNIR Devices, LLC), and reduced using fNIRSoft, a stand-alone software package designed to process, analyze, and visualize fNIRS signals (Ayaz, 2010).

Raw light intensity fNIRS data (16 optodes × 2 wavelengths) were low-pass filtered with a finite impulse response, linear phase filter with order 20 and cut-off frequency of 0.1 Hz to attenuate the high frequency noise, respiration and cardiac cycle effects (Ayaz et al., 2011). All data were screened for potential saturation (when light intensity at the detector was higher than the analog-to-digital converter limit) and motion artifact contamination by means of a coefficient of variation based assessment (Ayaz et al., 2010). The fNIRS data for each task block were extracted using time synchronization markers of task onset and end marked during the experiment, and hemodynamic changes for each of 16 optodes during each trial block were calculated separately using the Modified Beer Lambert Law (MBLL). The final output of each optode was mean block deoxygenated hemoglobin (HbR), mean block oxygenated hemoglobin (HbO₂), and the sum of the first two measures represented as mean block total hemoglobin (Total Hb).
Mean HbR, HbO2, and Total Hb were then averaged across blocks per stimulus type (e.g., alcohol-cues, natural reward cues, etc.). Between-block subtraction contrasts were performed to compare active versus control conditions. Final contrasts for each condition were as follows: (1) HbO2 (Stroop effect) = HbO2 (incongruent – congruent stimuli), (2) HbO2 (alcohol cues) = HbO2 (alcoholic – non-alcoholic beverage stimuli), and (3) HbO2 (natural reward cues) = HbO2 (affectively positive – affectively neutral stimuli). These contrasts will henceforth be assumed in this dissertation when referring to PFC responses mediating “Stroop,” “Alcohol Cues,” and “Natural Reward Cues”. Main effects were examined using one-sample t-tests at a significance level of \( p < .05 \). Correlations between activation contrasts and behavioral variables were assessed at significance level of \( p < .05 \).

2.4 Statistical Analyses

2.4.1 Behavioral Data Analysis

Stroop reaction time (RT) data were analyzed using a 2 (group) x 2 (condition; incongruent vs. congruent) repeated-measures ANOVA for patients versus controls and abstainers versus relapsers. Cue-reactivity craving ratings were also analyzed using a 2 (group) x 2 (condition; pre vs. post) repeated-measures ANOVA for patients versus controls and abstainers versus relapsers. Additional group differences between patients and controls, as well as abstainers and relapsers, were explored using two-sample t-tests and Wilcoxon-Mann-Whitney tests, when data failed to meet parametric assumptions.

2.4.2 fNIRS Data Analysis

Neuroimaging data were first examined using descriptive statistics. Summary statistics and graphical plots (e.g., boxplot) were generated to explore data distributions and to identify outliers.
Any extreme data points of concern were investigated. Data normality was assessed using Shapiro-Wilk tests and relevant graphical tools, including quantile-quantile (Q-Q) plots. Univariate two-sample t-tests or nonparametric Wilcoxon-Mann-Whitney tests were then used to determine group differences in fNIRS measurements between patients versus controls and subsequent relapsers versus abstainers.

Due to random motion artifacts, light intensity saturation, and imperfect forehead-sensor alignment, fNIRS recordings included missing data. Because of the high correlations among same-condition neuroimaging variables, we used a principal component analysis (PCA)-based method to impute missing values (Audigier, Husson, and Josse, 2016; Josse and Husson, 2012). Using this method, estimation of missing values was based on between-subject and between-variable correlations. Functional NIRS variable correlations and univariate analyses results of neuroimaging-based relapse risk remained similar after imputation.

2.4.3 Prediction Modeling

Multiple logistic regression analyses were conducted to examine the collective predictive value of significant fNIRS variables. Prediction performance was evaluated using the receiver operating characteristic (ROC) curve, which was generated by plotting true positive rate (sensitivity) against the false positive rate (1 − specificity) at various discrimination thresholds. Area under the ROC curve (AUC) was calculated as an ROC curve summary statistic, representing the discrimination accuracy of fNIRS measurements in determining outcome. Sensitivity and specificity were calculated using the optimal threshold (i.e., Youden’s index criteria).

One common problem in predictive modeling is poor test-retest reliability, such as when a model fitted from one population is applied or validated in a new population (i.e., overoptimism; Whelan and Garavan, 2014). To address this problem, leave-one-out cross-validation was applied to
multiple logistic regression analysis to adjust model-based AUCs. Furthermore, given the number of fNIRS variables relative to the sample size, a penalized maximum likelihood estimation (PMLE) method, the least absolute shrinkage and selection operator (LASSO) technique, was used for variable selection. PMLE methods, such as LASSO, are a more rigorous modeling approach than post-hoc methods because adjustment for overfitting is built into the prediction model, rather than relying on shrinkage of coefficients after model development (Moons et al., 2004). In particular, LASSO was developed as a method for variable selection when the number of predictors is larger than the sample size, and is used to control overoptimism of model performance without sacrificing discriminative accuracy (Tibshirani, 1996).

Finally, ROC contrast estimates were used to determine whether fNIRS measurements significantly improved outcome prediction accuracy (increases AUC) compared to self-report predictor variables alone. We estimated and compared the AUCs for prediction models based on: (1) fNIRS variables, (2) self-report variables, and (3) a combination of fNIRS and self-report variables.

2.5 Follow-Up (Outcome) Data Collection

Alcohol-dependent patients were followed for alcohol intake weekly for 12 weeks after discharge from residential treatment. Retrospective alcohol use was reported using a web-based self-administered 7-day Timeline Followback (TLFB). The 7-day TLFB has been shown to have good correspondence to the standard 30-day TLFB. Marginally greater levels self-reported drinking have been found using the 7-day TLFB, relative to the 30-day version, which has attributed to improved behavioral recall due to shorter reporting intervals (Hoepner et al., 2010). The web-based TLFB has also demonstrated strong psychometric properties and strong positive correlations with telephone
interview TLFB (Rueger et al., 2012; Thomas & McCambridge, 2008) and concurrent validity with the in-person TLFB interview (Pedersen et al., 2012).

Weekly online TLFB data was obtained using a HIPAA-compliant institutional web service, Research Data Electronic Capture (REDCap; Harris et al., 2009). REDCap is a secure, online application designed to support data collection for research studies, providing a user-friendly interface for validated data entry and export procedures to analyze data in common statistical packages (Harris et al., 2009). Importantly, REDCap is capable of recording automated longitudinal survey entry, allowing patients to report their drinking patterns on a weekly basis for the study outcome period. The approximate time to complete each survey was 3 minutes. Once completed, the provided information and notification of survey submission were sent automatically to the REDCap database. If a participant did not complete the follow-up questionnaire within the allotted time window, an email was sent to remind the participant to complete the report.

Although there is no indisputable definition of relapse within alcohol populations, any return to heavy drinking (5 or more drinks/day for men; 4 or more drinks/day for women), has been considered to be an acceptable definition (Sobell et al., 2003; Falk et al., 2010), is a recommended efficacy endpoint in clinical trials (FDA, 2015), and was selected as the definition of relapse in this investigation.
CHAPTER THREE

RESULTS

3.1 Demographic and Group Characteristics

Compared with control participants, AUD patients scored higher on the Severity of Alcohol Dependence Questionnaire (SADQ), had higher levels of self-reported impulsivity (as measured by the Barratt Impulsiveness Scale; BIS), reported greater attempts to control their drinking (based on the Impaired Control Scale; ICS), scored higher on the Obsessive Compulsive Drinking Scale (OCDS), and reported more family members with alcohol problems (on the Family History Questionnaire; FHQ) (Table 1). Alcohol-dependent patients and healthy controls did not differ in self-reported sleep disturbances (based on the Insomnia Severity Index) or years of education. Mean group age, however, was higher in the AUD group than in healthy controls, although this difference was not significant between subsequent abstainers and relapsers (see Table 2). Group differences between abstainers and relapsers were not significant for any of the above-listed self-report measures ($p > .20$ for all), except for scores on the Severity of SADQ, which was higher in relapsers than abstainers ($t = -2.32, p = .02$).

