USING PREFRONTAL CORTICAL ACTIVITY AS A BIOLOGICAL MARKER TO PREDICT RELAPSE RISK IN PRESCRIPTION OPIOID DEPENDENT PATIENTS:
A STUDY USING FUNCTIONAL NEAR-INFRARED SPECTROSCOPY

A Dissertation in
Neuroscience
by
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ABSTRACT

The incidence of prescription opioid dependence has reached epidemic proportions in the United States. For addicted individuals and their families, the behavioral manifestations and long-term health consequences associated with opioid dependence are both baffling and disconcerting. As in all addictions, treatment of prescription opioid dependence is extremely challenging due to high relapse rates. Identifying sensitive and specific markers of relapse risk is critical in (1) characterizing risk factors that should be targets of treatment, and (2) categorizing high risk individuals that may require further treatment for opioid dependence. Self-report measures have not been reliable in predicting treatment outcome, and the entire field lacks a gold standard in regard to assessment of relapse risk in treatment seeking individuals.

Identifying biological markers of relapse risk is critical in recognizing high risk individuals that may require extended residential treatment for opioid dependence. To address this issue, we conducted a study at the Caron Treatment Center in Wernersville, PA which sought to establish a predictive model for relapse risk using prefrontal cortical activity. Furthermore, our study sought to delineate the course of reregulation of biological and psychological factors relevant to prescription opioid dependence. The study sample consisted of 76 patients and 40 age/gender matched healthy controls. Participants in the study provided self-report data about their affective state and personality traits, gave salivary cortisol samples, and also performed a risky decision-making and drug cue paradigm adapted for functional near-infrared spectroscopy (fNIRS). We collected repeated measures on a subset of 22 patients that stayed in residential treatment beyond 28 days. We also collected information regarding relapse for 90 days post-discharge from residential treatment.
Opioid dependent patients exhibited dysregulation of a triad of relapse risk factors when compared to controls. These factors include increased risky decision-making, anhedonia, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. We found that patients that relapse to opioids display differential neural activity in the prefrontal cortex compared to patients that remain abstinent. More specifically, neuroimaging results showed that, during a risky decision-making task, neural activity in the ventromedial and dorsolateral prefrontal cortices are reliable biomarkers of relapse risk. As such, we were able to accurately predict relapse to opioids in the first 90 days post-residential treatment.

The results from this study improve our understanding of biological indicators of relapse risk in opioid dependent patients. Importantly, our model identifies prefrontal cortex measurements that predict treatment outcome in the first three months post-discharge from residential treatment. Moreover, these data characterize symptomatology during the post-withdrawal state in a way that is both relevant and beneficial to the clinical and scientific communities. Identifying those individuals at heightened relapse risk is extremely important, both in guiding clinicians in determining next level of care, and convincing patients that additional care is warranted. Continued focus on clinically translatable research should seek to develop biotechnologies aimed at improving treatment outcome.
# TABLE OF CONTENTS

List of Tables........................................................................................................................................viii

List of Figures........................................................................................................................................ix

List of Abbreviations.................................................................................................................................xi

Acknowledgments.......................................................................................................................................xiii

CHAPTER 1: INTRODUCTION .....................................................................................................................1
  Prescription Opioid Addiction..................................................................................................................2
  The Neurobiology of Addiction..............................................................................................................3
    The Reward System...............................................................................................................................3
    Opioids and Reward...............................................................................................................................5
  Models of Addiction.................................................................................................................................6
    Allostasis................................................................................................................................................6
    Impaired Response Inhibition and Salience Attribution........................................................................8
  Risk Factors Associated with Relapse......................................................................................................9
    HPA-Axis..............................................................................................................................................9
    Anhedonia..........................................................................................................................................11
    Reward Deficiency Syndrome............................................................................................................13
  Role of the Prefrontal Cortex in Addiction..............................................................................................14
    PFC Response to Natural Reward.........................................................................................................15
    Functional Near-Infrared Spectroscopy: Clinical Application..............................................................16
    Drug-Cue Exposure and PFC Activity....................................................................................................18
  Risky Decision-Making, Impulsivity, and Compulsivity........................................................................19
    Neurological Drivers of Impulsivity.......................................................................................................24
    The Reflective System...........................................................................................................................25
    Impulsivity: Risk Factor, Relapse Predictor, or Both?..........................................................................27
    The Balloon Analogue Risk Task........................................................................................................28
  Summary..............................................................................................................................................30

CHAPTER 2: STUDY DESIGN....................................................................................................................34
  Methods..............................................................................................................................................35
    Summary of Data Bursts.......................................................................................................................35
    Participants.........................................................................................................................................35
    Questionnaire-Based Measurements....................................................................................................37
    Cortisol Measurement via ELISA.........................................................................................................39
CHAPTER 7: GENERAL DISCUSSION

Clinical Relevance ................................. 100
Conceptual Understanding ...................... 103
Conclusion ............................................. 111

BIBLIOGRAPHY .......................................... 113
**LIST OF TABLES**

**Table 2.1**: Adapted from Rao et al., (2008): Balloon Analogue Risk Task; the risk of explosion (probability set by the program), the actual probability of explosion, the value of wager, and the reward variance associated with each balloon inflation……………………………………………… 42

**Table 2.2**: Demographics for all Caron patients included in the NIDA study. *We were not able to determine treatment outcome (relapse or abstinent) for 19 patients……………… 48

**Table 3.1**: Demographics of opioid dependent patients (ODPs) and healthy controls. No significant differences in age and gender between groups…………………………………… 58

**Table 3.2**: Neural activity in the following regions/conditions to predicted relapse to opioids and/or return to any substance: ventromedial PFC (vmPFC) while making decisions (optode 10), in response to a win (optode 10), and in response to a loss (optode 9) as well as dorsolateral PFC (dlPFC) activity in response to a loss (optode 9)……………………………………………… 60

**Table 4.1**: Participant Demographic Characteristics: Recently Withdrawn Patients versus Healthy Controls…………………………………………………………………… 72
LIST OF FIGURES

Figure 2.1: A) Breakdown of patient tasks during a typical 12 day data burst. B) Schedule of data bursts. Each patient participated in up to three 12 day data bursts over a 4 month period. Follow-up drug tests via hair sample occur at 1 & 3 months post discharge; short surveys are collected weekly over this time period. Combinations of survey and drug tests are used to determine abstinence from drug and thus, treatment outcome. Ecological Momentary Assessment (EMA); functional Near Infrared Spectroscopy (fNIR); Acoustic Startle Response (ASR)................................................................................................................................. 37

Figure 2.2: Sample visual stimuli used in cue-reactivity paradigm and affect-modulated acoustic startle response paradigm........................................................................................................ 40

Figure 2.3: Image adopted from Cazzell et al., 2012. Example of visual stimuli (a) following a winning trial, and (b) following a losing trial........................................................................................................ 45

Figure 3.1: Survival analyses were run on the top three predictor variables: decision-making in the right vmPFC $X^2 = 9.365$, $p = .002$, Hazard Ratio (HR) = 2.14, 95% CI, 1.32-3.48; reaction to winning trials in right vmPFC $X^2 = 4.329$, $p = .037$, Hazard Ratio (HR) = .61, 95% CI, .38 -.97; reaction to loss in the left dlPFC $X^2 = 6.15$, $p = .01$, Hazard Ratio (HR) = 2.79, 95% CI, 1.28-6.08. ROC curve shows the unique contribution of each predictor to sensitivity and specificity, and the subsequent model........................................................................................................ 62

Figure 3.2: Comparison of prefrontal cortex (PFC) activity between opioid dependent patients (ODPs) and healthy controls. In the passive version of the BART, (A) ODPs displayed increased neural activity while passively viewing the decision-making task i.e. the computer was pumping the balloon ($t(96)= -2.131$; $p=.037$). (B) ODPs had increased neural activity in reaction to a winning trial ($t(96)=-3.515; p=.001$). (C) ODPs had increased neural activity in reaction to a losing trial ($t(96)=-3.775; p=.001$). In the active – passive condition, (D) ODPs displayed increased activity during decisions leading to a reward ($t=-2.091; p=.041$). (E) ODPs displayed increased activity in reaction to a loss ($t=-3.092; p=.003$). (F) ODPs displayed decreased neural activity in reaction to a loss ($t=2.021; p=.047$)........................................................................................................ 63

Figure 3.3: Comparison of PFC activity in the active version of the BART (subtracting the passive version) in ODPs that relapse to opioids (RO) and those that remain abstinent. (A) RO patients displayed increased neural activity when making a decision that lead to reward ($t= -3.176; p=.003$). (B) RO patients displayed increased activity in reaction to a loss trial ($t=-2.336; p=.025$). (C) RO patients displayed decreased activity in reaction to a winning trial ($t=2.348; p=.025$). (D) RO patients displayed increased activity while actively pumping the balloon ($t= -3.066; p=.006$)........................................................................................................ 64
Figure 3.4: Scores on the Barratt Impulsivity Scale cognitive complexity subscale were correlated with neural activity in response to a winning trial in the left dLPFC, r(65)=.437, p=.002, in ODPs (upper right), but the opposite association was found in controls, r(31)=−.428, p=.067 (upper left). Similarly, response to a losing trial was correlated with activity in right dLPFC in ODPs, r(65)=.281, p=.05 (lower right); but the opposite association was found in controls, r(31)=−.575, p=.01 (lower left)…………………………………………………………67

Figure 4.1: Recently withdrawn prescription opiate dependent patients (ODP) display dysregulated processing of emotionally valenced stimuli via affect-modulated acoustic startle response. Response to negative stimuli is significantly lower (p<.05) for ODP and response to positive stimuli is significantly higher (p<.05). Neg=negative stimuli; Neu=neutral stimuli; Pos=positive stimuli; * = p<.05 error bars = SEM………………………………………………………………….74

Figure 4.2: Recently withdrawn opiate-dependent patients display reduced brain activity in response to naturally rewarding stimuli compared to healthy controls. Each number represents an optode on the functional near-infrared spectroscopy device; blue dots correspond to areas of decreased activity (p<.05)……………………………………………………………………………………………75

Figure 4.3: Recently withdrawn opiate-dependent patients split into two categories: patients self-reporting anhedonia (as evident by score > 2 on the Snaith-Hamilton Pleasure Scale), and patients failing to report anhedonia. When comparing these two sub-groups, patients self-reporting anhedonia show reduced brain activation to social and food stimuli. Each number represents an optode on the functional near-infrared spectroscopy device; blue dots correspond to areas of decreased activity (p<.05)………………………………………………………………………………………………76

Figure 5.1: Diurnal and total mean cortisol. Upper left: comparison of diurnal cortisol between patients and controls during data burst 1. Lower left: comparison of mean daily cortisol between patient and controls in data burst 1. Upper right: Change in diurnal cortisol across three data bursts. Lower right: Change in mean cortisol across data bursts for the full cohort and three data burst subset (and comparison with controls). *=p<.05; **=p<.01……………………………………86

Figure 5.2: Associations between mean cortisol and brain activity during the Balloon Analogue Risk Task. Neural response to a winning trial in the right DLPFC is correlated with high mean cortisol (Optode 16; r=.324, p=.028). Neural activity in the right DL/VMPFC in response to a losing trial is correlated with high mean cortisol (Optode 11; r=.433, p=.006).………………………………………………………………………………86

Figure 6.1: Upper left: correlation between brain activity during the drug-cue paradigm (optodes 1 &2) and baseline measurement of craving (avoid craving) (r=.357, p=.006). Upper right: correlation between brain activity in response to wins during the passive trial of the BART (optodes 2-4) and cue-induced craving (r=.348, p=.006). Lower left: correlation between brain activity during drug-cue paradigm (optode 5) and cue induced craving (control over use; r=.256, p=.043). Lower right: correlation between brain activity in response to loss during the active trial of the BART (optode 5) and baseline craving (r=.400, p=.003)…………………………………………………………95
## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC</td>
<td>anterior cingulate cortex</td>
</tr>
<tr>
<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
</tr>
<tr>
<td>AMSR</td>
<td>affect-modulated startle response</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>BART</td>
<td>Balloon Analogue Risk Task</td>
</tr>
<tr>
<td>BIS/BAS</td>
<td>Behavioral Inhibition/Behavioral Activation Scale</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CRF</td>
<td>corticotropin releasing factor</td>
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<tr>
<td>DA</td>
<td>dopamine</td>
</tr>
<tr>
<td>DLPFC</td>
<td>dorsolateral prefrontal cortex</td>
</tr>
<tr>
<td>DSM-IV-TR</td>
<td>Diagnostic and Statistical Manual for Mental Health Disorders – Fourth Edition – Text Revision</td>
</tr>
<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>EMA</td>
<td>ecological momentary assessment</td>
</tr>
<tr>
<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
</tr>
<tr>
<td>fNIRS</td>
<td>functional near-infrared spectroscopy</td>
</tr>
<tr>
<td>Ham-D</td>
<td>Hamilton-Depression Rating Scale</td>
</tr>
<tr>
<td>HbO₂</td>
<td>oxygenated hemoglobin</td>
</tr>
<tr>
<td>HbR</td>
<td>deoxygenated hemoglobin</td>
</tr>
<tr>
<td>HPA</td>
<td>hypothalamic-pituitary-adrenal</td>
</tr>
<tr>
<td>IGT</td>
<td>Iowa Gambling Task</td>
</tr>
<tr>
<td>iRISA</td>
<td>impaired response inhibition and salience attribution</td>
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<tr>
<td>OPD</td>
<td>opioid dependent patient</td>
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<tr>
<td>OFC</td>
<td>orbitofrontal cortex</td>
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NA  negative affect
NAc  nucleus accumbens
PA  positive affect
PET  positron emission tomography
PFC  prefrontal cortex
ODP  prescription opiate dependent patient
RPFC  rostral prefrontal cortex
SCID  Structured Clinical Interview for DSM IV-TR
SUD  substance use disorder
VLPFC  ventrolateral prefrontal cortex
VMPFC  ventromedial prefrontal cortex
VTA  ventral tegmental area
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CHAPTER 1

INTRODUCTION
Prescription Opioid Addiction

The prescription opioid epidemic has had devastating consequences in the United States. According to the Centers for Disease Control and Prevention, opioid related overdose deaths and admissions to treatment centers have risen in parallel since the year 2000 (SAMHSA, 2014). Likewise, the annual quantity of painkillers prescribed in the United States has quadrupled since the turn of the century, despite the absence of an increase in reported pain (SAMHSA, 2013).

Even though federal regulations and physician awareness has curtailed the rising rate of prescription opioid abuse (SAMHSA, 2014), many opioid abusers have turned to heroin, which is cheaper and often more readily available (Muhuri et al., 2013). In spite of this, abuse of opioid analgesics still accounts for more illicit drug use than cocaine, methamphetamine, and heroin combined (SAMHSA, 2014). Opioid dependence, like all substance use disorders (SUDs), is a progressive disease that is prolonged and exacerbated by chronic relapse. Indeed, chronic relapse is the major defining element of all SUDs, and as such, addressing factors that affect the risk of relapse is essential in improving the efficacy of treatment for opioid dependence (O'Brien et al., 1998; Tkacz et al., 2012). Current assessment of relapse risk is dependent on self-report measures which have not been reliable in predicting treatment outcome (e.g., Dijstra et al., 2008). Therefore, it is essential that we identify biological markers that are indicative of positive and negative treatment outcomes. Understanding the biological factors that drive relapse will aid clinicians in personalizing treatment approaches and determining next level of care for patients in residential treatment.

A major obstacle in treating opioid dependence is that, post-withdrawal, there is a relatively short period of continued dysregulation termed abstinence syndrome; furthermore, some individuals experience protracted abstinence syndrome wherein dysregulation persists over
a long period of time marked by increased drug craving and susceptibility to relapse (Martin & Jasinski, 1969). The level of relapse susceptibility appears to be unique to each individual and consists of a triad of symptoms, namely stress reactivity, impaired executive function, and dysregulation of emotional processes (Koob, 2013; Sinha, 2011; Goldstein & Volkow, 2011). During this period, it is unclear how re-regulation of the central nervous system (CNS) affects lingering symptoms and subsequent risk of relapse (Heilig et al., 2010). Current addiction treatment lacks objective markers of relative risk, which would give clinicians an indication of response to treatment and likelihood of relapse. Moreover, understanding the factors that lead to relapse will allow clinicians to take targeted approaches to therapy, and correctly identify individuals who are benefiting from, or not benefiting from, current treatment methods.

The following sections will explore (1) biological factors that drive addiction, (2) empirically grounded models of addiction, (3) risk factors associated with relapse, and (4) the prefrontal cortex and its role in emotional processes and risky decision-making.