Of the above-listed measures, the SADQ, the BIS, and the ICS were divided into subscales which further differentiated the patient and control group and, on the SADQ total score, the abstinent and relapse groups. On the SADQ, AUD patients differed from healthy controls on total score ($t = 10.89, p < .001$) and on all subscales ($p < .001$ for PHYSICAL, AFFECT, NEED, ALCOHOL, and POST). On the BIS, patients differed from controls on total score ($t = 2.62, p = .011$) and on the subscales ATTENTION ($t = 2.12, p = .038$), COGNITIVE INSTABILITY ($t = 2.30, p = .025$), NON-PLANNING ($t = 2.41, p = .019$), and SELF-CONTROL ($t = 2.94, p = .004$). The only self-report variable that differentiated subsequent relapsers from abstainers was the SADQ total score ($t = -2.32, p = .024$).
Table 1. Patients vs. Control Group Demographic and Inventory Comparisons

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alcoholic Patients n = 50</th>
<th>Healthy Controls n = 20</th>
<th>T/χ²</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>48.08 (8.75)</td>
<td>41.70 (11.72)</td>
<td>2.19</td>
<td>.037</td>
</tr>
<tr>
<td>Sex</td>
<td>(13 females)</td>
<td>(12 females)</td>
<td>7.19</td>
<td>.012</td>
</tr>
<tr>
<td>Educationᵇ (years)</td>
<td>16.52 (2.44)</td>
<td>17.10 (3.39)</td>
<td>-0.80</td>
<td>.425</td>
</tr>
<tr>
<td>Lifetime Heavy Drinkingᶜ (years)</td>
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<td>0.00 (0.00)</td>
<td>11.25</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Inventories</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia Severity Index</td>
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<td>2.70 (3.31)</td>
<td>1.62</td>
<td>.109</td>
</tr>
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<td>Barratt Impulsiveness Scale</td>
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<td>52.95 (8.45)</td>
<td>2.62</td>
<td>.011</td>
</tr>
<tr>
<td>Attention</td>
<td>15.79 (3.31)</td>
<td>14.05 (1.48)</td>
<td>2.12</td>
<td>.038</td>
</tr>
<tr>
<td>Motor</td>
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<td>18.80 (3.22)</td>
<td>1.70</td>
<td>.094</td>
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<td>Non-Planning</td>
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<td>20.10 (4.73)</td>
<td>2.14</td>
<td>.019</td>
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<td>Family History Questionnaire</td>
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<td>1.25 (1.48)</td>
<td>3.15</td>
<td>.002</td>
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<td>Severity of Alcohol Dependence Questionnaire</td>
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<td>&lt;.001</td>
</tr>
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<td>&lt;.001</td>
</tr>
<tr>
<td>Need</td>
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<tr>
<td>Alcohol</td>
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<td>&lt;.001</td>
</tr>
<tr>
<td>Post</td>
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<td>0.30 (0.80)</td>
<td>5.92</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Impaired Control Scale (Attempted Control)</td>
<td>9.98 (5.52)</td>
<td>0.85 (2.23)</td>
<td>9.85</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Obsessive Compulsive Drinking Scale</td>
<td>6.77 (6.31)</td>
<td>2.80 (2.35)</td>
<td>3.78</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

ᵃResults from χ² test  
bTotal number of years completed  
cDrinking history obtained from SCID-IV-TR

3.2 Task-Related Behavioral and Self-Report Measures

3.2.1 Stroop-Task Performance

Comparing patients and controls, a 2 (stimulus type; incongruent vs. congruent) x 2 (group; patients vs. controls) repeated measures ANOVA revealed a main effect for stimulus type on mean reaction time (RT; incongruent RT = 936.25 msec; congruent RT = 767.95 msec; p < .001),
**Table 2.** Relapse vs. Abstinent Outcome Group Demographic and Inventory Comparisons

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Relapsers ( n = 18 )</th>
<th>Abstainers ( n = 32 )</th>
<th>( T/\chi^2 )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>46.83 (8.16)</td>
<td>48.72 (9.12)</td>
<td>0.73</td>
<td>.470</td>
</tr>
<tr>
<td>Sex</td>
<td>(7 females)</td>
<td>(6 females)</td>
<td>0.79(^a)</td>
<td>.501(^a)</td>
</tr>
<tr>
<td>Education(^b)</td>
<td>16.26 (2.16)</td>
<td>16.66 (2.60)</td>
<td>0.53</td>
<td>.603</td>
</tr>
<tr>
<td>Years of Heavy Drinking(^c)</td>
<td>13.50 (7.51)</td>
<td>14.97 (9.81)</td>
<td>0.55</td>
<td>.587</td>
</tr>
<tr>
<td>Inventories</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia Severity Index</td>
<td>3.78 (4.17)</td>
<td>5.09 (5.12)</td>
<td>0.92</td>
<td>.362</td>
</tr>
<tr>
<td>Barratt Impulsiveness Scale</td>
<td>58.76 (10.65)</td>
<td>59.94 (9.45)</td>
<td>0.93</td>
<td>.696</td>
</tr>
<tr>
<td>Attention</td>
<td>16.24 (3.27)</td>
<td>15.55 (3.36)</td>
<td>-0.68</td>
<td>.497</td>
</tr>
<tr>
<td>Motor</td>
<td>20.59 (4.21)</td>
<td>20.32 (3.48)</td>
<td>-0.24</td>
<td>.815</td>
</tr>
<tr>
<td>Non-Planning</td>
<td>21.94 (5.67)</td>
<td>24.06 (4.70)</td>
<td>1.39</td>
<td>.171</td>
</tr>
<tr>
<td>Family History Questionnaire</td>
<td>2.72 (2.02)</td>
<td>3.00 (3.27)</td>
<td>0.33</td>
<td>.746</td>
</tr>
<tr>
<td>Severity of Alcohol Dependence Questionnaire</td>
<td>24.33 (12.81)</td>
<td>16.47 (10.70)</td>
<td>-2.32</td>
<td>.024</td>
</tr>
<tr>
<td>Physical</td>
<td>3.17 (3.17)</td>
<td>1.75 (1.81)</td>
<td>-1.74</td>
<td>.094</td>
</tr>
<tr>
<td>Affect</td>
<td>4.67 (3.76)</td>
<td>3.13 (3.26)</td>
<td>-1.52</td>
<td>.135</td>
</tr>
<tr>
<td>Need</td>
<td>5.00 (3.34)</td>
<td>3.31 (2.99)</td>
<td>-1.84</td>
<td>.072</td>
</tr>
<tr>
<td>Alcohol</td>
<td>5.22 (2.46)</td>
<td>4.00 (2.78)</td>
<td>-1.55</td>
<td>.127</td>
</tr>
<tr>
<td>Post</td>
<td>6.28 (3.88)</td>
<td>4.28 (3.10)</td>
<td>-2.00</td>
<td>.052</td>
</tr>
<tr>
<td>Impaired Control Scale (Attempted Control)</td>
<td>9.67 (6.88)</td>
<td>10.16 (4.71)</td>
<td>0.30</td>
<td>.767</td>
</tr>
<tr>
<td>Obsessive Compulsive Drinking Scale</td>
<td>7.35 (6.01)</td>
<td>6.45 (6.54)</td>
<td>-0.47</td>
<td>.641</td>
</tr>
</tbody>
</table>

\(^a\)Results from \(\chi^2\) test  
\(^b\)Total number of years completed  
\(^c\)Drinking history obtained from SCID-IV-TR  