The Neurobiology of Addiction

The Reward System

Like all drugs of abuse, prescription opioids are thought to share a common behavioral and biological process as drug abuse progresses to drug dependence. Behaviorally, this process is a reoccurring cycle consisting of (1) preoccupation/anticipation, (2) binge/intoxication, and (3) withdrawal/negative affect (Koob, 2010). Current understanding of the neuobiology of addiction indicates a central role for the ventro-striatal reward system in the addiction cycle (APA, 2013; Volkow et al., 2004). Reward signaling primarily occurs via dopaminergic neurons that project from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). Dopamine (DA)
mediates reward through reinforcement, learning, and reward salience, all of which are integral in the progression of opioid dependence (Di Chiara and Imperato, 1988; Robinson and Berridge, 1993). In healthy individuals, the reward system is thought to operate in a state of homeostasis wherein natural rewards are given predictable reward value. However, repeated drug use highjacks the reward system and results in shifting homeostatic set points (Koob & LeMoal, 2001). As these set points shift, motivation to seek and take drugs is shifted from positive reinforcement (getting a good feeling) to negative reinforcement (removing a bad feeling; Koob & LeMoal, 2001). In the later stages of addiction, when withdrawal symptoms are severe, negative reinforcement plays a larger role in driving relapse behavior (Koob & Le Moal, 2001; George et al., 2012).

The cycle of addiction is mediated by intracellular and extracellular changes in the reward system. In the early stages of abuse, drug use elicits sharp increases in extra-cellular DA in the NAc, saturating available DA receptors (Volkow et al., 1994). In turn, there is reduced DA release from the VTA and reduced expression of D2 DA receptors in the NAc; this down-regulation leads to increasing levels of drug intake which achieve diminished rewarding effects (Volkow & Fowler, 2000). The down-regulation of D2 DA receptors simultaneously results in blunted responses to the much less potent effects of natural rewards (Volkow and Fowler, 2000). As this reward deficit ensues, there is an upregulation of stress signaling in the brain, which initially occurs in the hypothalamic-pituitary-adrenal (HPA) axis and continues in the extended amygdala (Koob, 2010). These stress signals contribute to the withdrawal/negative affect and the preoccupation/anticipation stages of addiction, and as such, stress signals are a primary contributor to the vicious cycle of chronic relapse. In the same way that acute withdrawal is affected by short-term stress signals, symptoms of the abstinence syndrome are likely driven by
long-term changes in stress-signal and reward neuro-circuitry (Diana et al., 1996; Koob, 2010). Overall, stress has a profound effect on the rate of relapse, primarily due to neuroendocrine and neurotransmitter changes in stress signaling (Koob, 2010; Fox et al., 2014; Sinha, 2008).

**Opioids and Reward**

Opioid receptors are found on complex neuromodulatory systems throughout the central and peripheral nervous systems. In addition to gating pain, prescription opioids act directly on the neural reward system. Endogenous opioid peptides, namely β-endorphins, enkephalins, and dynorphins, act on three main G-protein-coupled opioid receptors: mu, kappa, and delta (MOR, KOR, and DOR respectively; Lutz & Kieffer, 2013). Animal models have shown that MORs have the primary role in signaling reward (Matthes et al., 1996), whereas KORs are thought to constitute an anti-reward system that directly opposes MOR activation (Wee & Koob, 2010). The contribution of DORs is more complex; they may strengthen the learning component of reward and decrease anxiety but there is still debate in the field as to their exact role in signaling reward (Lutz & Kieffer, 2013). The NAc contains MOR hotspots, wherein endogenous and exogenous opioids can act directly on the liking and wanting components of reward (Pecinia & Berridge, 2005). In this way, opioids are able to drive feelings of motivation and pleasure in the neural reward system, independent of DA signaling. Opioids also act indirectly on the NAc by inhibiting GABAergic interneurons in the VTA, thereby increasing DA to the NAc (Pecinia & Berridge, 2005)

Prescription opioids are excellent analgesics, and in many instances are the best/only option for treatment of pain following injury or for various medical conditions. Because of this, many individuals with acute or chronic pain enter the addiction cycle through medical treatment, as opposed to exposure to illicit drugs. As analgesics, opioids act to block pain through both top-
down and bottom-up processes (Purves et al., 2001). Because there is a high concentration of opioid receptors in the dorsolateral horn of the spinal cord, prescription opioids can block pain before the message ever gets to the brain (this is considered a bottom-up mechanism). In addition, top-down pain suppression involves areas of the brain stem including the periaqueductal grey and the rostral ventromedial medulla; when stimulated by opioids, these brain areas descend on the spine to inhibit the pain signal (Purves et al., 2001).

Models of Addiction

Allostasis

In some sense, George Koob’s allostatic model of addiction can be seen as an extension of Solomon’s opponent process theory (Koob, 1997; Koob & LeMoal, 2001; Solomon & Corbit, 1973). As a way to explain the neurobiology of motivation via affect, Solomon and Corbit (1974) postulated that hedonic, or emotional states, once instigated, are automatically modulated by the brain in order to reduce the intensity of hedonic feelings. On one hand, this leads to affective or hedonic habituation; however, opposing systems result in affective or hedonic withdrawal (Koob, 2013). Koob’s allostatic model explains that the progression of substance abuse to dependence is driven by shifting homeostatic set points related to opposing systems of the CNS (Koob & LeMoal, 2001). This model highlights the HPA-axis, reward system, and autonomic nervous system as areas of the CNS that are particularly susceptible to drug-induced short-term alterations (Fisher & Reason, 1988; Koob & LeMoal, 2001; McEwen & Wingfield, 2003). In the long-term, the cost of repeated short-term alterations culminates in neural adaptations and the establishment of new homeostatic set points; this can result in pathological states such as addiction (McEwen, 2000). During the cycle of addiction, hedonic habituation
leads to a reduction of reward signaling to positive reinforcers (Koob, 2013). New hedonic set points correlate closely with the intensity, quality, and duration of the drug reinforcer; over time, this may or may not be linked with drug tolerance. In contrast, hedonic withdrawal may occur after a positive hedonic response has terminated, or in anticipation of drug use. Hedonic withdrawal consists of negative hedonic responses, is sluggish in onset, builds and decays over a protracted period of time, and most importantly, gets larger with repeated exposure (Koob, 2013).

During the development of new homeostatic set points, addicted individuals are motivated by both positive and negative reinforcement (Koob, 1996). Positive reinforcement is defined as the process by which presentation of a stimulus increases the probability of a response; while negative reinforcement is defined as the process by which removal of an aversive stimulus (or negative emotional state) increases the probability of a response (Koob, 1997; 2013). As drug abuse transitions to drug dependence, motivation is still driven by reward systems, defined as positive reinforcement and positive hedonic response. However, given that neural reward pathways are downregulated in drug dependence, motivation to seek and take drugs is increasingly driven by negative reinforcement, such as removal of stress associated with withdrawal symptoms. Neuroadaptations of the brain reward and stress systems are key in determining new homeostatic set points; likewise, these systems are also required for survival through motivation and reinforced learning (Koob, 2013).

Koob’s allostatic model describes three stages of addiction: (1) a compulsion to seek and take drugs, (2) loss of control over drug intake, and (3) emergence of a negative emotional state (e.g., dysphoria, anxiety, and irritability; Koob, 1997). This last stage further defines a motivational withdrawal syndrome when access to the drug is prevented (Koob, 1997). Research
in animal models, summarized by Koob and Le Moal (2001), provides support for an allostatic model of addiction, in which the natural homeostatic mechanisms of the HPA-axis and brain reward system are altered over the course of chronic drug self-administration. As a consequence of these adaptations, addicted individuals are more susceptible to stress, less responsive to natural rewards, and more responsive to drug cues. These allostatic changes persist following drug withdrawal, and are believed to contribute substantially to continued drug salience and risk of relapse (Koob & Kreek, 2007; Koob & Volkow, 2010).

**Impaired Response Inhibition and Salience Attribution (iRISA)**

Whereas Koob’s allostatic model of addiction focuses on subcortical brain areas such as the limbic system, and more specifically, the nucleus accumbens, as well as stress response via the HPA-axis, there is strong evidence that the human experience of addiction is greatly influenced by impaired executive function. Given that the prefrontal cortex (PFC) mediates allocation of attention, behavioral inhibition, and working memory (Miller & Cohen, 2001), a well-rounded understanding of addiction must take into account the contributions of the PFC. Impaired response inhibition and salience attribution (iRISA) is a model of addiction that focuses on disruption of PFC function; excessive salience is attributed to drugs and drug-related cues, while sensitivity to non-drug reinforcers and the ability to inhibit maladaptive behaviors is diminished (Goldstein & Volkow, 2002; 2011). These core deficits in PFC function lead to (and explain) motivation to seek and take drug, even at the expense of other activities (Volkow et al., 2003). Often times, the extreme motivation to seek and take drugs culminates in extreme behaviors that are detrimental to the both the individual and the community (Volkow and Li, 2004). The following sections will address these issues in more depth.
Risk Factors Associated with Relapse

HPA-Axis

The HPA-axis is responsible for the neuroendocrine response to stress in addition to several homeostatic systems in the human body including immune function, metabolism, and circadian rhythm (Turnbull & Rivier, 1999). There are strong connections between the amygdala and hypothalamus that stimulate both the HPA-axis and the sympathetic nervous system in reaction to environmental stressors or threats (Herman & Cullinan, 1997). Whereas the HPA-axis is a complex system, it primarily consists of three major neuroendocrine organs with three major hormone factors: (1) the paraventricular nucleus of the hypothalamus releases corticotropin releasing factor (CRF) from neurosecretory terminals in the median eminence; this stimulates release of (2) adrenocorticotroic hormone (ACTH) from the anterior lobe of the pituitary gland; ACTH enters the blood stream and stimulates release of (3) cortisol from the adrenal cortex (which sits on the rostral portion of the kidneys in humans; Herman & Cullinan, 1997). Cortisol acts as a stress hormone, but also regulates the HPA-axis via negative feedback, shutting down the signal from the anterior pituitary and hypothalamus; over-activation of the HPA-axis has also been linked to atrophy of the hippocampus and subsequent deficits in working memory (Herman & Cullinan, 1997).

The stress response plays a major role in opioid dependence (Kreek et al., 2005). Preclinical models have shown that opioids stimulate plasma corticosterone (analogous to cortisol in humans), and that morphine tolerance leads to modulation of the HPA-axis (Iyengar et al., 1987). Piazza and Le Moal (1998) note that glucocorticoids increase the sensitivity of mesencephalic DA neurons and facilitate self-administration of drugs, both during initial drug intake and after prolonged periods of abstinence. Furthermore, animal models have shown that
stressors such as intermittent foot shock and CRF injections reinstate heroin seeking in rats (Shaham & Stewart, 1995; Shaham et al., 1997), and that CRF antagonists attenuate stress-induced relapse (Shaham et al., 1997). In healthy adult males, genotyping studies have linked the A118G mu-opioid receptor polymorphism to a greater cortisol response during a naloxone challenge, providing further evidence that opioid receptors alter stress sensitivity (Wand et al., 2002). Indeed, opioid dependent individuals undergoing naloxone-induced withdrawal display HPA-axis hypersensitivity (Culpepper-Morgan & Kreek, 1997), suggesting that HPA measurements are likely a good indicator of withdrawal severity.

There is less known, however, regarding the specific impact of stress on decision-making processes in SUDs. Impulsivity, risk taking, and stress reactivity each have profound effects on the progression of addiction, although whether these constructs interact with each other to exacerbate the addictive condition, particularly as it relates to risk for relapse, remains elusive (Kreek et al., 2005). Studies such as Helen et al. (2010) and Ansell et al. (2012) have looked at the relationship between stress and SUDs, although these studies relied on questionnaire-based measurements. Oswald et al. (2007) found that high stress and/or high trait impulsivity were associated with reduced DA release in the striatum in response to amphetamines. The same study also notes that high trait impulsivity is associated with self-reported pleasant effects of amphetamines. Furthermore, stress response has been linked to binge patterns of behavior (Kreek, 1997; Sinha, 2008). What is not clear, however, is whether high stress responsiveness induces impulsive behaviors, or whether individuals with high trait impulsivity naturally have a higher neuroendocrine response to stressors. Stress-induced craving and HPA-reactivity has been used to predict time to relapse in cocaine dependent individuals (Sinha et al., 2006), but it is still
unknown whether these measurements would have predictive value in other SUDs such as prescription opioid dependence.

**Anhedonia**

There is growing evidence that anhedonia, clinically defined as an impaired capacity to experience pleasure (Snaith, 1993), plays an important role in vulnerability to relapse across addictive disorders (Franken et al., 2007; Garfield et al., 2014; Janiri et al., 2005; Koob & Le Moal, 2001; Volkow et al., 2002). Anhedonia has been found to be a common symptom of the abstinence syndrome associated with both acute and protracted withdrawal in substance-dependent populations (Bovasso, 2001; Gawin & Ellinwood, 1988; Garfield et al., 2014; Hatzigiakoumis et al., 2011; Heinz et al., 1994; Leventhal et al., 2009; Leventhal et al., 2010; Loas, 1996), including opiate-dependence (Martin et al., 1963; 1973; Zijlstra et al., 2009). Emotional disturbances, including anhedonia, have been thought to contribute to the high rates of relapse in substance use disorders (SUDs; Alling et al.; 1982, Begleiter & Porjesz, 1979; Martin et al., 1963; 1973).

Whereas clinical phenomena such as craving, tolerance, withdrawal and enhanced response to drug cues have been studied in recovering opioid dependent patients (e.g., Koob & Volkow, 2010; Kühn & Gallinat, 2011; Lubman et al., 2009; Zijlstra et al., 2009), relatively few studies have evaluated the role of reduced responses to natural rewards in these clinical populations. This is notable, given the potential role of anhedonia in explaining vulnerability to relapse and the supporting evidence from preclinical models (e.g., Grigson and Twining, 2002; Koob & Volkow, 2010; Markou & Koob, 1991). In addition to anhedonic mood, behavioral measures have validated reduced ratings of pleasant stimuli among current and abstinent heroin users (de Arcos et al., 2008). Anhedonia has been associated with greater drug salience and drug
craving among recently withdrawn opioid-dependent (Janiri et al., 2005; Martinotti et al., 2008a) and alcoholic patients (Martinotti et al., 2008a; 2008b). Tobacco smokers attempting to quit are more likely to relapse if they are anhedonic (Cook et al., 2010; Leventhal et al., 2009; Versace et al., 2011). A recent review of the literature suggests that the explanatory role of anhedonia in substance use disorders cannot be accounted for simply as a factor of comorbidity with other psychiatric diagnoses in which anhedonia is common (e.g., depression; Garfield et al., 2014). These findings suggest anhedonia warrants investigation as an independent construct.

There is a strong link between SUDs and emotional dysregulation that cannot be explained by psychiatric comorbidities, highlighting the importance of the role of affect in SUDs (Cheetham et al., 2010; Goldstein & Volkow, 2011). These dysregulations include anhedonia, irritability, anxiety, and dysphoric mood, which may influence stress reactivity and craving; furthermore, these symptoms are common during the post withdrawal period termed protracted abstinence syndrome in opioid dependent patients (Koob & LeMoal, 2001; Martin, Jasinski, Haertzen et al., 1973). Similar symptomatology has been described in alcohol, cocaine, cannabis, stimulants, (Bovasso, 2001; Gawin & Ellinwood, 1988; Gawin & Kleber, 1986; Heinz, et al., 1994; Miller et al., 1993), and polysubstance abuse (Martinotti et al., 2009). Moreover, post-withdrawal affective dysregulation had been linked to vulnerability to relapse (Heilig et al., 2010). Little is known, however, about the role of low positive affect (PA) as it relates to craving and relapse in the early stages of recovery from prescription opiate dependence. This lack of knowledge stems from fewer studies that evaluate the role of low PA as it contributes to craving and relapse in early abstinence, relative to studies that examine the role of negative affect (NA; Cheetham et al., 2010).
One reason that low PA may have been overlooked is that many investigators (tacitly) ascribe to a circumplex model of affective space; within this model, PA and NA are conceptualized as opposite ends of a continuum, rather than as independent neural systems with separate neurophysiological underpinnings (Ameringer & Leventhal, 2010; Bujarski, et al., 2015). As such, many investigators focus on NA and stress response systems to the exclusion of the PA system. Indeed, NA, or dysphoria, is regularly cited as a persistent symptom of withdrawal from opiates that contributes to risk of relapse (Nestler, 2001; De Vries & Shippenberg, 2002; Epstein et al., 2009; Moore et al., 2013). However, there is considerable evidence that NA and PA are indeed relatively independent, and as such, may function together or independently (Cacioppo & Berntson, 1994; Cacioppo et al., 1999; Norman et al., 2011).

Blunted response to natural reward persists long after withdrawal (Heilig et al., 2012; Lutz et al., 2013). Among opioid dependent individuals, opiate use relieves feelings of anhedonia (Blum et al., 2013), hence the increased risk for relapse in recovering addicts suffering from anhedonia (Goeldner et al., 2011). Anhedonia can be measured by a lack of positive response to positive stimuli (Bunce et al., 1995), and concurrent with stress, measuring anhedonia may offer insight into the rate of neural re regulation that accompanies positive treatment outcomes in recovering opiate addicts. What remains unclear is whether the same individuals that experience anhedonia prior to onset of substance abuse/dependence, as predicted by the reward deficiency syndrome, are at heightened risk for relapse when leaving the addiction cycle.