Demonstrating the Stroop effect (i.e., slower RT for incongruent versus congruent stimuli in both groups; Table 3). No main effect was found for group (\(F = .584, p > .1\)) or group-by-stimulus interaction (\(F = 1.59, p > .10\)). Reaction times correlated with age across both groups (\(r = .426, p = .003\)). No between-group differences were found in errors to incongruent stimuli (\(t = .535, p > .10\)).
Table 3. Patient vs. Control Group Comparison of Task-Related Behavioral and Self-Report Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Patients</th>
<th>Controls</th>
<th>T</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroop Paradigm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction Time (msec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral</td>
<td>834.12 (125.35)</td>
<td>809.77 (134.74)</td>
<td>0.50</td>
<td>.623</td>
</tr>
<tr>
<td>Congruent</td>
<td>775.07 (136.42)</td>
<td>760.82 (109.59)</td>
<td>0.28</td>
<td>.783</td>
</tr>
<tr>
<td>Incongruent</td>
<td>964.79 (128.60)</td>
<td>907.71 (87.50)</td>
<td>1.19</td>
<td>.239</td>
</tr>
<tr>
<td>Interference(^a)</td>
<td>189.71 (90.73)</td>
<td>146.90 (66.35)</td>
<td>1.26</td>
<td>.213</td>
</tr>
<tr>
<td><strong>Errors (total)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Incongruent</td>
<td>2.84 (2.60)</td>
<td>2.00 (3.46)</td>
<td>0.53</td>
<td>.595</td>
</tr>
<tr>
<td><strong>Cue-Reactivity Paradigm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cue-Elicited Ratings (PRE)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craving</td>
<td>5.90 (10.48)</td>
<td>0.45 (1.51)</td>
<td>3.48</td>
<td>.001</td>
</tr>
<tr>
<td>Control</td>
<td>87.20 (14.76)</td>
<td>100.00 (0.00)</td>
<td>-6.07</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Cue-Elicited Ratings (POST)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craving</td>
<td>11.67 (16.78)</td>
<td>3.18 (9.02)</td>
<td>2.31</td>
<td>.028</td>
</tr>
<tr>
<td>Control</td>
<td>85.50 (19.81)</td>
<td>100.00 (0.00)</td>
<td>-4.97</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>ACQ (PRE)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>2.26 (0.99)</td>
<td>1.86 (0.86)</td>
<td>1.58</td>
<td>.120</td>
</tr>
<tr>
<td>Compulsivity</td>
<td>2.03 (0.98)</td>
<td>1.20 (0.37)</td>
<td>5.09</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Expectancy</td>
<td>2.24 (1.03)</td>
<td>2.05 (1.07)</td>
<td>0.68</td>
<td>.498</td>
</tr>
<tr>
<td>Purposefulness</td>
<td>2.15 (1.11)</td>
<td>2.35 (1.54)</td>
<td>-0.61</td>
<td>.547</td>
</tr>
<tr>
<td>Emotionality</td>
<td>2.61 (1.57)</td>
<td>1.83 (1.37)</td>
<td>1.94</td>
<td>.057</td>
</tr>
<tr>
<td><strong>ACQ (POST)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>2.33 (1.07)</td>
<td>1.92 (0.94)</td>
<td>1.48</td>
<td>.144</td>
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<tr>
<td>Compulsivity</td>
<td>2.04 (1.06)</td>
<td>1.33 (0.65)</td>
<td>3.38</td>
<td>.001</td>
</tr>
<tr>
<td>Expectancy</td>
<td>2.55 (1.22)</td>
<td>2.02 (1.18)</td>
<td>1.67</td>
<td>.099</td>
</tr>
<tr>
<td>Purposefulness</td>
<td>2.24 (1.15)</td>
<td>2.23 (1.31)</td>
<td>0.02</td>
<td>.987</td>
</tr>
<tr>
<td>Emotionality</td>
<td>2.48 (1.55)</td>
<td>2.10 (1.60)</td>
<td>0.92</td>
<td>.360</td>
</tr>
</tbody>
</table>

ACQ, Alcohol Craving Questionnaire
RT, reaction time
Data are given as mean ± standard deviation
\(^a\)Interference = Incongruent RT – Congruent RT

Comparing subsequent relapsers and abstainers, a 2 (stimulus type; incongruent vs. congruent) x 2 (group; relapsers vs. abstainers) repeated measures ANOVA revealed a main effect for stimulus type on mean RT (incongruent = 962.57 msec; congruent = 770.05 msec; p < .001), demonstrating the Stroop effect (Table 4). No main effect was found for group (F = .258, p > .10) or group-by-stimulus interaction (F = .293, p > .10).
## Table 4. Relapse vs. Abstinent Group Comparison of Task-Related Behavioral and Self-Report Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Relapsers</th>
<th>Abstainers</th>
<th>T</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroop Paradigm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reaction Time (msec)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral</td>
<td>814.02 (130.22)</td>
<td>844.17 (124.21)</td>
<td>0.70</td>
<td>.486</td>
</tr>
<tr>
<td>Congruent</td>
<td>754.99 (157.97)</td>
<td>785.12 (126.48)</td>
<td>0.65</td>
<td>.523</td>
</tr>
<tr>
<td>Incongruent</td>
<td>955.93 (147.56)</td>
<td>969.21 (120.94)</td>
<td>0.30</td>
<td>.766</td>
</tr>
<tr>
<td>Interference&lt;sup&gt;a&lt;/sup&gt;</td>
<td>200.94 (86.94)</td>
<td>184.10 (93.73)</td>
<td>-0.54</td>
<td>.591</td>
</tr>
<tr>
<td><strong>Errors (total)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incongruent</td>
<td>3.56 (3.10)</td>
<td>2.45 (2.25)</td>
<td>-1.39</td>
<td>.172</td>
</tr>
<tr>
<td><strong>Cue-Reactivity Paradigm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cue-Elicited Ratings (PRE)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craving</td>
<td>7.22 (9.43)</td>
<td>5.13 (11.12)</td>
<td>-0.67</td>
<td>.506</td>
</tr>
<tr>
<td>Control</td>
<td>84.44 (18.14)</td>
<td>88.81 (12.44)</td>
<td>1.00</td>
<td>.324</td>
</tr>
<tr>
<td><strong>Cue-Elicited Ratings (POST)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craving</td>
<td>17.78 (19.57)</td>
<td>7.75 (13.68)</td>
<td>-2.05</td>
<td>.047</td>
</tr>
<tr>
<td>Control</td>
<td>83.33 (17.41)</td>
<td>86.89 (21.40)</td>
<td>0.59</td>
<td>.540</td>
</tr>
<tr>
<td><strong>ACQ (PRE)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>2.56 (1.04)</td>
<td>2.09 (0.93)</td>
<td>-1.62</td>
<td>.113</td>
</tr>
<tr>
<td>Compulsivity</td>
<td>2.26 (1.06)</td>
<td>1.91 (0.93)</td>
<td>-1.20</td>
<td>.241</td>
</tr>
<tr>
<td>Expectancy</td>
<td>2.43 (1.17)</td>
<td>2.14 (0.95)</td>
<td>-0.96</td>
<td>.344</td>
</tr>
<tr>
<td>Purposefulness</td>
<td>2.61 (1.27)</td>
<td>1.91 (0.95)</td>
<td>-2.19</td>
<td>.034</td>
</tr>
<tr>
<td>Emotionality</td>
<td>2.96 (1.37)</td>
<td>2.43 (1.66)</td>
<td>-1.13</td>
<td>.263</td>
</tr>
<tr>
<td><strong>ACQ (POST)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>2.58 (1.04)</td>
<td>2.19 (1.00)</td>
<td>-1.22</td>
<td>.228</td>
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<tr>
<td>Compulsivity</td>
<td>2.39 (1.20)</td>
<td>1.85 (0.93)</td>
<td>-1.73</td>
<td>.090</td>
</tr>
<tr>
<td>Expectancy</td>
<td>2.67 (1.31)</td>
<td>2.49 (1.18)</td>
<td>-0.48</td>
<td>.632</td>
</tr>
<tr>
<td>Purposefulness</td>
<td>2.61 (1.23)</td>
<td>2.04 (1.08)</td>
<td>-1.67</td>
<td>.102</td>
</tr>
<tr>
<td>Emotionality</td>
<td>2.67 (1.56)</td>
<td>2.38 (1.56)</td>
<td>-0.60</td>
<td>.550</td>
</tr>
</tbody>
</table>

ACQ, Alcohol Craving Questionnaire  
RT, reaction time  
Data are given as mean ± standard deviation  
<sup>a</sup>Interference = Incongruent RT – Congruent RT

### 3.2.2 Cue Reactivity Self-Report Ratings

Comparing patients and controls, a 2 (condition; pre- vs. post-cue reactivity craving rating) x 2 (group; patients vs. controls) repeated measures ANOVA revealed a trend towards a main effect for condition [$F = 3.774, p = .057$]; post-cue exposure craving ratings greater than pre-cue exposure...
craving ratings]), and for group [(F = 3.477, p = .068); craving ratings higher in patients compared to controls]). No significant group-by-condition interaction was found (F = .406, p > .10; Figure 5a).

Comparing relapsers and abstainers, a 2 (condition; pre- vs. post-cue reactivity craving rating) x 2 (group; relapsers vs. abstainers) repeated measures ANOVA revealed a main effect for condition (F = 11.11, p = .002), demonstrating increased craving across groups in response to alcohol cue exposure (Figure 5b). Additionally, a group-by-condition interaction (F = 5.014, p = .03) showed that relapsers reported significantly increased craving in response to alcohol stimuli, whereas abstainers did not. Additionally, post-cue craving ratings were greater in relapsers than in abstainers (Table 4). In contrast to the visual-analogue scale, the subjective rating on the Alcohol Craving Questionnaire (ACQ) total score did not differ between patients and controls, before and after the cue-reactivity paradigm. However, AUD patients scored higher than healthy controls on the subscales pre-COMPULSIVITY and pre-EMOTIONALITY as well as post-COMPULSIVITY. Subscale pre-PURPOSEFULNESS was the only subscale of ACQ total or subscale scores that was found to discriminate between subsequent relapsers vs. abstainers. All other ACQ subscales were not significant.

Figure 5. Pre-Post Cue Reactivity Visual-Analogue Craving Ratings

A, pre-post cue reactivity craving ratings for AUD and control groups (mean ± S.E.); B, pre-post cue reactivity craving ratings for abstainers and relapsers (*p < .05).
Table 5. Group Differences in Task-Related ROI Activations in PFC

<table>
<thead>
<tr>
<th>Task Conditions</th>
<th>Location</th>
<th>BA</th>
<th>Hemisphere</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol-Dependent Patients vs. Healthy Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Cue Reactivity</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol Cues</td>
<td>Optode 2</td>
<td>45</td>
<td>Left</td>
<td>.024</td>
</tr>
<tr>
<td>Relapsers vs. Abstainers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Stroop</em></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Incongruent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Optode 2</td>
<td>45</td>
<td>Left</td>
<td>.019</td>
</tr>
<tr>
<td></td>
<td>Optode 4</td>
<td>46,47</td>
<td>Left</td>
<td>.037</td>
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<tr>
<td></td>
<td>Optode 11</td>
<td>10,46</td>
<td>Right</td>
<td>.008</td>
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<tr>
<td><em>Cue Reactivity</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natural Reward Cues</td>
<td>Optode 8</td>
<td>10</td>
<td>Left</td>
<td>.045</td>
</tr>
<tr>
<td>Alcohol Cues</td>
<td>Optode 11</td>
<td>10,46</td>
<td>Right</td>
<td>.029</td>
</tr>
</tbody>
</table>

ROI, Region of Interest
BA, Brodmann Area

3.3 Neuroimaging Results

Differences in cue-related PFC activations between AUD patients vs. healthy control participants were found in response to Alcohol stimuli (Table 5). No significant group differences in Stroop-related PFC activations (incongruent vs. congruent stimuli) were found between patients and controls. Between abstainers vs. relapsers, Stroop-related PFC activations were found in OPTODES 2, 4, and 11. During the cue-reactivity paradigm, greater activity in OPTODE 11 was found in response to Alcohol cues in abstainers compared with relapsers. In response to Positive stimuli, relapsers exhibited greater PFC activity in OPTODE 8.

3.4 Correlations among Self-Report and Behavioral Variables and PFC Activity

Several self-report inventories demonstrated moderate to strong correlations in AUD patients (Table 6). Self-reported attentional impulsivity (on BIS ATTENTION) correlated with alcohol dependence and affective withdrawal severity (from SADQ AFFECT), sleep disturbances (on the ISI), and the urge and intention to drink (reported in ACQ PURPOSEFULNESS). Sleep disturbances as
measured by the ISI were moderately associated with scores on the OCDS. Cue-induced craving along a visual-analogue scale was strongly associated with total ACQ and subscales, including PURPOSEFULNESS. Years of heavy drinking was positively correlated with age ($r = .42, p = .002$), but not with scores on the SADQ, ISI, OCDS, and post-cue subjective craving ratings (all $p > .10$).

The relationship between self-report and neuroimaging variables were also examined. No significant correlations were found between neuroimaging variables and scores on the ISI, OCDS, ACQ, and post-cue subjective craving ratings. A positive correlation was found between scores on the SADQ total, as well as subscales PHYSICAL, AFFECT, and POST, and vmPFC activity in response to natural reward stimuli (optode 8; $r = 0.36, p = .019$). BIS subscale ATTENTION was positively correlated with Stroop-related activity in the right IFC (optode 15; $r = 0.43, p = .010$). Scores on the ISI were positively correlated with Stroop-related activity in the left vIPFC (optode 2; $r = 0.40, p = .036$) and dIPFC activity during alcohol cue exposure (optode 11; $r = 0.37, p = .022$).
### Table 6: Within-Group Self-Report Correlations (Alcohol-Dependent Patients)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (SD)</th>
<th>SADQ AFFECT</th>
<th>ISI</th>
<th>OCDS</th>
<th>Craving</th>
<th>ACQ PURP</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIS ATTENTION</td>
<td>15.79 (3.31)</td>
<td>.40&lt;sup&gt;c&lt;/sup&gt;</td>
<td>.41&lt;sup&gt;c&lt;/sup&gt;</td>
<td>.19</td>
<td>.28</td>
<td>.39&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SADQ AFFECT</td>
<td>3.68 (3.49)</td>
<td>.17</td>
<td>.24</td>
<td>−.11</td>
<td>.06</td>
<td></td>
</tr>
<tr>
<td>ISI</td>
<td>4.62 (4.85)</td>
<td>.39&lt;sup&gt;b&lt;/sup&gt;</td>
<td>.14</td>
<td>−.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCDS</td>
<td>6.77 (6.31)</td>
<td>.07</td>
<td>.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craving</td>
<td>11.67 (16.78)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACQ PURP</td>
<td>2.24 (1.15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BIS, Barratt Impulsiveness Scale; SADQ, Severity of Alcohol Dependence Questionnaire; ISI, Insomnia Severity Index; OCDS, Obsessive Compulsive Drinking Scale; ACQ PURP, Alcohol Craving Questionnaire, subscale PURPOSEFULNESS; Craving, cue-induced craving along a visual-analogue scale.

Data are given as mean ± standard deviation.

<sup>a</sup>p ≤ .05  
<sup>b</sup>p ≤ .01  
<sup>c</sup>p ≤ .005

### 3.5 Treatment Outcome Prediction Models

#### 3.5.1 Hypothesis-Driven Neuroimaging Model

Univariate analyses revealed the following neuroimaging variables as predictors of relapse (Table 5): Stroop Interference (Optode 2, 4, 11), Natural Reward Cues (Optode 8), and Alcohol Cues (Optode 11). A multiple logistic regression analysis was performed post-hoc to model the collective effects of these variables on the likelihood that AUD patients would relapse following residential treatment (Table 7). The logistic regression model was statistically significant, χ²(5) = 16.73, p = .005. The model explained 39.0% (Nagelkerke R²) of the variance of model and correctly classified 80.0% of cases. Sensitivity was 72.0%, and specificity was 75.0%. Of the variables included in the model, only PFC activity during Natural Reward and Alcohol Cues were significant. Increases in PFC activity to Natural Reward stimuli and decreases in PFC activity to Alcohol stimuli were associated with an increased likelihood of subsequent relapse.
3.5.2 LASSO Neuroimaging Prediction Model

To avoid overoptimistic findings in the prediction model, a Least Absolute Shrinkage and Selection Operator (LASSO) analysis was performed on the neuroimaging variables. The final variables in the model included: PFC activity during Stroop (Optodes 2, 4, and 11), Natural Reward Cues (Optodes 5, 8, and 12), and Alcohol Cues (Optode 11). AUC of this model was 80.6%, with 72.0% sensitivity and 72.0% specificity.