**Reward Deficiency Syndrome**

The reward deficiency syndrome hypothesis posits that genetically-conferred deficits in hedonic capacity, particularly hypodopaminergic activity in the mesolimbic system, lowers the capacity to cope with stress, and increases the risk of seeking pharmacological reinforcers (Blum
et al., 2000). As a consequence, anhedonia has been postulated to play a role in the onset of drug abuse/dependence (Blum et al., 2000). This inherent form of anhedonia would not only place the individual at increased risk for developing a substance use disorder, but would also make them more vulnerable to relapse as they attempted to maintain abstinence. In this way, reward deficiency syndrome and Koob’s allostatic model suggest potentially overlapping mechanisms by which anhedonia may confer risk in recovery from substance use disorders.

**Role of the Prefrontal Cortex in Addiction**

The PFC plays a major role in several addiction-related neural functions, including decision-making (Fu et al., 2008 & Gilbert et al., 2006), impulsivity (Rao et al., 2008), self-control (Brody et al., 2007), emotional regulation (Kringelbach & Rolls, 2004; Wang et al., 2010), motivation and salience attribution (Ventura et al., 2007). Although the PFC has been the subject of copious research studies, overall, it has been difficult to attribute function to specific PFC regions across studies (Goldstein & Volkow, 2011). For example, the dorsal anterior cingulate cortex (ACC) and dorsolateral PFC (DLPFC) may be involved in the craving response, control over craving, or both (Goldstein & Volkow, 2011). Neuroanatomical flexibility, cognitive flexibility and differences in methodology likely contribute to the sometimes disparate results between neuroimaging studies. Participants may use multiple strategies when performing neuropsychological tasks, and prefrontal systems seem to have a greater level of functional flexibility than primary sensorimotor and/or subcortical systems (Goldstein & Volkow, 2011). Since the PFC is densely interconnected with other brain regions, computational modeling and connectivity studies may help in elucidating cognitive and emotional function to select PFC
regions, enhancing our understanding of their involvement in drug addiction (Kohno et al., 2016).

**PFC Response to Natural Reward**

Individuals in withdrawal or early abstinence from prescription opioids display decreased response in the PFC to natural rewards when compared to healthy controls (Bunce et al., 2015; Huhn et al., 2015). It has been suggested that decreased sensitivity to natural rewards is an allostatic adaptation (Volkow et al., 2004). In this interpretation, repeated drug use leads to compensatory brain changes that limit natural hedonic and motivational processes (reward), at the same time strengthening aversive (opponent or anti-reward) systems (Koob & LeMoal, 2001). In this way, new homeostatic set points are directly related to repeated drug exposure, and are manifest in PFC response to positive natural reward cues. Once again, this extends the opponent-process hypothesis set forth by Solomon and Corbit (1973; 1974) to addiction-related opposing emotional responses. It is likely that diminished PFC response to natural rewards is related to regulation of affect, which, insofar as emotions are defined as ‘states elicited by reinforcers’ (Rolls, 2000), are bound to be impaired in drug addiction (Goldstein & Volkow, 2011). Indeed, decreased sensitivity to natural rewards presents a difficult challenge to clinicians, especially in the early stages of treatment. Therefore, it is critical to better understand how reduced positive affect, or anhedonia, affects individuals in early recovery from SUDs, and whether PFC correlates of anhedonia can be used as a biomarker to predict treatment outcome.

Anhedonia is an important but underrepresented construct in neuroimaging research on clinical treatment for SUDs. Criteria for anhedonia are met by many drug-addicted individuals, for example, 50% of cocaine-addicted individuals (Gold, 1997), and 39% of recovering prescription opioid users (Huhn et al., 2015) report clinical levels of anhedonia on the Snaith-
Hamilton Pleasure Scale (Snaith et al., 1995). The link between emotional states and SUDs is not limited to depressive symptoms per se (Cheetham et al., 2010); emotional distress and negative affect are known risk factors for drug relapse (Sinha, 2007; Goldstein and Volkow, 2011). However, neuroimaging studies examining the relationship between anhedonia and addiction are sparse, although relevant findings are discussed in the following paragraphs.

Neuroimaging studies looking at the blood oxygenated level dependent (BOLD) response in functional magnetic resonance imaging (fMRI) have found that affectively positive stimuli elicit decreased neural activity in limbic (right amygdala; Wang et al., 2010), posterior cortical (Wang et al., 2010), and anterior cortical locations (Zijlstra et al., 2009) in abstinent heroin dependent patients relative to controls. Of particular relevance, Zijlstra et al. (2009) used fMRI to evaluate neural responses to positive hedonic stimuli and drug cues among recently detoxified heroin-dependent males. They found that the pleasant cues activated bilateral DLPFC, ventrolateral PFC (VLPFC), and anterior prefrontal gyrus (or rostral prefrontal cortex; RPFC) in both opioid-dependent and control participants. Patients differed from controls only in the bilateral anterior PFC (i.e. RPFC), where heroin-dependent participants showed reduced neural activation relative to controls. Although the data presented by Zijlstra et al. (2009) appear to be relevant to the construct of anhedonia, they did not find group differences on a well-validated self-report measure of anhedonia; the Snaith–Hamilton Pleasure Scale (SHAPS; Franken and Muris, 2006 and Snaith et al., 1995). This is likely due to the low number of opioid dependent participants (n=12) in the study.

**Functional Near-Infrared Spectroscopy: Clinical Application**

Even though previous neuroimaging studies of cue response to natural rewards have relied heavily on fMRI and PET, the real-world clinical application of these technologies is
limited by high cost coupled with the reality that the vast majority of addiction treatment programs exist apart from functional brain imaging centers. In order to use neuroimaging as a clinical tool, there is a pressing need to develop technologies that are easy to use, cost effective, and portable. The data presented in this thesis is part of a larger effort to develop objective CNS measures that have clinical relevance and potential utility in the assessment of patients recently withdrawn from opioids. Functional near-infrared spectroscopy (fNIRS) is a neuroimaging tool that monitors hemodynamic response in the PFC, analogous to the BOLD response in fMRI. In brief, light in the near-infrared range (between 700–900 nm) is able to pass through most biological tissue (Villringer et al., 1993), creating an optical window for the noninvasive assessment of brain activation (Bunce et al., 2006). In fNIRS application, the source of light, either a light-emitting diode (LED) or fiberoptic bundle, is held constant on the forehead and a predictable amount of light is scattered back out of the CNS following a banana shaped path (Bunce et al., 2006). A light detector at a fixed point on the forehead collects the light after it has interacted with CNS tissue and measures small changes in the capillary beds as oxygenated hemoglobin becomes deoxygenated; this is a secondary measure of neural activity (Bunce et al., 2006). There are several advantages to using fNIRS in substance abuse treatment centers, including cost, ease of use, portability, and clinical application (Bunce et al., 2012; Irani et al., 2007; Ehlis et al., 2014). Furthermore, fNIRS can be easily deployed in residential or outpatient treatment facilities, and can be used to assess PFC activity in drug and/or natural reward cue response paradigms. If fNIRS data can identify relapse risk factors such as anhedonia and monitor treatment induced changes in PFC activity, it can be used to predict treatment outcome and improve patient care for treatment seeking opioid dependent patients.
In the pilot study on prescription opioid dependence that lead to the work presented in this thesis, Bunce et al. (2015) used a drug/natural reward cued response task adapted for fNIRS in opioid dependent patients. PFC responses were compared between extended care patients who had been abstinent for an average of 79 days (n = 7), recently withdrawn patients who had been abstinent for an average of 19 days (n = 7), and healthy controls (n = 7). In this cross-sectional study, recently withdrawn and extended care patients displayed increased neural activity in the right lateral PFC in response to natural reward cues as well as to drug cues, whereas the responses of the extended care patients did not differ from those of the controls. Similar results have also been demonstrated in an alcohol-dependent population using fNIRS (Bunce et al., 2012).

**Drug-Cue Exposure and PFC Activity**

Activation of the PFC in response to drug cues has previously been attributed to incentive salience and reward sensitivity in individuals with SUDs (Goldstein & Volkow, 2011). More specifically, the left DLPFC, left medial frontal gyrus, and right subcallosal gyrus (Brodmann area 34) are activated by cigarette cues in young smokers (Yalachkov et al., 2009); bilateral DLPFC and ACC are activated in response to alcohol cues in short-term (Heinz et al., 2007) and long-term (Grusser et al., 2004) abstinent alcoholics; and right lateral PFC is activated in recently withdrawn opioid dependent patients (Bunce et al., 2015). However, there are some exceptions in alcoholics and opioid users (deGreck et al., 2009; Myrick et al., 2004; Ziljstra et al., 2009). Similar to fMRI results, PET studies have found increases in PFC activation in cocaine-addicted individuals watching cocaine-related videos (Garavan et al., 2000), and in heavy smokers watching cigarette-related videos (while handling a cigarette; Brody et al., 2002). Furthermore, cue-induced PFC response is correlated with subjective reports of craving (Brody et al., 2002),
and severity of drug use (Yalachkov et al., 2009). PFC response to drug cues may also be clinically relevant, as PFC activity predicts both subsequent performance on a primed emotion recognition task (Artiges et al., 2009) and relapse in the first three months post-treatment (Grusser et al., 2004). Conversely, drug-related masked cues (subliminal cues) do not elicit PFC activation (Zhang et al., 2009), and instead elicit subcortical response (Childress et al., 2008). Because of this, PFC response to drug cues is thought to be driven by conscious perception and working memory. Although the aforementioned studies have increased our knowledge of cue-elicited PFC responses, there is a need to clarify the effects of specific drugs in regard to post-withdrawal time (i.e. time away from drug), thereby increasing our understanding of drug-cue-elicited brain responses in individuals with SUDs (Goldstein & Volkow, 2011).

**Risky Decision-Making, Impulsivity, and Compulsivity**

Internal and external factors affect the way we make and carry out decisions. Decision-making may be either perceptual or behavioral, depending on whether action is taken; decisions are frequently accompanied by a certain degree of risk to the individual. In SUDs, this risk may include repercussions such as physical danger e.g. violence or overdose, as well as loss of monetary rewards. Moreover, risky decision-making in SUDs may have larger implications on society as a whole, such as crime and loss of workplace productivity. Behavioral phenotypes, such as impulsivity and compulsivity, affect the process of risky decision-making, often to the detriment of the individual. Impulsivity can be defined as ‘a predisposition toward rapid, unplanned reactions to internal or external stimuli, with diminished regard to negative consequences to the impulsive individual or to others’ (Chamberlain and Sahakian, 2007; Potenza, 2007). In contrast, compulsivity is defined by the performance of repetitive overt or
covert behavior, performed in a habitual or stereotyped fashion, either according to rigid rules or as a means of avoiding perceived negative consequences (Chamberlain et al., 2006; Hollander, 1996; Fineberg et al., 2014). Although these constructs may have similarities in behavioral phenotype, there are, by definition, stark differences between impulsivity and compulsivity that involve dissociable cognitive functions (Everitt et al., 2008). Moreover, these differences are mediated by neuroanatomically and neurochemically distinct components of the PFC and subcortical brain regions (Everitt et al., 2008). In SUDs, the switch from impulsive to compulsive drug seeking/taking is accompanied by a transition of behavioral control from the PFC to subcortical regions including the amygdala and striatum; in other words, decision-making in individuals with severe SUDs is marked by deficits in executive function (Everitt et al., 2008).

Historically, impulsivity and compulsivity were viewed as opposing conditions; risk-seeking was attributed to impulsivity while harm-avoidance was attributed to compulsivity (Fineberg et al., 2014). Nonetheless, there is a strong overlap between the two constructs that revolves around intense feelings of “lack of control”, and as such, they appear to be linked by shared neuropsychological mechanisms involving deficits in behavioral and perceptual inhibition (Stein & Hollander, 1995; Grant & Chamberlain, 2014).

Almost by definition, the behavioral phenotypes observed in SUDs contain elements of both impulsivity and compulsivity. For example, SUDs are marked by reduced willingness (or ability) to shift thoughts away from drug use and control urges to consume the substance, and behaviorally, there is strong preference for immediate reward (Dalley et al., 2011; de Wit and Dickenson, 2009; Ersche and Sahakian, 2007; Garavan and Stout, 2005; Goldstein and Volkow, 2011; Jentsch and Taylor, 1999; Fineberg et al., 2014; Robbins et al., 2012). In addition, substance use is repeated despite the delayed benefits of a healthy, drug-free lifestyle; repeated
behaviors are indicative of compulsivity and lack of foresight is indicative of impulsivity. Several studies have shown evidence of impulse-control deficits and compulsive behaviors in SUDs. For example, tasks that measure impulsive action such as go-nogo and stop signal reaction time in cocaine users (Castelluccio et al., 2013; Li et al., 2006), measures of impulsive choice such as delayed discounting task in heroin users (Kirby et al., 1999), as well as self-report measures of impulsivity and compulsivity (Everitt et al., 2008; Moeller et al., 2001; Koob 2009), denote the importance of understanding the relationship between impulsivity, compulsivity, and addiction. Moreover, tasks that assess cognitive flexibility, such as set-shifting paradigms and probabilistic reversal-learning tasks, have also demonstrated impairments in decision-making in individuals with SUDs (Dalley et al., 2011; Ersche and Sahakian, 2007; Goldstein and Volkow, 2011; Fineberg et al., 2014). This leads to a proverbial chicken-egg question: on one hand, impulsivity and compulsivity may represent vulnerability factors to onset of addiction, on the other hand, if these constructs occur as a result of addiction, they may be useful in predicting relapse, and thus, measures of decision-making could be useful clinical tools. The extent to which either or both of these considerations are true requires further research looking at the relationship between early risk factors and subsequent risk for relapse, taking into account both subcortical (bottom-up) and cortical (top-down) alterations before, during, and after initiation of the addiction cycle.

A model described by Whiteside and Lynam (2001) has taken a more granular approach to understanding the perceptual and behavioral traits of impulsivity. In this model, the traits (or dispositions), include: positive urgency, negative urgency, lack of planning, lack of perseverance, and sensation seeking (Dick et al., 2010). *Urgency* is the tendency to act from a high-valence emotional state, and is hypothesized to relate to performance or neurophysiological
measures of inhibitory control (Bechara & Van der Linden 2005), or the ability to suppress or stop maladaptive behaviors, such as excessive drinking (Dalley, Everitt, and Robbins, 2011). Indeed, urgency is particularly relevant to addiction as it has been shown to predict problem drinking (Dick et al., 2010; Smith et al., 2007; Fischer and Smith, 2008; Cynders et al., 2009). Furthermore, negative urgency, or the tendency to act rashly when experiencing extreme negative mood, fits our understanding of the allostatic model of addiction; dysphoria and risky decision-making are core contributors to relapse in the vicious cycle of addiction (Dick et al., 2010; Koob, 2013; Whiteside and Lyman, 2003;). Interestingly, urgency is also hypothesized to be captured by the attention subscale measure of the Barratt Impulsivity Scale (BIS; Patton et al., 1995; Dick et al., 2010). In line with the iRISA model of addiction, investigations of the neurobiological processes underlying impairment in inhibitory control (i.e. impulsivity) have highlighted dysregulation of the PFC as a major factor in SUDs (Jentsch and Taylor, 1999; Goldstein and Volkow, 2002, 2011; Bechara, 2005; Dalley, Everitt, and Robbins, 2011).

Similar to the balance of stress and reward, balance of executive function and impulsivity remain dysregulated following withdrawal from opioids. Long term opioid abuse causes anatomical changes in the PFC leading to decreased grey matter and deficits in executive function (Lyoo et al., 2006). These anatomical and functional changes attenuate executive function rendering the addict more susceptible to relapse (Bechara, 2005). More impulsive people are also thought to be pre-disposed to the initial stage of addiction i.e. anticipation/motivation (George et al., 2012). In addition, cognitive paradigms have shown that risky decision-making predicts abstinence in opioid use disorders (Passetti et al., 2008).

The ventromedial PFC (VMPFC) is critical in several components of decision-making such as cognitive branching and value calculation (Schonberg et al., 2012). Likewise, deficits in
VMPFC result in increased impulsivity, and there appear to be overlapping behaviors between individuals with SUDs and those with VMPFC damage (Bechara, 2005). For example, both display characteristics such as denial, lack of awareness (especially concerning consequences), and preference for immediate reward. More specifically, patients with VMPFC damage tend to recover normal intelligence and memory, but emotion and social behavior are altered, leading to financial losses, loss in job, and even loss of family and friends (Damasio, 1994; Bechara, 2005).

Remarkably, cognitive paradigms such as the Iowa Gambling Task (IGT) capture the overlapping deficits in decision-making between patients with VMPFC damage and patients with SUDs; both persist in making disadvantageous choices and show preference for short-term gain (Bechara, 2001; Grant et al., 2000; Passetti et al., 2008). Abnormalities in the VMPFC are likely common to all SUDs, and have been observed in opioid dependence (Badiani et al., 2012; Dalley, Everitt, & Robbins, 2011), alcohol dependence (Seo et al., 2013), and cocaine dependence (Badiani et al., 2012; Volkow et al., 2004), with specific deficits in decision-making linked to VMPFC function (Grant et al., 2000). Because of this linkage, several studies have tried to elucidate the relationship between substance use disorders (SUDs), impulsivity, and risky decision-making (Audrain-McGovern et al., 2009; Ayduk et al., 2000; Bickel, Odum, & Madden, 1999; Petry, 2005; for review see Bechara, 2001; 2005; Goldstein and Volkow, 2002; 2011).