3.5.3 Self-Report Prediction Model

Univariate analyses revealed the following self-report variables as predictors of relapse: SADQ total score and cue-elicited craving (following the cue-reactivity paradigm). A multiple logistic regression analysis was performed to determine the collective effects of these variables on the likelihood that alcohol-dependent patients would relapse following residential treatment (Table 8). The logistic regression model was statistically significant, $\chi^2(2) = 10.95$, $p = .004$. The model explained 28.7% ($\text{Nagelkerke } R^2$) of the variance of relapse and correctly classified 63.0% of cases. Sensitivity was 44.4%, specificity was 75.0%. Both predictor variables were significant in the model. Increases in both variables were associated with an increased likelihood of subsequent relapse.
Table 8. Post-Hoc Logistic Regression Model Predicting Likelihood of Relapse based on Self-Report Data

<table>
<thead>
<tr>
<th>Measure</th>
<th>Condition</th>
<th>Location</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>Odds Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SADQ</td>
<td></td>
<td></td>
<td>0.08</td>
<td>.031</td>
<td>5.90</td>
<td>1.08</td>
<td>.015</td>
</tr>
<tr>
<td>Cue-Elicited Craving</td>
<td></td>
<td></td>
<td>0.05</td>
<td>.023</td>
<td>4.38</td>
<td>1.05</td>
<td>.037</td>
</tr>
</tbody>
</table>

SADQ, Severity of Alcohol Dependence Questionnaire
S.E., standard error

3.5.4 Combined Prediction Model

A multiple logistic regression analysis was performed to determine the combined effects of self-report variables and neuroimaging variables selected by the LASSO method on the likelihood that alcohol-dependent patients would relapse following residential treatment (Table 9). The logistic regression model was statistically significant, $\chi^2(9) = 31.83, p < .001$. The model explained 67.7% (Nagelkerke $R^2$) of the variance of relapse and correctly classified 93.8% of cases. Sensitivity was 92.3%, specificity was 90.9%. Decreases in PFC activity during the Stroop effect and Alcohol cues, as well as increase in PFC response to Natural Reward cues, were associated with an increased likelihood of subsequent relapse. Increases in SADQ scores and craving ratings were also associated with increased likelihood of relapse.

Table 9. Logistic Regression Model Predicting Relapse Likelihood based on Neuroimaging & Self-Report Data

<table>
<thead>
<tr>
<th>Measure</th>
<th>Condition</th>
<th>Location</th>
<th>Condition</th>
<th>Location</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>Odds Ratio</th>
<th>p</th>
</tr>
</thead>
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<tr>
<td>Neuroimaging Variables</td>
<td></td>
<td></td>
<td>Incongruent</td>
<td>Optode 2</td>
<td>-3.41</td>
<td>3.32</td>
<td>1.06</td>
<td>0.03</td>
<td>.304</td>
</tr>
<tr>
<td>SADQ</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craving</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol Cues</td>
<td></td>
<td></td>
<td>Positive Cues</td>
<td>Optode 5</td>
<td>0.92</td>
<td>2.63</td>
<td>0.12</td>
<td>2.51</td>
<td>.727</td>
</tr>
<tr>
<td>SADQ</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Craving</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol Cues</td>
<td></td>
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<td></td>
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</tbody>
</table>

Abbreviations: S.E., standard error; Incongruent (incongruent vs congruent condition); Positive Natural Reward Cues (positive vs neutral stimuli), Alcohol Cues (alcoholic vs non-alcoholic beverage stimuli); SADQ, Severity of Alcohol Dependence Questionnaire.
Figure 7. ROC Curves for Neuroimaging, Self-Report, and Combined Models

ROC contrast estimates were used for model comparison to determine whether AUC discriminant power from the combined model was significantly different than neuroimaging or self-report models alone (Table 10). The test revealed that the Combined Model AUC was superior to the Neuroimaging Model AUC as well as the Self-Report Model AUC. No significant differences in AUCs were found between the Neuroimaging Model and the Self-Report Model.

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Estimate</th>
<th>S.E.</th>
<th>$\chi^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined Model vs Hypothesis-Driven Neuroimaging Model</td>
<td>0.12</td>
<td>.056</td>
<td>4.55</td>
<td>.033</td>
</tr>
<tr>
<td>Combined Model vs LASSO-based Neuroimaging Model</td>
<td>0.12</td>
<td>.053</td>
<td>5.32</td>
<td>.021</td>
</tr>
<tr>
<td>Combined Model vs Self-Report Model</td>
<td>0.15</td>
<td>.058</td>
<td>6.31</td>
<td>.012</td>
</tr>
<tr>
<td>Neuroimaging Model vs Self-Report Model</td>
<td>0.02</td>
<td>.097</td>
<td>0.05</td>
<td>.822</td>
</tr>
</tbody>
</table>
CHAPTER FOUR
DISCUSSION

4.1 Discussion of Findings

To the author’s knowledge, this study is the first to investigate prefrontal cortical activity as a marker of prospective relapse in alcohol-dependent patients in residential treatment, using both (1) an inhibitory control paradigm, the color-word Stroop task, and (2) a visual cue reactivity paradigm. To measure task-related prefrontal cortical function, we employed functional near-infrared spectroscopy (fNIRS). Importantly, this technology enabled us to collect functional neuroimaging data within a clinical setting (e.g., Caron Treatment Centers). After patients were discharged from treatment, they were followed for relapse on a weekly basis for 12 weeks using online self-report questionnaires.

Neuroimaging predictors of relapse including reduced dIPFC and vIPFC activity during the Stroop task, increased vmPFC activity in response to Natural Reward cues, and reduced dIPFC activity in response to Alcohol cues. In addition to neuroimaging variables, two subjective measures predicted relapse: total scores on the Severity of Alcohol Dependence Questionnaire (SADQ) and subjective craving ratings following the cue reactivity paradigm. A relapse prediction model was developed combining neuroimaging and self-report variables, using the Least Absolute Shrinkage and Selector Operator (LASSO) method for neuroimaging variable selection to reduce overoptimism in our model’s discriminative accuracy (Moons, et al., 2004). We then entered these variables into a multiple logistic regression analysis to determine our models accuracy in categorizing subsequent relapsers versus abstainers (93.8% accuracy; 92.3% sensitivity; 90.9% specificity). Results demonstrated that the predictive accuracy of the combined model was superior to neuroimaging and self-report variables alone. These findings support the hypothesis that PFC function, in
combination with self-report severity and cue-elicited craving scores, may serve as an objective marker of relapse liability in alcohol-dependent patients approaching discharge from residential treatment.

4.1.1 Relevance of Neuroimaging Results to Previous Studies of Relapse

In support of our hypothesis, subsequent relapse was associated with Stroop-related hypoactivity in the dIPFC and vIPFC. Blunted PFC activity during inhibition-related tasks has been associated impulsive behavior, in general (Asahi et al., 2004), and with substance use disorders, in particular (Nestor et al., 2011). Numerous studies have investigated the neural substrates of Stroop-related inhibitory processes in substance-dependent populations. Reduced activity in PFC regions during the Stroop task have been found in marijuana-abusing males (Eldreth et al., 2004), methamphetamine-dependent participants (Nestor et al., 2011; Salo et al., 2009), and cigarette smokers (Azizian et al., 2010), relative to control subjects. One study found decreased Stroop-related PFC activity as a function of increased treatment retention in cocaine-dependent patients, which the authors interpreted as a reflection of more efficient inhibitory processing (Brewer et al., 2010). This discrepancy may be attributed to differences in study design, such as the time of neuroimaging data acquisition relative to treatment admission. While Brewer and colleagues performed fMRI scans within the first week of treatment, patients in our study were scanned 14-28 days after admission to treatment in order to avoid the potential confounding effects of acute withdrawal.