Both the amygdala and VMPFC are critical in the decision-making process; the amygdala responds to events that occur in the environment (bottom-up processing), whereas the VMPFC relies on memories, knowledge and cognition (top-down processing; Bechara, 2005). During the decision-making process, numerous and conflicting signals may be triggered simultaneously, however stronger signals gain selective advantage over weaker signals (Bechara and Damasio,
In essence, when pondering a decision, the signal with the strongest reinforcement prevails (whether impulsive or reflective).

Neurological Drivers of Impulsivity

Impulsivity is characterized by rapid responses that lack reflection; executive functions normally act to supervise or filter impulsive behaviors. Anatomically, the basis for impulsive decision-making can be attributed, in part, to the dominance of signaling within the amygdala relative to dampened executive control via the PFC (Bechara, 2005). Responses triggered by the amygdala are short-lived and habituate very quickly (Büchel et al., 2000; Crews & Boettiger, 2009). Therefore, the amygdala's ability to drive impulsive decision-making is directly related to its key role in forming conditioned responses to aversive or appetitive stimuli (Balleine & Killcross, 2006). Furthermore, conditioning in the amygdala is thought to underlie drug craving triggered by people, places, and things associated with drug use (Weiss, 2005). Animal studies have shown that repeated drinking and withdrawal-abstinence cycles increase anxiety and negative affect; these effects are mediated by activation and subsequent neuroadaptation in the amygdala and extended amygdala (Breese et al., 2005; Koob, 2010; Richter et al., 2000). In addition, long-term neuroadaptations in the amygdala sensitize stress/anxiety signaling, which has been linked to negative reinforcement in severe SUDs, e.g., motivation to remove stress and dysphoria associated with withdrawal. Koob’s model describes this as the “dark side” of addiction (Koob, 2009; 2010). Conversely, studies have shown that suppressing corticotropin-releasing factor (CRF) in the amygdala reduces negative affect during withdrawal from morphine (Heinrich et al., 1995). In humans, neuroimaging studies have revealed amygdala hyper-activation in response to stimuli that induce craving (Breiter et al., 1997; Childress et al., 1999; Kilts et al., 2001). Overall, the amygdala is responsive to stress and cue-induced cravings and
plays a key role in anxiety signaling, which can influence behavioral responses to external stimuli. The amygdala mediates impulsivity, in part, through conditioned learning; however, it is only through an imbalance with reflective systems (e.g. PFC) that amygdala activity drives impulsive behaviors. Because of this, it is important that research on SUDs use sophisticated approaches to understand the dynamic among learning, emotion, and impulsivity, especially as these systems may affect treatment outcome in SUDs.

Although natural rewards such as food and positive social interaction have inherent emotional properties, money, a secondary reward, acquires emotional properties only through learning; consequently, monetary rewards have the ability to trigger affective response via the amygdala system (Bechara, 2005; Montague, 2002). Indeed, monetary rewards have no direct biological significance, however money can be used to obtain biologically relevant incentives, such as drugs (Lea & Webley, 2006). Similar to the effects of monetary gain, individual with SUDs display automatic and exaggerated amygdala-driven responses triggered by drug cues (Bechara, 2001). Indeed, several studies looking at neurological and behavioral evidence support the view that conditioned behavior to drug cues relates to abnormal activity in the amygdala (and ventral striatum) system, thereby increasing impulsivity and exaggerating the incentive value of substance-related cues (Everitt et al., 1999; Crews and Boettiger, 2009; Fineberg et al., 2014). In this way, the striatum and amygdala likely work in a bottom-up framework to increase motivation and impulsive (often risky) decision-making during drug seeking.

The Reflective System

If impulsivity is conceptualized as a quick response to stimuli, absent of inhibitory control, the reflective system can be thought of as a filter that weighs the options in lieu of acting immediately. Reflective decision-making depends on executive functions that control cognition
and affect. The DLPFC is essential for allocation of attention, behavioral inhibition, determining importance in the environment, and actively selecting goals (Abe & Hanakawa, 2009). The DLPFC, along with the hippocampus, is also critical in organizing, maintaining, and retrieving memories over a delayed period (Balconi, 2013; Bechara, 2004; Blumenfeld & Ranganath, 2006). Indeed, patients with damage to the DLPFC display deficits in judgement (Clark et al., 2004); consequently, addicts who have deficits in working memory also show deficits in judgement (Bechara and Martin, 2004; Martin et al., 2003). The impulsive behaviors demonstrated in SUDs lack reflection, compromising the ability to make decisions that are advantageous in the long term.

In some in stances decision-making is determined, in part, by affective patterns due to prior experience with reward and punishment; these affective state patterns develop in brainstem nuclei (e.g. parabrachial nuclei) and somatosensory cortices (e.g. insula, somatosensory, and posterior cingulate cortices; Damasio, 1994). There appear to be “hot” cognitions (influenced by affect), and “cold” cognitions (absent of affective influence). The VMPFC is a critical neural substrate in recall and planning based on affective states (Bechara, 2004). These processes depend on connections between the VMPFC, insula, and other somatosensory cortices involved in representing patterns of emotion (Damasio, 1994; Bechara, 2005). For example, patients with damage to the right insula and somatosensory cortex display impairments in decision-making (Bechara, 2004; 2005). In addition, lesions to the medial prefrontal/cingulate circuit, which is critical for feedback monitoring and motivation, result in profound apathy (Bonelli & Cummings, 2007). Damage to the VMPFC alters emotional/affective experience, and results in poor decision-making and abnormal social functioning (Bechara, 2004; Clark et al., 2004). Not
surprisingly, individuals with SUDs show functional abnormalities in the same regions when performing decision-making tasks (Ernst and Paulus, 2005; Goldstein & Volkow, 2011).

Impulsivity: Risk Factor, Relapse Predictor, or Both?

The literature reviewed in this section indicates that chronic substance abuse is associated with elevated impulsivity. However, two subjects remain unclear (1) to what extent does trait impulsivity predict the onset of SUDs, and (2) do measurements of impulsivity or risky decision-making predict treatment outcome? It appears that individuals with elevated trait impulsivity are more vulnerable to develop SUDs (Crews & Bottiger, 2009). This would imply a genetic component or predisposition; in favor of this view, Ersch et al. (2012) found that impaired response inhibition (i.e. elevated impulsive action) is present in first-degree relatives of people with stimulant use disorder, even if the relatives had no history of stimulant dependence themselves (2012). Moreover, longitudinal studies have found that, during development, elevated impulsive choice is associated with subsequent initiation of smoking (Audrain-McGovern et al., 2009); and drug use into adulthood some 20 years later (Ayduk et al., 2000). Elevated impulsivity appears to persist into recovery from alcohol and nicotine use disorders (Bickel, Odum, & Madden, 1999; Kohno et al., 2014; Petry, 2005). In addition, a study by Paessetti et al. (2008) used cognitive paradigms such as the Iowa Gambling Task and Cambridge Gambling Task to predict clinical outcome in opioid use disorders, however neither measure predicted at high specificity and sensitivity. It could be that there are heritable markers indicative of elevated impulsivity (and subsequent risky decision-making), which could be useful in (1) identifying people at risk for SUDs, and (2) identifying individuals in recovery that are at high risk for relapse.
The Balloon Analogue Risk Task

Assessing risky decision-making and its underlying neural substrates has proven to be a Janus-faced proposition for the field of neuroimaging. On one hand, cognitive paradigms that are designed/adapted for fMRI studies generally involve simple chance gambles that are relatively easy to interpret (Paulus et al., 2003; Kuhnen & Knutson, 2005; Preuschoff et al., 2006); however, naturalistic decision-making (reflecting real-life scenarios) is more complex and often influenced by affective states, learning, and escalating risk/reward propositions (Schonberg et al., 2012; Rao et al., 2014). Simple cognitive tasks translate well to neuroimaging studies because they attribute simple components of cognitive function to discrete brain regions. Chance gambles studies (i.e. simple risk taking) have identified subcortical regions involved with the components of risky decision-making; the anterior insula is involved in risk aversion and risk prediction (Paulus et al., 2003; Kuhnen & Knutson, 2005; Preuschoff et al., 2006), whereas the nucleus accumbens is involved in risk-seeking (Kuhnen & Knuston, 2005). Even though chance gamble studies have yielded useful information concerning the neural substrates of risk-taking in a vacuum, naturalistic risk-taking behavior, such as behavior that leads to substance use, is more complex. Unfortunately, chance gamble paradigms offer only moderate predictive value of naturalistic or real-world risk-taking behaviors (such as drug abuse, physically risky sports, or aggressive financial investment; Figner & Weber, 2011; Fox & Tannenbaum, 2011; Schonberg et al., 2011). Although there is limited evidence that these paradigms serve as predictors of naturalistic risk taking (Barsky et al., 1997; Pennings & Smidts, 2000; Brown et al., 2006; Jaeger et al., 2010), other studies have either found negative results (e.g., Brockhaus, 1980) or note that simple self-report about general risk propensity is a more consistent predictor of real-world risky decision-making (Dohmen et al., 2011).
The major limitation of using simple cognitive paradigms to understand addiction is that they may fail to evoke the anticipatory emotions accompanying naturalistic risky decisions, such as escalating tension and exhilaration. The Balloon Analogue Risk Task (BART; Lejuez et al., 2002) was designed to capture real-life tension via escalating risk/reward propositions. Behavioral results from the BART have been found to predict real-world risk-taking behaviors in adolescents (Lejuez et al., 2003b; 2007), nicotine use (Lejuez et al., 2003a), risky sexual behavior (Lejuez et al., 2004) and substance abuse (Lejuez et al., 2007; Bornovalova et al., 2005; Khono et al., 2014). A key component of the dynamic between escalating risk and reward is value calculation, i.e. weighing risk against reward during decision-making. Schonberg et al. (2012) used an fMRI version of the BART to show that activity in the VMPFC decreases with increasing risk (progressive balloon pumps) in healthy individuals, suggesting that increased risk actually decreases expected value. If risk and reward were not coupled in value calculation, one would expect increasing activity in the VMPFC in response to increasing potential reward, regardless of the risk involved. It is possible that the individuals with SUDs have reduced capacity to weigh risk/reward propositions, resulting in altered value calculation which might be measurable in the VMPFC (see Chapter 3 for further discussion).

BART performance and associated neural substrates may be predictive of treatment outcome in opioid dependent patients because (1) the BART models real-world risky decision-making, and (2) BART performance activates the VMPFC (Schonberg et al., 2012; Rao et al., 2008; 2014), an area of the brain that has previously been identified as a cortical marker associated with relapse risk in alcohol dependent patients (Seo et al., 2013). Predictive models using the BART have thus far been relegated to the cognitive, non-neuroimaging version of the task, although risk-taking propensity has been found to predict induction to naltrexone treatment.
in opioid dependent patients (Aklin et al., 2012). In addition, Holmes et al. (2009) found that individuals with comorbid bipolar disorder and alcohol abuse/dependence showed impaired performance on the BART compared to healthy controls. More specifically, bipolar participants had increased loss trials (balloon pops), suggesting that they engage in increased risky decision-making. Furthermore, individuals comorbid for bipolar and alcohol abuse/dependence failed to adjust their performance in response to negative feedback (balloon pops) when compared to controls or bipolar individuals without SUDs. This suggests that SUDs (such as alcohol abuse/dependence) may affect not only decision-making, but also the ability to modify one’s behavior in response to prior experience. Overall, neuroimaging versions of the BART may be superior to simple cognitive paradigms in capturing addiction-related alterations in PFC function, and could ultimately serve as a useful tool in predicting treatment outcome.

Summary

The literature reviewed in this introduction highlights the role of the prefrontal cortex in SUDs and identifies risk factors that increase the probability of relapse in opioid dependent individuals. Although there are conceptual differences, Koob and LeMoals’s allostatic model (2001), and Goldstein and Volkow’s iRISA model (2011) both conceptualize addiction as a progressive disease marked by poor decision-making, altered reward circuitry, and increased stress reactivity. Furthermore, both models describe opposing physiological systems, such as reward versus stress, or impulsivity versus reflection. In this way, addiction can be seen as an imbalance of neural systems that becomes exacerbated over time. Reward signaling, stress reactivity, and risky decision-making can be thought of as a triad of risk factors that lead to chronic relapse and continuation of the cycle of addiction. The data described in this thesis
address, to some extent, the role of this triad in early recovery from prescription opioid dependence. In particular, we were interested in elucidating the relationship between stress and risky decision-making, especially in regard to their predictive value as biological markers for risk of relapse.

In the following chapters, data will be presented from the Caron Study that examine anhedonia, stress, and impulsivity in recently withdrawn opioid dependent patients to identify markers, especially PFC responses, that are indicative of risk for relapse in the early stages of recovery. Furthermore we will integrate these results with current conceptualizations of addiction such as the iRISA model and Koob’s allostatic model. Overall, this study sought to increase our understanding of the biology and psychology of addiction in a way that provides relevant and utilitarian information to the clinical community, as well as the scientific community, to better serve those individuals suffering from prescription opioid dependence.

On the basis of this literature review, the initial, over-arching hypothesis for the study was that, in particular, objective measures of stress, anhedonia, impulsivity, and cue reactivity would predict treatment outcome in recovering opioid dependent individuals. These hypotheses were tested in a longitudinal study of opioid dependent patients undergoing long-term residential treatment, using both objective and subjective measures. Most notably, the study focused on post-withdrawal neural re-regulation; as such, the current thesis (which focuses on risky decision-making and stress), was integrated with results on affective states as a driver of relapse in prescription opioid dependence.
Approach: Specific Aim 1. To evaluate objective measures of stress in predicting treatment outcome from prescription opioid abuse. **Hypothesis:** Opioid dependent patients in extended-care residential treatment are expected to show a decrease in stress as treatment progresses; the degree to which stress hormones decrease over time will predict treatment outcome. Stress was measured in three ways 1) salivary cortisol measurements taken 5x daily for 3 consecutive days; 2) total sleep time as measured by actigraphy and subjective reports; 3) ecological momentary assessment (EMA) of daily stressors.

Specific Aim 2: To evaluate the presence of anhedonia during early recovery from opioid dependence. **Hypothesis:** Measurements of anhedonia will predict treatment outcome; high levels of anhedonia are expected to be associated with relapse, whereas low levels are expected to be associated with positive treatment outcome. This specific aim utilized functional near infrared spectroscopy (fNIR), acoustic startle response (ASR), and EMA to measure persistent post-withdrawal anhedonia.

Specific Aim 3: To evaluate the role of risky decision-making/impulsivity in recovery from opioid dependence. **Hypothesis:** Higher levels of risky decision-making will be related to increased risk of relapse. Risky decision-making and impulsivity were measured using the balloon analogue risk task (BART). fNIRS to was used to monitor the dorsolateral and ventromedial prefrontal cortex as a biological marker of risk taking.

This thesis addresses the specific aims with a particular focus on (1) targeting the neural substrates of risky decision-making as a predictor of treatment outcome, (2) delineating the role
of stress in risky decision-making, and (3) reregulation of the HPA-axis in treatment seeking, opioid-dependent patients. The results, presented in the following chapters, suggest that PFC activity during a risky decision-making paradigm was indicative of relapse risk. In addition, reward sensitivity during a risky decision-making task was associated with elevated neuroendocrine measures of stress, and diurnal measures of the HPA-axis appear to reregulate over a 4 month period. Importantly, the data presented in this thesis marks the first time that fNIRS has been used to identify risk for relapse in opioid dependent individuals.
CHAPTER 2

STUDY DESIGN
Methods

Summary of Data Bursts

All participants in the study underwent an initial screening session to assess psychiatric comorbidities, history of drug use, and personality traits. If participants met criteria for the study, they were asked to complete ecological momentary assessments (EMA) 4X daily for 12 consecutive days in addition to sleep monitoring via actigraphy. Within this 12 day period, participants also provided salivary cortisol samples 5X daily for three days, and underwent a neurophysiology session consisting of fNIRS and affect modulated acoustic startle response. We termed this 12 day period a “data burst” (see Figure 2.1). EMA and actigraphy data is not included in this thesis; in addition, we only included personality trait and symptom state measurements that were directly applicable to our hypotheses. A subset of patients (n=22) stayed for at least one month of extended residential treatment and underwent repeated measures at approximately day 45. Of these patients, an additional subset (n=12) stayed for three months of extended treatment and a third repeated measure was taken at approximately day 100 (see Figure 2.1 for breakdown of data burst). All healthy controls competed one data burst and an additional neurophysiology session 30 days later. Specifics, including participant criteria and measurements relevant to this thesis are described below.

Participants

Opioid dependent patients (ODPs; n = 76) were recruited from the Caron Treatment Center, a residential treatment facility in Wernersville, Pennsylvania (see Table 2.2 for specifics). Patient recruitment occurred approximately 10–14 days after entering treatment; patients completed
medically assisted withdrawal in the first 3-10 days. Data acquisition began approximately 15–25 days after entry into the treatment center (Figure 2.1). The study was approved by the Penn State Hershey Medical Center IRB, and all participants signed IRB-approved consent forms after a full explanation of procedures, prior to their engagement in the study. Patient inclusion criteria included: (1) capable and willing to comply with the research protocol; (2) met criteria for opioid dependence {Diagnostic and Statistical Manual for Mental Health Disorders – Fourth Edition – Text Revision (DSM-IV-TR; American Psychiatric Association, 2000), as determined by clinical staff at the Caron Foundation, and the Structured Clinical Interview for DSM-IV-TR (SCID; First et al., 2002), and Form-90D (Westerberg et al., 1998)}; (3) prescription opioids were the primary drug of choice; (4) over the age of 18; (5) staying in residential treatment for at least 30 days; (6) right handedness. Exclusion criteria included (1) any history of Bipolar I disorder, cyclothymia, schizophrenia or psychosis, as diagnosed by the SCID; (2) current major depressive disorder (MDD); 3) intravenous drug use; 4) history of traumatic brain injury; (5) current use of any opioid agonist (methadone or buprenorphine) or antagonist (Naltrexone). ODPs displaying current depressive symptoms, which are common in post-withdrawal ODPs, were allowed in the study as long as they did not meet criteria for MDD. Healthy controls (n = 40) were recruited at the Hershey Medical Center in Hershey, Pennsylvania. Control participants, matched for age and gender, had no history of drug or alcohol dependence, and no current DSM-IV-TR Axis I disorders (as determined by the SCID and Form-90D).
Questionnaire-Based Measurements

The Snaith–Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995) is a 14-item questionnaire designed to assess the relative capacity or incapacity to experience pleasure hedonic tone, or, conversely, anhedonia. Each item (e.g., “I would enjoy seeing other people’s smiling faces”) is rated on a 4-point Likert scale, labeled Strongly disagree, Disagree, Agree, or Strongly agree. With a total score of 0–14, higher total scores on the SHAPS indicate higher
levels of anhedonia. A cutoff score of 2 was established to identify which participants could be labeled as anhedonic (Franken et al., 2007 and Snaith et al., 1995). The SHAPS was designed to keep gender, age, and cultural biases to a minimum and the items refer to common experiences that are likely to be encountered by most people (Snaith et al., 1995). The scale has been shown to be highly reliable, with good internal consistency and test–retest reliability in both community and patient samples (Franken et al., 2007). It has also been demonstrated to correlate with related measures of affect and personality in a theoretically meaningful way. Patients with substance dependence, depression, and psychosis have been found to have higher scores on the SHAPS than non-patient controls (Franken et al., 2007). Convergent validity derives from correlations with the Hedonic Tone item on the Montgomery Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979), the Anhedonic Depression subscale on the Mood and Anxiety Symptom Questionnaire, and the Positive Affect subscale from the Positive and Negative Affect Schedule (Franken et al., 2007, Gilbert et al., 2002 and Snaith et al., 1995). Its discriminant validity has been supported by its lack of association with MADRS Depressed Mood and Anxiety items (Franken et al., 2007 and Snaith et al., 1995).

Upon entering the study, participants also completed the Barratt Impulsiveness Scale (Barratt et al., 1975). The Barratt Impulsiveness Scale consists of three 2nd order subscales: non-planning, self-control, and cognitive complexity. These subscales measure specific aspects of trait impulsivity. There is high comorbidity of impulsivity and psychiatric disorders including substance abuse; summary scores have previously been associated with the biological substrates of psychiatric disorders (Moeller et al., 2001). In order to determine current depressive symptoms (likely associated with post-withdrawal syndrome) we used the Hamilton-Depression
Rating Scale (Ham-D; Hamilton, 1960). The Ham-D gauges levels of current depression from *mild* to *very severe*.

**Cortisol Measurement via ELISA**

Salivary cortisol is considered a reliable and valid measure of unbound plasma cortisol, and provides a direct and non-invasive measure of HPA-axis activity (Vinning & McGinley, 1987). Participants provided saliva samples using the Salivette sampling device (Sarstedt, Rommelsdorf, Germany). Saliva collection occurred at five points throughout the day (7 AM, 11:30 AM, 2 PM, 5 PM, and 9 PM) for three consecutive days; the third day corresponded with the neuroimaging session. Saliva was held at −20 °C until time of analysis. Cortisol levels were measured via saliva samples for each time-point. For analysis, salivary samples were thawed and centrifuged at 2000G for five minutes. Samples were then analyzed via enzyme-linked immunosorbent assay (ELISA; ALPCO Diagnostics, Salem, NH, USA).
All participants completed a standard visual cue reactivity paradigm while being monitored with fNIRS. Stimuli (see Fig. 2.2) consisted of three categories of hedonically positive stimuli – highly palatable food, positive social interactions (e.g., a happy family at the dinner table), and emotional intimacy (couples embracing or kissing, but no erotic images), as well as emotionally neutral stimuli. Natural reward and neutral images were selected from the IAPS (Lang et al., 2008). Images were presented on a 16 in monitor (75 Hz refresh rate) using E-Prime software (Psychology Software Tools Inc., PA). Stimuli of drug cues (e.g. prescription opioids; Figure 2.2) and hedonically positive stimuli were presented. Drug cues were either created by the PI (S.C.B.) or chosen from an internet search results, and validated by a panel of recovering addicts. Stimuli were presented in 25 s blocks comprised of 5 pictures from a single category,
each displayed for 5 s. The order of images within blocks and the order of blocks within the experiment were randomized for each individual. A black screen with a crosshair in the center was shown for 10 s between blocks.

Functional near-infrared spectroscopy measures regional changes in cerebral blood flow (an indirect measure of neural activity) by detecting infrared light spectra for oxygenated and deoxygenated hemoglobin (e.g. Villringer & Chance, 1997; for recent reviews see Ferrari & Quaresima, 2012; Scholkmann et al., 2014). In the current study, data were recorded using a continuous wave system (fNIR1100, fNIR Devices, LLC, USA) and a 4 × 10 (4 LED light sources and 10 photodetectors) optode set yielding 16 channels. Hemodynamic response was recorded during each 25 second block (positive, drug cue, and neutral). Sensors were located by aligning the bottom row of optodes with the International 10–20 sites F7, FP1, FP2, F8 line (Jasper, 1958). This placement situated the sensor over bilateral rostral prefrontal cortex (Brodmann Area 10) and ventrolateral prefrontal cortex (Okamoto et al., 2004).

All participants provided self-reported craving scores on a 100-point Likert scale before and after being confronted with drug cues. Questions included (1) How much do you want to use right now? (2) How much do you want to avoid using right now? (3) How much control do you feel you have over using right now?

**Balloon Analogue Risk Task**

The Balloon Analogue Risk Task (BART) was modified in MatLab™ for use with an fNIR system; this protocol was used by Cazzell et al. (2012) and was originally adapted from the BART paradigm used in a previous fMRI study (Rao et al., 2008). This version of the BART
paradigm included two modes of the risky decision-making task: an active mode wherein the participant is actively pumping the balloon and a passive mode wherein the computer has control of the balloon (no active pumping; see Figure 2.3). The probability of balloon explosion (for either mode) was randomly selected by the program for each trial. There was a maximum of 12 inflations possible for each trial. The current study replicated the fNIR-BART protocol from Cazzell et al. (2012) [originally from Rao et al., (2008)], concerning information on risk of explosion, actual probability of explosion, value of winnings (wager), and reward variance associated with balloon inflation (Table 2.1). Previously, studies collecting BART data measured the following: (1) total number wins in active mode, (2) total number losses in active mode, (3) average adjusted-win: inflations in active mode that led to a win (average number of pumps per balloon excluding losses); and (4) average adjusted-loss: inflations in active mode that led to a loss (average number of pumps per balloon excluding wins; Cazzell et al., 2012; Lejuez et al., 2002; Rao et al., 2008).
Prior to the start of the study, the following instructions were read to each participant to ensure consistency in BART participation:

"Thank you for participating in the research study. In this part of the study, your task is to blow up a balloon without letting it pop. Each time you press “continue” with the mouse, the balloon will grow larger, and your reward (in virtual dollars) will increase incrementally. At the same time, the probability that the balloon will pop (in which case you receive no reward) also increases incrementally. The dollar amount gained and the probability of a popped balloon both increase with every pump. Press “stop” when you want to cash out a balloon and continue to the next one.

A couple of things to note: every time you press “continue” there is a one second pause (the icon turns gray) where the balloon cannot be pumped again. Also, try to move as little as possible while performing this task.

Table 2.1: Adapted from Rao et al., (2008): Balloon Analogue Risk Task; the risk of explosion (probability set by the program), the actual probability of explosion, the value of wager, and the reward variance associated with each balloon inflation.
During the passive version of the task you will push start but the balloon will pump up on its own; you have no control over when it stops.

The goal of this task is to gain as much virtual money as possible.

Are there any questions?”

Participants were asked to close their eyes for two minutes prior to initiation of the BART protocol, in order to take baseline measurements. Presentation of active and passive mode was counterbalanced to account for order effects. Both active and passive modes consisted of 20 trials. Each trial began when the participant initiated inflation of the balloon. In the passive version, the program took control over the pumping of the balloon at this point. In the active version, the participant actively pumped the balloon but there was a one second off time i.e. they had to wait one second in between pumps. The end of each trial was marked by either and the balloon popping (You Lose!!), or the participant choosing to stop and thus cashing out the balloon (You Win!!; Figure 2.3). It took about 5 seconds for the participants to make the decision and/or observe the outcome (either win or lose) on the computer screen.

Resting state PFC signal was recorded via fNIR for two minutes prior to initiation of the BART protocol in order to take baseline measurements. Presentation of active and passive conditions were counterbalanced to account for order effects. Both active and passive modes consisted of 20 trials. Each trial began when the participant initiated inflation of the balloon. In the passive version, the program took control over pumping the balloon (one second off time between pumps), and participants passively viewed the escalating risk/reward proposition. Hemodynamic response was recorded from initiation to termination of each behavioral and
passive block. In the active version, participants actively pumped the balloon although they had to wait for one second between pumps. The end of each trial was marked by either the balloon popping (You Lose!!), or the participant choosing to stop and thus cashing out the balloon (You Win!!). Hemodynamic response was measured following each trial outcome; measurement began at 2 seconds post outcome and lasted until 8 seconds post outcome to determine the participant’s reaction to gain/loss of monetary reward. After completing each trial, the participant had a 15-second recovery time to allow hemodynamic response to return to baseline (for more information see Cazzell et al., 2012). Overall, it took approximately 20 s to finish one block (trial plus rest) and approximately 15 minutes to complete both active and passive conditions of the BART.

![Figure 2.3: Image adopted from Cazzell et al., 2012. Example of visual stimuli (a) following a winning trial, and (b) following a losing trial.](image)

\textit{fNIRS Signal Processing}
fNIR data were processed using a software suite developed at Drexel University and implemented in Matlab (The Mathworks, Inc., Sherborn, MA). Raw light intensity data from the 16 optodes and two wavelengths were low-pass filtered with a finite impulse response, linear phase filter with order 20 and a cut-off frequency of 0.1 Hz to attenuate high frequency noise, respiration and cardiac cycle effects (Ayaz et al., 2011). All data were inspected for potential saturation (when light intensity at the detector is 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 data for each task block were extracted and hemodynamic changes for each of the 16 optodes were calculated separately for each block using the Modified Beer Lambert Law. The final output of each optode was mean deoxygenated hemoglobin (HbR), mean oxygenated hemoglobin (HbO2), and mean total hemoglobin (Total Hb) calculated for each stimulus type, palatable food, positive social interactions, and emotional intimacy, and hedonically neutral stimuli. Analyses in this study were calculated using mean HbO2.

Affect Modulated Acoustic Startle Response

Affect-modulated acoustic startle response (AMSR), a well-known psychophysiological measure of emotional valence (Lang 1995; Bradley et al., 1999), was used to assess the participant’s hedonic responses to standardized reward-related stimuli. Participants viewed 12 pictures in each of four categories. Three categories, emotionally positive, negative, and neutral stimuli, were drawn from the International Affective Picture System (IAPS; Lang et al., 2008). Stimuli for the fourth category, drug-related images, were created by authors AH & SB (responses to be reported in a separate paper). Stimulus order was randomized for each individual, and no stimuli were shared with the cued-reactivity task. The acoustic startle probe, a
50-ms burst of 104 dB white noise with instantaneous rise time, was presented at variable points during the 6-second slide viewing period, ranging from 3.5 to 5.5 s after slide onset. The probe was presented on 9 of the 12 slides for each type, and four startle probes were presented in the intervals between picture presentations to minimize predictability. Startle probes were presented binaurally through stereo headphones with presentation and timing of stimuli controlled by E-Prime software (Psychology Software Tools Inc., PA). The eye-blink component of the startle reflex was measured by recording electromyographic (EMG) activity from 4-mm Beckman miniature Ag/AgCl electrodes positioned over the orbicularis oculi muscle beneath the left eye. Startle responses were standardized within participants; Z scores for each participant were compared by condition (positive, negative, neutral). Two ODP and one control were nonresponders (i.e., no reliable startle response was detected), and were excluded from further analysis, and one ODP patient was excluded due to technical difficulties.

**Outcome Follow-up**

Upon leaving residential treatment, patients were followed for 90 days to determine relapse status. Of the 65 original patients, 8 patients did not provide any follow-up information. The remaining 57 were followed to determine return to any substance use. 49 ODPs were confirmed as abstinent or relapse to opioids (see Table 3.2 for breakdown and relapse rates). Because patients come to the Caron Treatment Center from across the United States, ODPs were tracked on a weekly basis via phone-call (patients also provided the name of an alternate contact if they could not be reached). In addition, patients were asked to provide two hair samples (at 30 and 90 days) while in the community at their local Quest Diagnostics Center; a 5-panel opioid screen was performed on each sample (Quest Diagnostics; Madison, NJ). As a further measure of
treatment outcome (or in the case of missed appointments), Caron Treatment Center provided research staff with urinalysis results from its Recovery Care Services. Patients with outcome data were either placed in sober living environments (SLEs; e.g. half-way house) where they had access to the community (and thus, a chance to relapse), or, went home with recommendation for outpatient therapy (Table 3.2).

**Demographics**

**Table 2.2:** Demographics for all Caron patients included in the NIDA study. *We were not able to determine treatment outcome (relapse or abstinent) for 19 patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Full Sample</th>
<th>Abstinent</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years (mean, SD)</td>
<td>μ= 29.8</td>
<td>σ= 10.0435</td>
<td>μ= 28.08</td>
</tr>
<tr>
<td>Education, years (mean, SD)</td>
<td>μ= 14.3</td>
<td>σ= 4.97197</td>
<td>μ= 14.56</td>
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<tr>
<td><strong>Treatment Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Patient Care Only (N, %)</td>
<td>N= 55</td>
<td>% = 72.37%</td>
<td>N= 28</td>
</tr>
<tr>
<td>Extended Patient Care</td>
<td>N= 21</td>
<td>% = 27.63%</td>
<td>N= 9</td>
</tr>
<tr>
<td>Routine Discharge</td>
<td>N= 72</td>
<td>% = 94.74%</td>
<td>N= 37</td>
</tr>
<tr>
<td>Discharge Placement Unknown</td>
<td>N= 1</td>
<td>% = 1.32%</td>
<td>N= 0</td>
</tr>
<tr>
<td>Discharge Placement Home</td>
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<td>% = 13.16%</td>
<td>N= 2</td>
</tr>
<tr>
<td>Discharge Placement Home/OP</td>
<td>N= 10</td>
<td>% = 13.16%</td>
<td>N= 6</td>
</tr>
<tr>
<td>Discharge Placement Home/OtherOP</td>
<td>N= 12</td>
<td>% = 15.79%</td>
<td>N= 5</td>
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<tr>
<td>Discharge Placement SLF</td>
<td>N= 43</td>
<td>% = 56.58%</td>
<td>N= 24</td>
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<tr>
<td>Discharge Placement - Transfer to Renaissance</td>
<td>N= 8</td>
<td>% = 10.53%</td>
<td>N= 8</td>
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<tr>
<td>Vivitrol @/prior to Discharge</td>
<td>N= 9</td>
<td>% = 11.84%</td>
<td>N= 5</td>
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<tr>
<td>Chronic Pain</td>
<td>N= 22</td>
<td>% = 28.95%</td>
<td>N= 10</td>
</tr>
</tbody>
</table>

**Mental Health**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Full Sample</th>
<th>Abstinent</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime MDD</td>
<td>N= 14</td>
<td>% = 18.42%</td>
<td>N= 5</td>
</tr>
<tr>
<td>HAM-D (mean, SD)</td>
<td>μ= 10.9</td>
<td>σ= 5.77</td>
<td>μ= 8.95</td>
</tr>
<tr>
<td>MDD</td>
<td>N= 14</td>
<td>% = 18.42%</td>
<td>N= 5</td>
</tr>
<tr>
<td>Dysthymic</td>
<td>N= 5</td>
<td>% = 6.58%</td>
<td>N= 3</td>
</tr>
<tr>
<td>Condition</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>----</td>
<td>-----</td>
<td>----</td>
</tr>
<tr>
<td>Depression NOS</td>
<td>23</td>
<td>30.26%</td>
<td>13</td>
</tr>
<tr>
<td>Mood Due to Medical</td>
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<td>1.32%</td>
<td>0</td>
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<tr>
<td>Substance Induced Mood</td>
<td>9</td>
<td>11.84%</td>
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</tr>
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**Drug Use/Substance Abuse History**

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**Days use in 30 days before treatment**

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CHAPTER 3

 PREFRONTAL CORTEX ACTIVITY DURING A RISKY DECISION-MAKING TASK PREDICTS TREATMENT OUTCOME IN PRESCRIPTION OPIOID DEPENDENT PATIENTS: A STUDY USING FUNCTIONAL NEAR-INFRARED SPECTROSCOPY
There is strong evidence that the human experience of addiction is greatly influenced by impaired executive function such as deficits in behavioral inhibition, and ultimately, a propensity for risky decision-making (Bechara, 2005; Brand et al., 2008; Goldstein and Volkow, 2002; 2011; Kohno et al., 2014). The impaired response inhibition and salience attribution (iRISA) model of addiction highlights the role of the prefrontal cortex (PFC) in (a) excessive salience to drug and drug-related cues, (b) decreased sensitivity to non-drug reinforcers, and (c) reduced ability to inhibit maladaptive behaviors (Goldstein and Volkow, 2002; Goldstein and Volkow, 2011). Indeed, individuals in withdrawal or early abstinence from opioids display decreased response in the PFC to non-drug related reward cues compared to healthy controls (Bunce et al., 2015; Huhn et al., 2015; Ziljstra et al., 2009). In addition, extreme motivation to seek and take drugs often culminates in extreme behaviors that are detrimental to the both the individual and the community (Volkow and Li, 2004). Whether risky decision-making leads to (Ayduk et al., 2000; Crews and Bottiger, 2009; Ersch et al., 2012; Kreek, 2005) or stems from the onset of substance use disorders (SUDs), propensity for risky decision-making contributes to risk for relapse in opioid dependence (Kreek, 2005; Passetti et al., 2008; 2011).