Also, to the author’s knowledge, this study was the first to examine Stroop-related PFC as a predictor of post-treatment relapse in alcohol-dependent patients. Our data suggest that impairments in inhibitory control, mediated by disruptions of PFC function, may be a contributing factor to, and thus a predictor of, relapse in alcohol-dependent patients. Importantly, relapse in our
study sample was predicted by PFC activity during an inhibitory control paradigm (i.e., the Stroop task) and not from self-report measures of impulsivity (i.e., the Barratt Impulsiveness Scale; BIS).

Contrary to our hypothesis, prospective relapse was associated with reduced dIPFC activity in response to Alcohol Cues. Based on the findings of previous studies examining the neural correlates of cue-elicited craving (Schacht, Anton, Myrick, 2012), we expected that increased PFC activity in response to visual alcohol-related stimuli would indicate heightened salience toward conditioned alcohol cues, thus signifying an elevated propensity to relapse when later afforded the opportunity to drink (i.e., following discharge from treatment). Rather than the attribution of salience to alcohol stimuli, dIPFC hypoactivity might reflect deficits in self-regulation, leading to disinhibited behavior and increased risk for subsequent relapse. In support of this hypothesis, recent fMRI research by Sinha and colleagues have found similar results examining cue-related PFC activations to alcohol imagery scripts (Seo et al., 2013). In this study, functional brain measures were obtained while alcohol-dependent patients listened to personalized scripts verbally depicting alcohol-related situations that lead to subsequent alcohol consumption. When contrasted with a neutral script, PFC hypoactivity during the alcohol script were predictive of high craving and shorter time to relapse. The authors contributed this blunted alcohol-related activity to regulatory deficits in the PFC. Despite the generally accepted hypothesis that heightened PFC activity to alcohol cues indicate elevated relapse risk (Courtney et al., 2015), the findings from Sinha and colleagues and the present study suggests that further investigation on the role of the PFC during alcohol cue exposure in treatment-seeking alcohol-dependent patients is warranted.

In addition to Alcohol cues, the direction of PFC activity in response to Natural Reward cues in subsequent relapers was counter to our hypothesis. We hypothesized that PFC activity in response to affective positive stimuli would be elevated in abstainers relative to relapers, signifying increased sensitivity to natural rewards and thus serving as a protective factor against relapse
Instead, subsequent relapers exhibited greater vmPFC activity than abstainers in response to Natural Reward cues. Importantly, however, activity in response to affectively positive visual stimuli was also examined as a neural predictor of treatment outcome in a previous investigation involving alcohol-dependent patients (Heinz et al., 2007). In their study, Heinz and colleagues examined PFC responses to both alcohol and natural reward cues using a visual cue-reactivity paradigm similar to the one used in the present study. Although the authors found no significant difference between subsequent abstainers and relapers to alcohol stimuli, outcome groups were discriminated by activity in response to affective positive stimuli in the vmPFC (BA 10), the same PFC subregion identified above. Additionally, activity in this same region was positively correlated with scores on the SADQ, including the subscales PHYSICAL, AFFECT, and POST. Therefore, greater self-reported severity was associated with increased vmPFC activity in response to Natural Reward cues, a finding consistent with respect to relapse risk. Although the process underlying this vmPFC activity to affectively positive stimuli remains unknown, these results indicate that this PFC subregion may play an important role in affect-related processes that are associated with relapse liability.

4.1.2 Relationships among Behavioral, Self-Report, and Neuroimaging Variables

As expected, we found several correlations in the patient group among theoretically related self-report inventories. Most notably, scores on the Barratt Impulsiveness Scale (BIS), and, in particular, the subscale ATTENTION, were moderately correlated with scores on the Severity of Alcohol Dependence Questionnaire (SADQ) subscale AFFECT, the Alcohol Craving Questionnaire (ACQ) subscale PURPOSEFULNESS, and the Insomnia Severity Index (IS). Of interest, total BIS scores were not associated with neuroimaging variables, including PFC activity during the Stroop effect, as well as alcohol and natural reward cue exposure. Scores on the BIS subscale ATTENTION, however,
were moderately correlated with Stroop-related activity in the right inferior frontal gyrus (rIFG). This finding is consistent with studies that have argued that the Stroop task is a measure of both inhibition and sustained attention (Trammell, 1977; Vendrell, et al., 1995), and that inhibitory control processes are mediated by the rIFG (Aron, Robbins, and Poldrack, 2014).

With the exception of the above-mentioned correlations between the SADQ AFFECT and BIS ATTENTION, scores on the SADQ were not associated with other self-report variables, including ISI, OCDS, and cue-elicited craving. Of note, however, SADQ total and subscales PHYSICAL, AFFECT, and POST scores correlated positively with fNIRS measures during natural reward stimuli in the vmPFC, the same region which predicted relapse. Because increased SADQ scores were also related to increased relapse likelihood, this positive correlation between SADQ scores and PFC activity in response to natural reward cues is consistent with our unexpected finding on the relationship between increased PFC activity in response to natural reward cues and increased relapse likelihood. SADQ scores were not, however, related to PFC activity in response to alcohol cues in areas relevant to treatment outcome. No relationship was found between SADQ and Stroop-related PFC activity.

Visual-analogue post-cue reactivity craving ratings correlated strongly with post-cue ACQ total and subscales scores, supporting the validity of both scales as measures of subjective craving. However, because of the inconsistent findings in previous studies involving the prediction of treatment outcome based on cue-elicited subjective craving (Carter and Tiffany, 1999; Tiffany and Conklin, 2000), we hypothesized that these self-report craving ratings would not be related to prospective relapse in our sample. We found, however, that cue-elicited craving ratings along the visual-analogue scale, but not from the ACQ, differentiated subsequent relapsers from abstainers. Visual-analogue craving ratings did not correlate significantly with any other inventories, including SADQ scores, signifying that these two self-report variables contributed unique variance in the prediction of relapse. Furthermore, these craving ratings did not correlate significantly with
neuroimaging variables, including PFC activity during alcohol cue exposure. Because subsequent relapse was predicted by reduced activity in response to alcohol cues, which is unlikely to reflect a process of salience attribution, the lack of a significant relationship between alcohol-related PFC activity and craving scores is not surprising. Additionally, this relationship has been reported in some studies (Myrick et al., 2004; Seo et al., 2013) but not in others (Beck et al., 2012; Grusser et al., 2004), likely due to differences in experimental designs and patient sample characteristics.

Behavioral performance measures during the Stroop task, including differences in reaction time to incongruent versus congruent stimuli (i.e., the Stroop effect), did not differentiate patients and controls or, as hypothesized, abstainers and relapers. Stroop-related behavioral measures were also not related to treatment outcome measures in cocaine-dependent patients (Brewer et al., 2008). The Stroop effect was, however, moderately correlated with age (i.e., slower reaction time with increasing age), a finding consistent with previous studies (Cohn, Dustman, and Bradford, 1984; West and Alain, 2000). Because age correlated with years of heavy drinking in the patient sample, it is likely that the effects of chronic alcohol consumption contributed to the observed cognitive and motor slowing, a well-known neuropsychological impairment in long-term alcoholics (Glenn and Parsons, 1992; Parsons, Butters, and Nathan, 1987). Importantly, outcome groups in the present study were not differentiated by task behavioral performance, although they were differentiated by the underling Stroop-related PFC activity. These findings highlight the clinical utility of neuroimaging measures in the prediction of treatment outcome.