The field of addiction has given much attention to the relationship between impairment of inhibitory control and dysregulation of the PFC (Jentsch and Taylor, 1999; Goldstein and Volkow, 2002, 2011; Bechara, 2005; Dalley, Everitt, & Robbins, 2011). Specific to opioid abuse, anatomical changes in the PFC such as decreased grey matter are associated with deficits in executive function (Lyoo et al., 2006). Executive function is critical to decision-making and response inhibition, and damage to areas such as the ventromedial PFC (VMPFC) leaves individuals more susceptible to relapse (Bechara, 2005). Abnormalities in VMPFC function are likely common to all SUDs, and have been observed in opioid dependence (Badiani et al., 2012;
Dalley, Everitt, & Robbins, 2011), alcohol dependence (Seo et al., 2013), and cocaine dependence (Badiani et al., 2012; Volkow et al., 2004), with specific deficits in decision-making linked to VMPFC function (Grant et al., 2000). Because of this linkage, several studies have tried to elucidate the relationship between SUDs, impulsivity, and risky decision-making (Audrain-McGovern et al., 2009; Ayduk et al., 2000; Bickel, Odum, & Madden, 1999; Petry, 2005; for review see Bechara, 2001; 2005; Goldstein and Volkow, 2002; 2011).

Even though gambling and behavioral inhibition studies have yielded useful information concerning SUDs, naturalistic risk-taking behavior is more complex in nature. The Balloon Analogue Risk Task (BART; Lejuez et al., 2002) was designed to capture real-life tension via escalating risk/reward propositions. Behavioral results from the BART have been found to predict real-world risk-taking behaviors in adolescents (Lejuez et al., 2003b; 2007), nicotine use (Lejuez et al., 2003a), risky sexual behavior (Lejuez et al., 2004) and substance abuse (Lejuez et al., 2007; Bornovalova et al., 2005; Khono et al., 2014). A key component of the dynamic between escalating risk/reward propositions is value calculation, i.e. weighing risk against reward during decision-making. Schonberg et al. (2012) used a functional magnetic resonance imaging (fMRI) version of the BART to show that activation in the VMPFC is indeed involved in value calculation. Other imaging studies have also shown that the BART captures response to rewards and losses in healthy (Cazzell et al., 2012; Rao et al., 2008; 2014) and methamphetamine-dependent individuals (Kohno et al., 2014).

Self-report measures have not been reliable predictors of treatment outcome in ODPs (e.g., Dijstra et al., 2008); however, individuals with opioid dependence have high rates of comorbid depression (Havard et al., 2006). Symptoms of depression including anhedonia persist after withdrawal (Huhn et al., 2015; 2016; Koob, 2013), and are thought to increase vulnerability
to relapse (Kosten et al., 1986). It is likely that post-withdrawal depressive symptoms affect cognitive function in opioid dependent individuals, and may exacerbate the propensity for risky decision making associated with relapse in the early stages of recovery from opioid dependence.

Recent evidence suggests that lower gray matter volume (Rando et al., 2011; Sinha, 2011), response to neutral cues (Seo et al., 2013), and response to alcohol-related cues (Grusser et al., 2004) predict time to relapse in the first 3 months of recovery among alcohol dependent patients. In cannabis dependent patients, activity in the ventrolateral PFC (VLPFC) during the Stroop-task was associated with abstinence at 1-year follow-up (Kober et al., 2014). Previous studies have also found that residential treatment ameliorates cortical hypoactivations in inhibitory control tasks in abstinent cocaine dependent individuals (Balodis et al., 2016; Bell et al., 2014; Moeller et al., 2012).

Although the PFC has been identified in several studies as a biomarker of treatment outcome, there is a paucity of literature looking at this biomarker in prescription opioid dependent patients. In addition, even though fMRI studies provide a wealth of knowledge concerning addiction-related neural activity, most addiction treatment centers exist apart from neuroimaging facilities, making it difficult if not impossible to apply this technology in most clinical settings. Functional near-infrared spectroscopy (fNIRS) is a neuroimaging tool that can be readily deployed in clinical settings and offers a similar profile of neural activity in the PFC relative to fMRI. Because of this, the current study used an fNIRS version of the BART (Cazzell et al., 2012) to assess risky decision-making in patients seeking residential treatment for prescription opioid dependence. We postulated that PFC activity would differ in regions associated with reward, behavioral inhibition, and value calculation. Furthermore, and most
importantly, we hypothesized that neural activity in the VMPFC during the BART would be a robust predictor of relapse in the first three months post-discharge. This study is an important step in using clinically applicable neuroimaging techniques to predict treatment outcome in ODPs.

**Methods**

*Overview*

These analyses were performed on the subset of participants that completed the BART protocol described in Chapter 2. This subset includes prescription opioid dependent patients (ODPs; n = 65) and healthy controls (HC; n = 31; for demographics see Table 3.1.) in the first data burst. All participants underwent the fNIRS-BART paradigm, as well as self-report measures of trait impulsivity (Barratt Impulsivity Scale) and current depressive symptoms (Ham-D; see Chapter 2 for details). ODPs were followed for three months post-discharge to determine treatment outcome; we were able obtain outcome data from 57 ODPs regarding return to any substance use and 49 ODPs regarding relapse to opioid use.
Chi square and independent sample Student’s t-tests were used to test for differences in gender and age among groups (Table 3.1). Independent Student’s t-tests were used to test for group differences on the Barratt Impulsiveness Scale (Barratt et al., 1975), and BART behavioral and neuroimaging data by optode (Figures 3.2 and 3.3). To correct for Family-Wise error, imaging data was considered significant at p<.01 in a single optode, or p<.05 on three or more conjoining optodes, or p<.05 in a priori regions of interest (ROI) identified from previous fNIR adapted BART studies (Cazzell et al., 2012) and fMRI adapted BART studies (Rao et al., 2008; Schonberg et al., 2012; Khono et al., 2014). Active and passive conditions of the BART were baseline corrected; mean change in HbO₂ was calculated during the decision-making process i.e. active or passive pumping as well as in reaction to the win/loss event. The passive version was
subtracted from the active version to isolate areas of the PFC responsible for behaviorally driven decision-making and response to active win/loss trials.

Prediction of treatment outcome was performed by discriminant function analysis including leave one out cross validation, a technique that pulls individuals out one by one and predicts outcome based on the rest of the group. For any subgroup that did not achieve over 80% specificity and sensitivity (requirement of biomarkers for clinical trials) on leave one out validation, binary logistic regression was used to examine predictive value within the group (Table 3.2). In general, no more than 1 variable were used for every 10 cases (Agresti, 2007; Vittinghoff & McCulloch, 2007; Table 2). Finally, Cox regression was performed on the relapse to opioids group to determine hazard ratios for time to relapse (Figure 3.1.). All statistical analyses were conducted with SPSS 21.0.0 (IBM SPSS Statistics).

Results

Patients versus Controls

Patients scored significantly higher on the Barratt Impulsivity (Table 3.1). Controlling for nicotine use and attention deficit hyperactivity disorder (ADHD), scores on the Barratt Impulsivity Scale cognitive complexity subscale were correlated with neural activity in response to a winning trial in the left DLPFC, r(65)=.437, p=.002, in ODPs, but the opposite association was found in controls, r(31)=-.428, p=.067 (Figure 3.4). Similarly, cognitive complexity scores were correlated with response to a losing trial in right DLPFC in ODPs, r(65)=.281, p=.05; again, the opposite association was found in controls, r(31)=-.575, p=.01.
During the passive condition (Figure 3.2), ODPs displayed increased neural activity in the left DL/VLPFC while passively viewing the decision-making task, and in reaction to a loss. Patients also displayed increased activity in the left DL/VMPFC in reaction to a win. In the active – passive condition (Figure 3.2), patients displayed increased activity during decisions leading to a reward in the right VLPFC, and reaction to a win in the right VMPFC, but showed decreased neural activity in the left DLPFC in reaction to a loss. In addition, patients had significantly more losses in the active version of the BART (M=9.48; SD=3.49) compared to controls (M=7.88; SD=3.05; p=.001), even though patients had a lower number of average inflations (M=5.09; SD=.51) than controls (M=5.41; SD=.69; p=.0001).

<table>
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<th>Leave-One-Out Cross-Validation</th>
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<tr>
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<td>Sensitivity</td>
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<tr>
<td></td>
<td>Return to Any Substance (n=57)</td>
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</tr>
<tr>
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<td>Discharge Placement</td>
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<tr>
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<td>Sober Living Environment (n=31)</td>
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<tr>
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</tr>
<tr>
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</table>

Table 3.2: Neural activity in the following regions/conditions to predicted relapse to opioids and/or return to any substance: ventromedial PFC (vmPFC) while making decisions (optode 10), in response to a win (optode 10), and in response to a loss (optode 9) as well as dorsolateral PFC (dLPFC) activity in response to a loss (optode 9).
Relapse to Opioids versus Abstinent Patients

Current depressive symptoms, measured by the Ham-D, were higher in those that relapsed to opioids in the first three months post-discharge compared to those who abstained, $t(49) = -2.258, p=.029$. In the active – passive condition (Figure 3.3.), patients that relapsed to opioids displayed increased neural activity in the right VMPFC while actively pumping the balloon, and in reaction to a loss (right VMPFC and left DLPFC), but displayed decreased activity in right VMPFC in reaction to a win. PFC activity was used to predict binary treatment outcome for relapse to opioids, return to any substance, and subgroups that either went on to a SLE or went home and may have participated in outpatient therapy (see Table 3.2 for breakdown of relapse rates and details). ODPs that went to SLEs (n=25) relapsed to opioids at a lower rate than those that went home/outpatient therapy (n=24), $X^2 (1, N=49) = 7.87, p=.005$. ODPs entering SLEs (n=31) also had lower rates of return to any substance use relative to ODPs that went home (n=26; $X^2 (1, N=49) = 6.22, p=.013$). Depressive symptoms, as measured by the Ham-D, did not add to either binary linear regression or discriminant function analysis in predicting binary treatment outcome in the first 90 days post-discharge.

Three biological variables were used to predict time to relapse: neural activity in the VMPFC during decision-making and in response to a win, and neural activity in the DLPFC in response to a loss, $X^2 (2, N=49) = 12.74, p=.005$ (see Figure 3.3). Furthermore, Ham-D scores independently predicted time to relapse in a Cox regression model, $X^2 = 7.815, p = .005$, Hazard Ratio (HR) = 1.152, 95% CI, 1.043-1.271. Combining Ham-D scores with the biological variables had a synergistic effect, such that prediction of time to relapse was improved, $X^2 (2,$
N=49 = 22.88, p<.001. No other personality traits were significant predictors of relapse risk in this study. Scores on the Barratt Impulsivity Scale did not predict treatment outcome.

Figure 3.1: Survival analyses were run on the top three predictor variables: decision-making in the right vmPFC $X^2 = 9.365$, p = .002, Hazard Ratio (HR) = 2.14, 95% CI, 1.32-3.48; reaction to winning trials in right vmPFC $X^2 = 4.329$, p = .037, Hazard Ratio (HR) = .61, 95% CI, .38 -.97; reaction to loss in the left dIPFC $X^2 = 6.15$, p = .01, Hazard Ratio (HR) = 2.79, 95% CI, 1.28-6.08. ROC curve shows the unique contribution of each predictor to sensitivity and specificity, and the subsequent model.
Figure 3.2: Comparison of prefrontal cortex (PFC) activity between opioid dependent patients (ODPs) and healthy controls. In the passive version of the BART, (A) ODPs displayed increased neural activity while passively viewing the decision-making task i.e. the computer was pumping the balloon ($t(96) = -2.131; p = .037$). (B) ODPs had increased neural activity in reaction to a winning trial ($t(96) = -3.515; p = .001$). (C) ODPs had increased neural activity in reaction to a losing trial ($t(96) = -3.775; p = .001$). In the active–passive condition, (D) ODPs displayed increased activity during decisions leading to a reward ($t = -2.091; p = .041$). (E) ODPs displayed increased activity in reaction to a win ($t = -3.092; p = .003$). (F) ODPs displayed decreased neural activity in reaction to a loss ($t = 2.021; p = .047$).
Figure 3.3: Comparison of PFC activity in the active version of the BART (subtracting the passive version) in ODPs that relapse to opioids and those that remain abstinent. (A) Relapsing patients displayed increased neural activity when making a decision that lead to reward ($t = -3.176; p = .003$). (B) Relapsing patients displayed increased activity in reaction to a loss trial ($t = -2.336; p = .025$). (C) Relapsing patients displayed decreased activity in reaction to a winning trial ($t = -2.348; p = .025$). (D) Relapsing patients displayed increased activity while actively pumping the balloon ($t = -3.066; p = .006$).
Discussion

One of the primary issues in treating prescription opioid dependence is determining relapse risk and subsequent level of care in patients seeking residential treatment. This study used a clinically applicable neuroimaging tool, fNIRS, to identify neural correlates of relapse in recently withdrawn ODPs. Interestingly, PFC activity during the BART was accurate in determining relapse to opioids at 87.8% correct classification (Table 3.2). These data suggest that PFC activity during a risky decision-making task may serve as a biomarker in assessing risk for relapse. Building on this finding, a survival analysis on PFC variables in the relapse to opioids group also predicted time to relapse. Similarly, depressive symptoms, as measured by the Ham-D also predicted time to relapse. The hazard ratio for this model (1.152) can be interpreted as a 15% increase in risk of relapse for every 1 point increase on the Ham-D. Combining depressive symptoms with the PFC correlates of risky decision-making had a synergistic effect on the survival analysis thereby increasing the significance of the Cox regression model; this effect was not found in predicting binary treatment outcomes. Given that our prediction model using PFC activity was robust for the entire relapse group, regardless of aftercare placement or numerous other factors that can affect relapse rates, our results are likely generalizable to a larger prescription opioid dependent population. In addition, we were able to identify neural correlates of relapse to opioids and return to any substance within groups that were placed at home with recommendation for outpatient therapy. Our model, using the PFC as a biomarker, could be applied in a clinical setting to provide objective feedback to patients and inform clinicians in determining appropriate next-level of care placement.
Neuroimaging adaptations of the BART have increased our understanding of value
calculation and response to reward or loss of reward in a naturalistic decision-making paradigm
(Rao et al., 2008; Schonberg et al., 2012); however, this is the first study to date that uses the
BART to assess these constructs in ODPs and uses neuroimaging results to predict treatment
outcome. Although the passive version of the BART has been shown to activate parietal areas in
healthy individuals (Rao et al., 2008), we found that ODPs show increased neural activity in the
left PFC (see Figure 1), suggesting that recovering ODPs may attribute increased reward value or
allocate increased attention to involuntary risk taking. Furthermore, ODPs display increased
activity in the right VLPFC during the behavioral part of the task, just inferior to similar studies
that looked at neural substrates of risky decision-making in healthy controls (Rao et al., 2008)
and in methamphetamine dependent patients (Kohno et al., 2014), although the latter related
risk/reward sensitivity in this area to connectivity with the striatum. Compared to healthy
controls, ODPs display altered reward sensitivity in the right VMPFC and left DLPFC; both
areas have been related to reward sensitivity in an fNIR-BART study looking at gender
differences in healthy individuals (Cazzell et al., 2012). Furthermore, correlations between trait
impulsivity and reaction to reward/loss were opposite for ODPs and HCs (Figure 3.4). Whether
these differences are attributable to pre-existing trait impulsivity or the long-term effects of
opioid dependence remains unclear, however, it appears that the relationship between reward
sensitivity and trait impulsivity is fundamentally different in ODPs in the early stages of
recovery.
Figure 3.4: Scores on the Barratt Impulsivity Scale cognitive complexity subscale were correlated with neural activity in response to a winning trial in the left dlPFC, \( r(65)=.437, \ p=.002 \), in ODPs (upper right), but the opposite association was found in controls, \( r(31)=-.428, \ p=.067 \) (upper left). Similarly, response to a losing trial was correlated with activity in right dlPFC in ODPs, \( r(65)=.281, \ p=.05 \) (lower right); but the opposite association was found in controls, \( r(31)=-.575, \ p=.01 \) (lower left).
Although the juxtaposition between ODPs and healthy controls is informative, understanding differences in neural processing in ODPs that relapse versus those that remain abstinent is an important step in assessing relapse risk in this population. In line with the iRISA model of addiction, insensitivity to non-drug reinforcers (such as monetary gain) and the inability to inhibit maladaptive behaviors is exacerbated during the cycle of addiction (Goldstein & Volkow, 2002; 2011); this study is an effort to identify PFC substrates of these constructs that differentiate ODPs at high risk for relapse from those that are likely to remain abstinent. In the current sample, differences were relegated to the right VMPFC and left DLPFC (Figure 2), and may reflect altered value calculation and reward sensitivity in ODPs that relapse to opioids. The VMPFC has previously been associated with value calculation (Rushworth et al., 2011; Schonberg et al., 2012), and seems a likely target in future neuroimaging studies that seek to predict relapse in SUDs (Seo et al., 2013). Previous studies have shown that increased PFC activity during the BART is associated with decreased striatal D2/D3 receptor binding (Kohno et al., 2015); this extends preclinical and neuroimaging studies that have found reduced D2/D3 receptor availability in SUDs is related to impulsivity and the propensity to self-administer drugs (Everitt et al., 2008; Lee et al., 2009; Volkow et al., 2012). Furthermore, studies linking genetics to neural substrates of decision-making have found that dopaminergic pathways moderate PFC activity in risky decision paradigms (Kohno et al., 2016).

There are, however, limitations to the current study. As fNIR does not have the same spatial resolution as fMRI, our study focused on larger regions of the PFC to discriminate between groups and predict treatment outcome. Also, we used a priori regions of interest to control for family-wise error, and therefore may be subject to reverse inference (Poldrack, 2006). There are a number of factors that contribute to heightened risk for relapse that were not
significant in this study, such as age and years of use. While we were able to predict relapse to opioids and return to any substance for the entire group and the subgroup that went straight to outpatient care, our model was not significant in predicting treatment outcome given placement in a SLE. This may be explained by a combination of low relapse rates and small sample size. Further research is needed to determine reregulation of PFC activity during decision-making tasks over time.

Conclusion

The current study extends prior work on alcohol dependent patients (Seo et al., 2013) to assess risk for relapse in prescription ODPs. We have shown that the PFC substrates of risky decision-making are indicative of risk to relapse in ODPs undergoing residential treatment. In addition, combining clinical assessments of depressive symptoms with PFC activity during the BART predicts time to relapse post discharge. Importantly, fNIRS technology is relatively low cost and could easily be deployed in most residential treatment facilities, offering clinicians an empirical measurement of relapse risk. The biological markers identified in this study could be used by clinicians to determine next level of care for patients at high risk for relapse.
CHAPTER 4

EVIDENCE OF ANHEDONIA AND DIFFERENTIAL REWARD PROCESSING IN PREFRONTAL CORTEX AMONG POST-WITHDRAWAL PATIENTS WITH PRESCRIPTION OPIOID DEPENDENCE
The purpose of this study was to use a multimodal approach to evaluate the presence of anhedonia among recently withdrawn prescription opiate dependent patients (ODPs) compared with control participants, including: (1) a well-validated self-report measure of anhedonia, the SHAPS (Snaith et al., 1995); (2) a well-validated psychophysiological measure of hedonic evaluation, the affect modulated acoustic startle response (AMSR; Bradley et al., 1999 and Lang, 1995); and (3) a cue response task to images of naturally rewarding stimuli while participants were monitored over bilateral rostral (RPFC) and ventrolateral prefrontal cortices (VLPFC) with fNIRS. We expected patients to report greater levels of anhedonia on the SHAPS (although not all studies have found patient-control differences, e.g., Zijlstra et al., 2009). The AMSR provides an objective measure of stimulus evaluation that is not subject to the biases of self-report. We also expected patients to show increased startle amplitude while viewing the positive images in the AMSR paradigm relative to controls, a response that is indicative of a less positive evaluation.

To increase our understanding about the specificity of response to natural reward cues in ODPs, participants viewed images of three distinct types of natural rewards: highly palatable food, positive social situations, and intimate interactions. Based on prior research, we hypothesized that these three categories of natural rewards would elicit reduced neural activity in anhedonic patients, relative to controls, in bilateral anterior prefrontal gyrus, also referred to as lateral RPFC, and VLPFC (Zijlstra et al., 2009). Finally, using the criteria established by Snaith et al. (1995) for identifying a clinical level of anhedonia, we hypothesized that patients who endorsed self-reported anhedonia, relative to patients who did not endorse anhedonia, would show reduced neural responses to images of natural rewards in these RPFC areas.
Methods

Overview

These analyses were performed on a subset of participants, midway through data collection (total population and procedures described in Chapter 2). This subset includes prescription opioid dependent patients (ODPs; n = 36) and healthy controls (HC; n = 10; for demographics see Table 4.1.) in the first data burst. All participants underwent the fNIRS-cue reactivity paradigm, affect-modulated acoustic startle response paradigm, as well as self-report measures of current anhedonia via the Snaith-Hamilton Pleasure Scale (SHPS; see Chapter 2 for details).

<table>
<thead>
<tr>
<th></th>
<th>ODP</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>36</td>
<td>10</td>
</tr>
<tr>
<td>% Female</td>
<td>25%</td>
<td>40%</td>
</tr>
<tr>
<td>Mean Age</td>
<td>28.8</td>
<td>25.1</td>
</tr>
<tr>
<td>SD Age</td>
<td>9.7</td>
<td>2.5</td>
</tr>
<tr>
<td>% Depression</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>% History of Depression</td>
<td>29%</td>
<td>20%</td>
</tr>
<tr>
<td>% GAD</td>
<td>38%</td>
<td>0%</td>
</tr>
<tr>
<td>% History of Anxiety</td>
<td>20%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Table 4.1: Participant Demographic Characteristics: Recently Withdrawn Patients versus Healthy Controls.

Statistical analysis

Chi square and Independent sample Student’s t-tests respectively were used to test for differences in gender and age among the groups. Independent sample Student’s t-tests were also used to test for group differences on the SHAPS, AMSR, and cue response task. Regions of interest (ROI) were identified for fNIRS analysis in bilateral RPFC and VLPFC based on prior
findings (Bunce et al., 2012; 2015; Zijlstra et al., 2009). For fNIRS data, optodes were analyzed using independent Student’s t-tests comparing ODP and controls on mean oxygenated hemoglobin in response to each positive stimulus category (food, social, and intimate) minus neutral blocks. For BA 10, the a priori region-of-interest (ROI) contrasts were thresholded at $P < 0.05$; regions outside of the defined ROI were thresholded at $P < 0.03$. All statistical analyses were conducted with SPSS 21.0.0 (IBM SPSS Statistics).

Results

**AMSR**

Inspection of the means from the startle response task revealed that control participants showed the expected pattern of results in response to negative, neutral, and positive stimuli (e.g., Bradley et al., 1999; see Fig. 4.1). As predicted, ODP showed less startle suppression (i.e., greater positive amplitude) than controls when viewing positive stimuli ($t(40) = -2.87, p < .01$), consistent with a less positive evaluation of the stimuli. Patients were found to have lower startle amplitude in response to the negative stimuli relative to controls ($t(40) = 2.03, p < .05$), suggesting a less negative appraisal of these stimuli.
Cue reactivity and fNIRS

As expected, ODP (M = −.072, SD = .12) relative to controls (M = .02, SD = .12), displayed reduced neural activation to images depicting positive social interactions in left VLPFC (corresponding to Optode 1; see Figure 4.2; t(40) = 2.04, p < .05). ODP (M = −.07, SD = .15) were also found to have reduced neural activation to images depicting highly palatable food relative to controls (M = .01, SD = .06) in left lateral RPFC/VLPFC (Optodes 2, 3, 4 see Fig. 4.2; t(42) = 2.6, p = .01); right VLPFC (Optode 16; Fig. 4.2; ODP (M = −.12, SD = .18) versus controls (M = .05, SD = .11); t(40) = 2.39, p = .02), and left medial RPFC (Optode 7; Fig. 3b; M = −.09, SD = .15 versus controls (M = .03, SD = .08; t(39) = 2.24, p = .03), No differences were found in response to the emotionally intimate images.

Figure 4.1: Recently withdrawn prescription opiate dependent patients (ODP) display dysregulated processing of emotionally valenced stimuli via affect-modulated acoustic startle response. Response to negative stimuli is significantly lower (p<.05) for ODP and response to positive stimuli is significantly higher (p<.05). Neg=negative stimuli; Neu=neutral stimuli; Pos=positive stimuli; * = p<.05 error bars = SEM.
Patients and controls showed evidence of differential responses to food and social stimuli consistent with anhedonia in patients. To further refine the relationship between self-reported anhedonia and the neuroimaging data, patients were categorized into two groups based on their response to the SHAPS. Patients were defined as anhedonic if they scored greater than 2 on the SHAPS (as defined by Snaith et al., 1995); those who scored 2 or less were considered to have normal hedonic tone. ROI analyses of lateral RPFC indicated that patients self-reporting anhedonia (n = 14) showed reduced neural activation in response to social stimuli relative to patients that did not endorse anhedonia (n = 22). More precisely, patients reporting anhedonia

Figure 4.2: Recently withdrawn opiate-dependent patients display reduced brain activity in response to naturally rewarding stimuli compared to healthy controls. Each number represents an optode on the functional near-infrared spectroscopy device; blue dots correspond to areas of decreased activity ($p<.05$).
showed relatively less activation in right medial/lateral RPFC and right lateral RPFC when viewing social stimuli (Optodes 3, 4, 5, and 6; \( t(28) = 2.32, p = .03 \); and Optodes 9, 11, 12, and 13; \( t(28) = 2.32, p = .03 \); see Fig. 4.3). Relative to patients who did not report anhedonia, patients who did report anhedonia showed reduced neural activation in left lateral RPFC (optodes 5 and 7) when viewing food-related stimuli \( t(28) = 2.33, p = .03 \). No differences in neural activity were found between patients reporting versus not reporting anhedonia in response to the emotionally intimate stimuli.

**Figure 4.3:** Recently withdrawn opiate-dependent patients split into two categories: patients self-reporting anhedonia (as evident by score > 2 on the Snaith-Hamilton Pleasure Scale), and patients failing to report anhedonia. When comparing these two sub-groups, patients self-reporting anhedonia show reduced brain activation to social and food stimuli. Each number represents an optode on the functional near-infrared spectroscopy device; blue dots correspond to areas of decreased activity (\( p < .05 \)).
Discussion

This study used three separate measures that, taken together, offer evidence anhedonia is present among some prescription opiate-dependent patients in the early stages of recovery. Relative to control participants, ODP endorsed higher levels of anhedonia on a validated self-report instrument of hedonic tone the day of neurophysiological testing. ODP were also found to have an affect-modulated startle response indicative of a less positive hedonic evaluation of putatively positive images relative to controls. Finally, when participants were viewing images depicting highly palatable food and positive social interactions, we found reduced neural activity among anhedonic patients in areas of bilateral rostral prefrontal cortex (Figure 4.3), consistent with those reported by Zijlstra et al. (2009). Together, this evidence supports the hypothesis that, following withdrawal from prescription opiates, a significant number of individuals experience an anhedonic state that may reduce their capacity to derive gratification from such natural rewards as positive social interactions and highly palatable food. This finding is consistent with a growing literature emphasizing the role of anhedonia in substance use disorders, particularly within the early stages of abstinence (e.g., Garfield et al., 2014, Hatzigiakoumis et al., 2011 and Janiri et al., 2005).

To our knowledge, the current study is the first to examine neural responses to distinct categories of positive/natural reward stimuli in a population of prescription opiate dependent patients. Of particular interest, ODP endorsing self-reported anhedonia showed reduced activation to positive social images in both right and left lateral RPFC relative to patients who did not endorse anhedonia. Food showed a similar pattern, but was limited to the left lateral RPFC. Rostral PFC has been shown to be involved in a wide range of tasks (Gilbert et al., 2006).
The area of RPFC activated by the social stimuli has been shown to be involved in the retrieval of episodic memories, and to a lesser degree, emotional material. It is possible that activation in this area may be associated with the process of linking social stimuli and food to episodic memories. This interpretation would suggest these positive memories may be less available to anhedonic patients. Similarly, with regard to the AMSR, we found that ODP exhibited larger startle responses to positive stimuli relative to controls (see Figure 4.1), indicative of a more negative evaluation of the stimuli (Bradley et al., 1999). This evidence suggests that viewing positive stimuli may not elicit the positive feelings, or evoke the positive memories, among ODP that it does among the healthy controls. Further research is needed to understand the exact nature of these responses in anhedonic patients.

Interestingly, emotionally intimate stimuli did not elicit group differences in the prefrontal areas that were monitored. One hypothesis is that emotional intimacy may elicit more complex emotions and memories than palatable food or even non-intimate positive social situations among ODP, as well as among control populations. Individual differences in patient response to emotionally intimate stimuli, rather than group differences, may still be related to vulnerability to relapse. Alternatively, more individualized stimuli, or imaging other brain areas may be necessary to understand the role of emotionally intimate imagery in anhedonic patients.

As 22 of 36 patients (61%) did not meet previously established criteria for clinically relevant anhedonia on the SHAPS (vs 0% among controls), it is likely that there are significant individual differences in anhedonia in this patient population. These individual differences are of particular interest, as greater anhedonia should theoretically be associated with greater risk for relapse. These risks may be exacerbated by increased stress, although their effect on risk for
relapse is yet to be determined. The inherent limitations of self-report instruments, however, make it likely that the outcome of the SHAPS, while informative, may not accurately characterize every patient with regard to clinically relevant anhedonia. Like the construct of craving, the measurement of anhedonia may benefit from conceptualization as a multidimensional phenomenon with subjective, behavioral, physiological, and neurochemical correlates. Just as neuroimaging techniques – coupled with cue-induced craving – have been shown to be a better predictor of treatment outcomes than self-reported craving (e.g., Goldstein et al., 2009 and O'Brien, 2012), the current data suggest a similar approach may be warranted for the construct of anhedonia. The multifaceted methodology used in this study represents an initial approach to a clinically relevant assessment of anhedonia. Further longitudinal research, evaluating anhedonia in conjunction with measures of negative affect, drug craving, stress, and HPA axis functioning (e.g., sleep, cortisol) over time in abstinence, would be necessary to fully elucidate the role of anhedonia in vulnerability to relapse. Repeated measures in longitudinal studies of abstinent patients would also help to clarify the time course and proportion of patients that might show evidence of hedonic reactivation.

There are several limitations to the current study. First, the study is cross-sectional. Whereas it is possible to identify neural correlates of purported anhedonia, it cannot be determined if these measures are valid predictors of treatment response or treatment outcome, and further research is necessary. Second, it cannot be determined from these data whether the anhedonic state found in these patients is the function of an allostatic process related to drug use (e.g., Koob and Le Moal, 2001 and Pettorruso et al., 2014), or a pre-existing condition that may have played a role in the onset of addiction (e.g., Blum et al., 2000 and Loas, 1996). In either case, the compromised capacity to derive pleasure from natural rewards among the anhedonic
patients is likely to have an impact on their efforts to remain drug-free. However, efforts to improve treatment in addiction might benefit from a more refined understanding of the etiology of anhedonia in substance use disorders. Medications that show efficacy for symptoms of depression are not always effective for anhedonia (Di Giannantonio and Martinotti, 2012). Efforts to develop medications (e.g., Di Giannantonio and Martinotti, 2012 and Martinotti et al., 2011) or neuro-nutrient therapies (Blum et al., 2012) that target anhedonia may benefit from the utilization of valid, affordable, and objective measures of hedonic tone that could be implemented in both research and clinical settings. Third, there are a number of different measures of anhedonia (Franken et al., 2007 and Garfield et al., 2014), which might produce different results. As in much of psychiatry, there is currently no gold standard for the assessment of anhedonia, which places an emphasis on developing objective measures with clinical relevance.