4.2 Clinical Implications

Because prospective relapse was predicted by PFC hypoactivity during the Stroop task and during alcohol cue exposure, results at first appear to implicate the theoretical model of psychiatric
disorders known as hypofrontality (Dackis and O’Brien 2005; Kalivas, 2008). Hypofrontality, a functional state associated with reduced cerebral blood in frontal brain regions and concomitant executive dysfunction, has also been implicated in schizophrenia (Goldman-Rakic, 1994; Hill et al., 2004; Kaneko et al., 2016), major depression (Galynker et al., 1998; Koenigs and Grafman, 2009; Rogers et al., 2004), and ADHD (Rubia et al., 1999; Zang et al., 2005). Given the overarching role of the PFC in the production of goal-directed behavior (Fuster, 2008), it follows that those patients with reduced resting and active PFC metabolic states would be at increased risk for relapse.

The major challenge to this interpretation, however, was our findings in PFC responses to natural rewards, which were increased in subsequent relapsers, relative to abstainers. Rather than an effect of functional hypofrontality, it is likely that the hypoactivity observed in the present study reflects a disruption only to specific PFC-mediated processes, such as cognitive and inhibitory processes, and not PFC-mediated processes in general, also including affective and motivational processes. These findings further support the theoretical framework for the iRISA model of PFC function in addiction. Disruptions in these processes could thus be identified and targeted by addiction treatment professionals to provide more effective interventions, including pharmacological and cognitive-behavioral therapies. Furthermore, the development of objective indices of clinically relevant PFC disruptions and relapse liability would provide treatment providers with better tools to inform clinical decision making and reduce post-treatment relapse rates.

4.3 Study Limitations

Functional NIRS confers several advantages over other neuroimaging methods (e.g., fMRI) in the monitoring of cerebral functioning, including clinical accessibility and low operating costs. However, the technology employed in this study was limited to obtaining functional brain imaging
data from the prefrontal cortex alone. Other cortical and subcortical regions were not measured. Although the prefrontal cortex (PFC) is known to play a predominant role in both the color-word Stroop task and the cue reactivity paradigm, a number of regions in addition to the PFC have also been implicated in these paradigms (Herd, Banich, and O’Rielly, 2006). During the Stroop task, activity involved in the processing of incongruent stimuli has been reported not only in the PFC, but also in the anterior cingulate cortex (ACC; Kerns et al., 2004; Gruber et al., 2002; Milham, Banich, and Barad, 2003) and the basal ganglia (Brewer et al., 2008; Potenza et al., 2003). Of these regions, the anterior cingulate may have been informative, due to its important role in conflict monitoring and adjustment (Kerns et al., 2004). Because our fNIRS technology was not able to detect activity in these regions, any Stroop-related activity in these areas was not able to be collected in the present study. Furthermore, numerous studies investigating cue reactivity have implicated subcortical reward networks, including the ventral striatum and the amygdala, during the elicitation of craving (Engelmann et al., 2012; Schacht, Anton, Myrick, 2012; Zijlstra et al., 2009). Because our fNIRS technology was also unable to detect activations in these regions, several key brain areas subserving the cue-elicited response of interest (i.e. attention and/or craving) were not measured in this study. Furthermore, because no structural data was obtained, we were unable to determine whether the reduced activity observed in our relapse group was due to disruption in the functional state of the PFC, possibly due to reduced D2 receptor availability (Volkow et al., 2010), or was a reflection of prefrontal cortical atrophy, which has been reported in individuals with a history of chronic ethanol consumption (Pfefferbaum et al., 1997).

A second consideration to this study was the inclusion of antidepressant medications in the patient sample. Because these medications are known to affect cerebral function, which can be measured using functional neuroimaging techniques (Anand et al., 2005; Sheline et al., 2001), they were potential confounding variables in our analyses. One approach to this complication would be
to exclude patients on any psychotropic medication from the study, an exclusion criterion which has been reported in other investigations (Adinoff et al., 2015). There are, however, several reasons that we included medicated patients our clinical research. As is the case in real-world settings, the administration of pharmacotherapy to patients in our study was ordered by the attending physician, who prescribed medication according to clinical need rather than for the facilitation of research. Although we were able to exclude medicated patients at recruitment, some of these patients were prescribed medications after enrollment. Due to the pragmatic time constraints involved in completing this study, we resolved to include these participants to avoid high withdrawal rates. Having included some patients on antidepressants, we were still able to control for medications statistically. By monitoring medication administration and including this as a covariate in our analyses, we were also able to determine the effects of medication on our neuroimaging variables. The cost of this statistical approach, however, was that our sample size was not large enough to include this variable in the predictive model. Because 40% of our patients were on antidepressant medication, we would have needed to increase the study sample to account for this factor in our model. Importantly, no group differences were observed between abstainers and relapsers in medication status.

Furthermore, we included medicated patients in this study because of the clinical value these findings offer to real-world populations. In the present-day treatment environment, such as Caron Treatment Centers, medication-assisted therapy is commonly administered in clinical practice. Research studies that yield findings in populations where medication-assisted therapy is excluded are not able to determine whether their results generalize to real-world treatment environments where medications are administered. Because one of the goals of our research was to develop a clinical and translational tool, we sought to research a sample which resembled a population which would benefit from this clinical predictor of treatment outcome.
Another limitation of the present study was our measure of treatment outcome. The length of follow up was chosen based on observational findings that most patients relapse by approximately three months from treatment (Hunt, 1971; Meyer, 2000). Recently, the authors of the FDA guidelines for outcome measures in pharmacotherapy trials have recommended a 6-month follow up (FDA Center for Drug Evaluation and Research, 2015). These recommendations, however, were pragmatically untenable in this study given the workload involved in following patients for this duration and the resources available for this investigation. Nonetheless, three months of follow-up data collection is regarded as clinically informative (Meyer, 2000).

In addition to follow-up duration, outcome was obtained using self-report methods. Although self-report measures of relapse have high positive predictive value (i.e., if a patient reports that he/she has relapsed, there is a high likelihood that he/she indeed has relapsed), no collateral information was gathered to confirm or deny the report of the participant. Additionally, no traditional biomarkers of alcohol consumption were obtained. These include, among others, carbohydrate-deficient transferrin (CDT), a biomarker with high sensitivity and specificity in the detection of heavy alcohol intake (Stibler, 1991), and ethyl glucuronide (EtG), a biomarker reportedly useful in long-term monitoring sobriety (Wurst et al., 2000). The reliability these biomarkers in the detection of heavy alcohol use, however, has been questioned (Borucki et al., 2005; Wojcik and Hawthorne, 2007). And although they provide a unique source of information on drinking status, alcohol-related biomarkers to date have generally been found to be less sensitive than standardized self-report measures (Allen and Litten, 2003). A developing line of novel protein markers, however, shows promise at detecting varying levels of ethanol consumption up to 4 weeks prior to sample collection (Vrana et al., 2014), which would be a useful measure in future outcome studies.
Another limitation is the potential time-of-day effects of running the neuroimaging protocol. Because subjects were scheduled to participate in neuroimaging at times accommodating their clinical schedule, we were unable to arrange the neuroimaging sessions at the same time each day. Some sessions were scheduled in the morning, while others were scheduled in the afternoon. Because certain times of day may be associated with craving more than others (i.e., craving may be less likely to be induced in the morning), this time-of-day variance was a factor in the present study.

In the patient sample, six patients were lost to follow up (86% follow-up rate). Similar studies have reported follow-up rates around 90% (Seo et al., 2013). Additionally, of the 50 patients followed, only 18 (36%) relapsed, compared to the expected 50%. This low relapse rate potentially signifies either (1) that the patient group underreported relapse throughout the follow-up period, or (2) the treatment provided by Caron is more effective than other addiction treatment services in the treatment of alcohol use disorders.

A final limitation to this study was our interpretation of impaired PFC function as a cause or effect of chronic alcohol abuse. Because this study included neuroimaging measures after patients had already progressed into severe alcohol use disorders, we are not able to determine how the PFC changed over the course of alcoholism. Patients may have exhibited PFC dysfunction prior to their alcoholism, which may have promoted the advancement of their disease. Alternatively, the impairment of PFC function may have emerged as a consequence of chronic ethanol exposure. Longitudinal investigations, examining PFC activity over the lifespan, beginning in adolescence, may provide more clarity on this subject. Currently, the National Institute on Drug Abuse (NIDA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) at the National Institutes of Health (NIH) are examining these factors by supporting collaborative research on the neurodevelopmental consequences of substance abuse, known as the Adolescent Brain Cognitive Development (ABCD) study (http://addictionresearch.nih.gov/abcd-study).
4.4 Future Directions

Follow-up studies are needed to replicate the findings of the present study. An investigation with a second and larger sample could provide further validation of our result. In addition to replication with a larger sample, a follow-up study employing fMRI in addition to fNIRS would also provide validation supporting both neuroimaging methods. Using fMRI would also allow us to measure cerebral activity in the subcortical structures which fNIRS was unable to detect. The ability to measure these regions is advantageous to the cue-reactivity paradigm, where reward-network regions, including the ventral striatum and amygdala (Thayer and Hutchison, 2013), have been strongly implicated in the processing of visual alcohol stimuli and craving for alcohol. To a lesser degree, functional analyses during the Stroop task would also benefit from whole-brain imaging as subcortical regions, such as the basal ganglia, have been reported during Stroop interference processing (Brewer et al., 2008).

Further studies are also needed to help clarify the interpretation of PFC function as a predictor of treatment outcome. Our finding showed that patients who relapse showed reduced PFC activity during the Stroop task, relative to those who abstained. We interpreted this reduction in PFC activity as a sign of impaired PFC function, leading to disinhibited behavior and contributing to relapse risk. There are, however, studies which suggest that impaired PFC function is reflected by increased PFC activity subserving an equivalent cognitive workload (DeVito et al., 2012). Investigators have argued that this increase in PFC response corresponds to a decrease in cerebral efficiency (i.e., more metabolic activity is needed to perform the same task). A follow-up study using a paradigm with varying cognitive workloads (e.g., the n-back test; Ayaz et al., 2012) would help to clarify the relationship between PFC activity and cognitive demand and confirm whether reduced PFC activity represents impaired inhibitory function.
In addition to Stroop-related activations, our interpretation of the functional correlates of the cue-reactivity paradigm remains a subject of further inquiry. Based on findings from previous studies (Courtney et al., 2015), we hypothesized that patients who subsequently relapsed would have exhibited increased prefrontal activity in response to alcohol and alcohol-related stimuli, relative to those who abstained. Contrary to our hypothesis, we found that, relative to those who abstained, relapsers exhibited blunted activation in the dIPFC during alcohol cue response. This finding challenges our inference that cue-related PFC activity represents an attentional or craving-related process. Instead, our findings promote the hypothesis that our observed PFC activity represents a regulatory or inhibitory process. Based on this interpretation, reduction in dIPFC activity would represent impairment in executive functioning, leading to an increased likelihood of disinhibited behavior (i.e., the resumption of drinking).

This challenge in interpretation reveals the problem of reverse inference in neuroimaging (i.e., inferring mental states from brain activity; Poldrack, 2006). Because behavioral and neuroimaging data are inherently correlational, and because any single cortical region likely mediates a number of different cognitive processes (i.e., pluripotentiality), it is difficult to determine the precise cognitive process which corresponds to task-relevant brain activity (Poldrack and Wagner, 2004). This problem also highlights the value of applying other neuroscience techniques, such as transcranial magnetic stimuli (TMS), which is capable of temporarily inactivating target brain regions (George, Lisanby, and Sackeim, 1999; Sliwinska, Vitello, and Devlin, 2014). Indeed, promising investigations on the effects of TMS on cue-induced craving have already begun (Rabin et al., 2015; Shen et al., 2016).

Also, future investigations could examine PFC activity as a function of abstinence duration using a longitudinal study design. Given the evidence for structural regeneration of the PFC in abstinent alcoholics (Moselhy, Georgiou, and Kahn, 2001), it follows that PFC function may also re-
regulate over the course of extended residential treatment. Preliminary findings of PFC reactivity to drug-related visual stimuli in prescription opioid-dependent patients support this hypothesis (Bunce et al., 2015). Furthermore, methods to aid in the normalization of prefrontal function, such as certain pharmacotherapies or neurofeedback, may confer direct clinical benefit to treatment-seeking individuals, supplementing treatment-as-usual approaches to achieving sustainable recovery.

Additionally, quality improvement of the visual stimuli presented in the cue-reactivity paradigm would confer great benefit to subsequent studies. With the advances in photography and the introduction of virtual reality paradigms, the salience of cue-reactivity stimuli may be strongly enhanced in future research. Techniques in digital photography are now able to capture and edit photographs similar to those in current stimulus set, but with greater spatial resolution, higher dynamic range, and broader color gamut. The present study included stimuli drawn from the National Affective Picture System (NAPS; Breiner et al., 1995), the International Affective Picture System (IAPS; Lang, Oehman, and Taitl, 1988), and a stimulus set validated by Pulido and colleagues (Pulido et al., 2010). The resolutions of these stimuli were approximately 800x600 pixels, whereas updated photographs could potentially be generated at 10x pixel resolution of the stimuli used in this study, presenting life-like images during the cue-reactivity paradigm. Additionally, presentation of these images on a large (i.e., 27-34 inch) widescreen monitor would likely elicit even greater salience than that evoked by the current stimulus set.

Future studies may also examine the effects of several variables not considered in the present study. By exploring the order effects of the inhibitory control (i.e., Stroop) and cue reactivity tasks, the impact of cue exposure on subsequent response inhibition (a clinically relevant effect), could be assessed. Previous studies have found cue-exposure carry-over reductions in working memory performance (Wilson et al., 2007) and inhibitory performance in the go/no-go (Noel et al.,
2007) and stop-signal paradigm (Gauggel et al., 2010). Given the copious variables potentially influencing cue-elicited craving discussed in this dissertation, including dependence severity, impulsivity, treatment status, and stress, a wealth of possible follow-up investigations will help further clarify the relationships among craving, salience, attention, inhibition, and prospective relapse.
4.5 Conclusion

Despite our advancing knowledge on the clinical phenomenology and underlying neurobiology of alcohol use disorders, relapse rates in alcohol-dependent patients following discharge from residential treatment remain unacceptably high. Certain factors, such as severity of dependence, are known to be associated with relapse, but lack the sensitivity and specificity to confer clinical benefit to addiction treatment professionals. The purpose of this study was to examine the function of the prefrontal cortex as a predictor of relapse, given its theoretical involvement in alcohol use disorders. PFC activity subserving inhibitory control and alcohol salience was measured. Using advanced statistical methods, including least absolute shrinkage and selection operator (LASSO) and multiple logistic regression analyses, we developed a prediction model to determine the accuracy with which we could correctly discriminate between subsequent abstainers and relapsers. The addition of neuroimaging variables in the prediction of treatment outcome significantly added to the prediction accuracy compared to self-report variables alone.

Importantly, in contrast to fMRI studies, where operational costs and geographical distances to addiction treatment centers are often prohibitive, this study utilized a clinically accessible neuroimaging technology, functional near-infrared spectroscopy (fNIRS) to measure PFC function. Readily deployable in the clinical setting and operable at near-zero run-time costs, fNIRS represents a brain imaging technology viable for clinical use. Further investigation with a larger sample of patients and a variety of treatment settings could aid in the development of an objective measure of early relapse risk in patients with alcohol use disorders.
REFERENCES


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Education and Degrees

Ph.D., Neuroscience (July 2016) The Pennsylvania State University, Hershey, PA
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<tr>
<th>Year</th>
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<tr>
<td>2016</td>
<td>Guest Lecturer for Introduction to Psychology at Penn State York</td>
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<td>2015</td>
<td>Instructor in Cognitive Psychology for Johns Hopkins CTY</td>
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<td>2013</td>
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<td>2013</td>
<td>Third Place Poster Award at PSU Graduate Exhibition</td>
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<td>2012</td>
<td>Clinical and Translational Science Institute (CTSI) TL1 Award</td>
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Harris JD, Meyer RE, & Bunce SC (2014). Prefrontal Cue Reactivity Discriminates 3 Month Alcohol Dependence Treatment Outcome, 44th Annual Society for Neuroscience Conference, D.C.

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