**Conclusion**

This study addressed several timely questions concerning the presence of anhedonia among individuals in the early stages of recovery from prescription opioid dependence. Our data suggest that some, but not all, ODP showed evidence of reduced response to stimuli depicting natural rewards in this stage in treatment. Further longitudinal research is necessary to address questions regarding the impact of anhedonia on the processes of recovery and relapse. Previous studies suggest that, post withdrawal, anhedonia decreases over time, and that reduction in anhedonia is related to reduction in drug craving (Janiri et al., 2005). However, further research is needed to determine the nature and time-course of the potential reversal of allostatic processes in substance use disorders. Further research is also needed to more fully explore the relationship
among anhedonia, drug related craving responses, and the risk of proximal relapse following discharge from residential treatment. Finally, our results suggest that further multimodal research on the construct of anhedonia is warranted, including assessments of its clinical utility.
CHAPTER 5

ASSOCIATIONS BETWEEN POST-WITHDRAWAL STRESS AND PREFRONTAL CORTEX ACTIVITY: POSSIBLE EVIDENCE OF HPA-AXIS REREGULATION
It is well established that opioid dependent individuals experience high levels of stress during withdrawal (Kreek, 1997; Sinha, 2006). Indeed, neuroendocrine stress signals contribute to the withdrawal/negative affect and preoccupation/anticipation stages of addiction, and as such, act as primary drivers in the vicious cycle of chronic relapse (Koob, 2010, Sinha, 2011). Opioid dependent individuals undergoing naloxone-induced withdrawal display HPA-axis hypersensitivity (Culpepper-Morgan & Kreek, 1997), suggesting that HPA measurements such as systemic cortisol are indicative of withdrawal severity. Furthermore, studies in cocaine dependent individuals have shown that measurements of stress-induced fluctuations in systemic cortisol are indicative of time to relapse (Sinha et al., 2006). However, the degree to which opioid dependent individuals experience reregulation of the HPA-axis during recovery is unclear. Creating a tangible understanding of the timeline of reregulation is an important step in understanding how risk factors such as stress induced craving hamper recovery from opioids.

Stress also affects impulsive behaviors. Studies using questionnaire based measurement have examined the relationship between stress and impulsivity in alcohol use (Helen et al., 2010) and smoking (Ansell et al. 2012). In response to amphetamines, high stress and/or high trait impulsivity are associated with reduced DA release in the striatum (Oswald et al., 2007). In addition, research done by Kreek et al. (2005) notes that impulsivity, risk taking, and stress reactivity each have profound effects on the various stages of addiction; however, it is unclear whether there is an association between HPA-axis measures of stress and the neural substrates of risky decision-making in recently withdrawn opioid dependent individuals.

The aim of this chapter is to (a) better understand the timeline of HPA-axis reregulation in ODPs in residential treatment, and (b) better understand the relationship between stress and the neural substrates of risky decision-making. As a non-invasive way to measure the HPA-axis,
we used salivary measures of cortisol which are known to correlate closely with plasma concentrations (Jung et al., 2014). We postulated that mean salivary cortisol would decrease over time in residential treatment, and approach levels of healthy controls in the 4th month of extended residential treatment. We also hypothesized that high stress, measured by salivary cortisol, would be correlated with PFC activity during a risky decision-making paradigm.

**Methods**

**Overview**

These analyses were performed on a subset of patients described in Chapter 2. This subset includes recently withdrawn prescription opioid dependent patients in the first data burst (n=66) and healthy controls (n=29). All participants in this analysis performed the fNIRS-BART paradigm and provided at least one salivary cortisol measurement for each of the five time points described in Chapter 2. A subset of patients that met this criteria (n=16) stayed in treatment for at least 30 additional days, and a smaller subset (n=7) stayed in treatment for an additional 90 days. Cortisol collection and laboratory measurements of the fNIRS–BART paradigm (Cazzell et al., 2012; see Chapter 2) were collected in the first, second, and fourth months of treatment for all eligible ODPs.

**Statistical Analysis**

Repeated measures ANOVAs were used to determine within person differences across data bursts; since the number of patients completing 3 data bursts and cortisol collection was small (n=7), and there were not significant differences between this small cohort and the larger group, we then used Independent Student’s t-tests to further assess group differences between the
1st, 2nd, and 3rd data bursts (DBs), as well as between patients and controls. In addition, we used paired sample t-tests to further examine within person differences across data bursts. Linear regression was used to determine correlations between PFC activity and cortisol in the 1st data burst. All statistical analyses were conducted with SPSS 21.0.0 (IBM SPSS Statistics).

Results

Diurnal Cortisol and Prefrontal Cortex Activity

Diurnal cortisol levels were elevated in ODPs compared to control participants at every time point in data burst 1 (p<.01; see Figure 5.1). To evaluate the potential reregulation of cortisol levels across four months of residential treatment, the small cohort (n=7) who completed all three data bursts was submitted to a repeated measures ANOVA. A linear contrast indicated a marginal reduction of cortisol across the three time points in this small group (F(6)=5.56, p = .056). Importantly, the mean levels of cortisol in this small cohort resembled those of the larger groups at DB1 and DB2 (see Figure 5.1). Total mean cortisol for the full cohort in DB1 (n=65, M=20.82, SD=8.7) did not differ from the smaller cohort (n=7, M=19, SD=9). In DB2, the full cohort (n=16, M=17.4, SD=7.2) did not differ from the smaller cohort (n=7, M=13.8, SD=4.8; See Figure 5.1). A Student’s t-test indicated a reduction of mean cortisol between data burst 1 versus data burst 3, and also between data burst 2 versus data burst 3 (see Figure 5.1).

Associations between mean cortisol and PFC activity during the BART were found in the data burst 1 cohort (n=65). Neural response to a winning trial in Opto 16 was correlated with high mean cortisol (r=.324, p=.028). In addition, neural response to a losing trial in Optode 11 was also correlated with high mean cortisol (Optode 11; r=.433, p=.006). Diurnal cortisol was not predictive of relapse in this study.
Figure 5.1: Diurnal and total mean cortisol. Upper left: comparison of diurnal cortisol between patients and controls during data burst 1. Lower left: comparison of mean daily cortisol between patient and controls in data burst 1. Upper right: Change in diurnal cortisol across three data bursts. Lower right: Change in mean cortisol across data bursts for the full cohort and three data burst subset (and comparison with controls). *=p<.05; **=p<.01.

Figure 5.2: Associations between mean cortisol and brain activity during the Balloon Analogue Risk Task. Neural response to a winning trial in the right DLPFC is correlated with high mean cortisol (Optode 16; r=.324, p=.028). Neural activity in the right DL/VMPFC in response to a losing trial is correlated with high mean cortisol (Optode 11; r=.433, p=.006).


**Discussion**

While the current study did not find diurnal cortisol to be predictive of relapse risk in recently withdrawn ODPs, we did find that ODPs have significantly elevated total mean and diurnal cortisol in the early stages of recovery compared to controls (Figure 5.1). In addition, this dysregulation appears to reregulate over a four month period in residential treatment; however the number of patients providing cortisol samples into the 3rd data burst was small (n=6). Because of this, we used two approaches to provide possible evidence of reregulation. First, we used all individuals in data burst 1, 2, and 3 cohorts to show significant reduction in mean cortisol over the four month period. Although this effectively makes the design cross sectional and thereby limits interpretation of reregulation, the smaller, 3 data burst cohort was not significantly different from the larger group, making it more likely that between group differences were indeed indicative of reregulation (See Figure 5.1). Second, we used paired sample t-tests to show that there was a marginal reduction in mean cortisol between the first and third data bursts. Although not significant at the .05 level, these data provide further evidence that mean cortisol reregulates in ODPs during extended residential treatment.

The DLPFC is known to be involved in several addiction related functions, such as motivation and reward sensitivity (e.g., Volkow et al., 2011). Our data show that there is an association between high mean cortisol and DLPFC response to wins during the BART, suggesting that high stress may affect reward sensitivity in recently withdrawn ODPs (Figure 5.2). Previous studies note the relationship between drug cues and/or stress that result in unrestrained hyper-activation of motivation/drive circuitry; these processes are thought to drive compulsive drug taking (Volkow et al., 2010). High mean cortisol was also correlated with
increased activity in the VM/DLPFC in response to losing trials during the BART (Figure 5.2). The VM/PFC has previously been associated with the intensity of either positive or negative outcomes in a cognitive task with monetary rewards/punishments (O'Doherty et al., 2003). It may be that high stress exacerbates response to loss in recently withdrawn ODPs. The positive correlations between stress and neural response to monetary gain/loss may also reflect a heightened state of arousal. In Chapter 3 we provided evidence that neural response to wins and losses are associated with risk for relapse; further research should examine the relationship between stress reactivity and response to monetary gain/loss in the BART, and whether this combination could be synergistic in predicting treatment outcome.

Dysregulation in the HPA-axis has been an important construct in the addiction literature (Koob and LeMoal, 2001; Kreek, 2005; Sinha, 2006); our study suggests that ODPs in residential treatment display prospective reregulation of the HPA-axis over a four month period. Whereas acute withdrawal is marked by a sharp increase in neuroendocrine stress signals via the HPA-axis, protracted abstinence symptoms are likely driven by long-term changes in stress-signal and reward neuro-circuitry (Diana et al., 1996; Koob, 2010). In addition, neuroendocrine measures of stress reactivity have been shown to predict relapse risk and relapse severity in both alcohol and cocaine dependent patients (Sinha, 2011). In cocaine dependent patients, stress-induced ACTH and cortisol levels have been associated with elevated cocaine consumption during relapse (Sinha et al., 2006). In alcohol dependent patients, stress induced cortisol/ACTH ratios predicted time to relapse (Sinha, 2011). Although the data presented in this study did not indicate that salivary measures of diurnal cortisol are predictive of relapse risk, plasma measures of the cortisol/ACTH ratio were not evaluated. Elevated mean cortisol, however, was associated with increased PFC activity in response to wins and losses during a risky decision-making task.
Future longitudinal research should focus on allostatic reregulation of stress signals in a larger cohort, and delineate the predictive value of stress reactivity measures, such as the cortisol/ACTH ratio, in recently withdrawn ODPs. In addition, further research is needed better understand the mechanism by which systemic cortisol levels affect decision-making, and how this interaction affects individuals with SUDs.
CHAPTER 6

DRUG CRAVING IS ASSOCIATED WITH PREFRONTAL CORTEX ACTIVITY DURING A RISKY DECISION-MAKING TASK
Persistent drug craving is a major hurdle in the treatment of opioid dependence. In the human experience of addiction, persistent drug craving intrudes on thoughts and generates considerable distress during recovery from SUDs. There is a vast literature on the topic of drug craving with a major focus on craving as a trait (tonic craving), or, as a state (e.g. cue or stress induced craving; Tiffany & Wray, 2012). Recently withdrawn ODPs display varying amounts of tonic craving, and within person, craving may be influenced by positive and negative affective states (Huhn et al., 2016). Preclinical models of cue-induced craving note that glutamatergic projections from the PFC to the NAc are necessary for cocaine-induced reinstatement of drug seeking behavior (McFarland et al., 2003). In addition, clinical studies on opioid users have shown that cue and stress induced cravings persist after withdrawal, even if the patient is being treated with anti-craving medication such as naltrexone (Hyman et al., 2007).

There may be only a small window, proximal to the actual behavior of relapse, where craving is predictive of relapse risk (Katz & Higgins, 2003); however, reduction of persistent craving has clinical value in treating individuals with SUDs. Traditionally, treatment outcome studies on SUDs have been aimed at reducing or eliminating drug consumption (Donovan et al., 2012). On the other hand, it has also been suggested that effective treatments should attend to consequences and features of addiction beyond drug use (Tai, 1993; Van den Brink et al., 2003; Tiffany et al., 2012). “Other” outcome measures, such as craving, may also be included as a standard outcome measures across treatment studies (Tiffany et al., 2012). Indeed, a panel convened by the National Institute on Drug Abuse confirmed that craving should be examined as an outcome measure for clinical trials of SUDs (Tiffany et al., 2012). While the association between subjective measures in of craving and risk of relapse has been mixed, these measurements are clearly not predictive if the patient relapses at some distal point in the future.
(Tiffany & Wray, 2012). Because of this, researchers have shifted to neurophysiological measurements of cue-reactivity as an objective measure of craving (Childress et al., 1993).

It is well established that the PFC plays a role in drug craving, however, the relationship between drug craving and decision-making is not well understood. Previous fMRI research has shown that drug cues increase activation in the left DLPFC and/or bilateral DLPFC in smokers and abstinent alcoholics (Grusser et al., 2004; Heinz et al., 2007; Yalachkov et al., 2009); although there are some exceptions in alcoholics and opioid users (deGreck et al., 2009; Myrick et al., 2004; Ziljstra et al., 2009; Harris et al. unpublished findings). PET studies have found drug cues increase PFC activation in cocaine-dependent individuals (Garavan et al., 2000), and in heavy smokers (Brody et al., 2002). Similarly, fNIRS studies have found that drug cues increase lateral PFC activation in alcohol dependent (Bunce et al., 2012) and opioid dependent patients (Bunce et al., 2015). Furthermore, subjective reports of craving are correlated with cue-induced PFC response (Brody et al., 2002), and severity of drug use (Yalachkov et al., 2009). Although the literature on drug-cue response and subjective craving is robust, there is a paucity of research studies linking craving to response to secondary rewards, such as monetary gain.

This chapter aims to better understand the relationship between drug craving and PFC response to monetary gains and losses during the BART. Our overall hypothesis was that ODPs with high drug craving would display decreased behavioral performance on the BART, and that baseline and cue-induced craving would be correlated with PFC activity in response to monetary gain/loss. As a way to validate the relationship between craving and BART-PFC activity, we also postulated that overlapping regions of the PFC would correlate BART related neural activity and craving as well as drug-cue induced neural activity and craving. This study marks an important
step in furthering our conceptual knowledge of the shared neural substrates associated with drug craving and risky decision-making.

**Methods**

**Overview**

The analyses in this chapter were performed on a subset of patients described in Chapter 2. This subset includes recently withdrawn prescription opioid dependent patients in the first data burst (n=65) that performed the fNIRS adapted BART paradigm and cue-reactivity paradigm described in Chapter 2. All participants provided self-reported craving scores on a 100-point Likert scale before and after being confronted with drug cues.

**Statistical Analysis**

Linear regression was used to determine correlations between PFC activity during the BART paradigm and self-reported baseline and cue-induced craving i.e. before and after the cue-reactivity paradigm. Similarly, linear regression was also used to determine correlations between PFC activity during the cue-reactivity paradigm and self-reported baseline and cue induced cravings. To control for family-wise error, correlations between craving and PFC activity were deemed significant if the area of the PFC overlapped between the two paradigms. All statistical analyses were conducted with SPSS 21.0.0 (IBM SPSS Statistics).
Results

Craving and Prefrontal Cortex Activity

Baseline craving (prior to cue exposure) on the day of testing was correlated with neural response to loss during active trials in optode 5 (r=.400, p=.003; see Figure 7.1). This brain area overlapped with correlations between cue induced craving (as measured by loss of control over drug intake) and neural response to pill cues in optode 5 (r=.256, p=.043). Cue-induced craving (craving following the drug-cue reactivity paradigm) correlated to response to wins during passive trials in the cluster of optodes 2, 3, and 4 (r=.348, p=.006). This area partially overlapped with correlations between baseline craving (as measured by reduced drug avoidance) and neural response to pill cues in optodes 1 and 2 (r=.357, p=.006; Figure 7.1). There were no significant correlations between craving and behavioral measurements during the BART. Self-reported baseline and/or cue-induced craving did not significantly predict treatment outcome in this study.
Figure 6.1: Upper left: correlation between brain activity during the drug-cue paradigm (optodes 1 & 2) and baseline measurement of craving (avoid craving) ($r=.357; p=.006$). Upper right: correlation between brain activity in response to wins during the passive trial of the BART (optodes 2-4) and cue-induced craving ($r=.348; p=.006$). Lower left: correlation between brain activity during drug-cue paradigm (optode 5) and cue induced craving (control over use; $r=.256; p=.043$). Lower right: correlation between brain activity in response to loss during the active trial of the BART (optode 5) and baseline craving ($r=.400; p=.003$).
Discussion

This study examined the relationship between drug craving and neural activity during a risky decision-making paradigm. We found that neural activity in the left VL/DLPFC in response to a win (during the passive BART) was correlated to cue-induced craving in recently withdrawn ODPs (Figure 6.1). In Chapter 3, we presented data showing that ODPs display elevated neural response to passive wins and active wins in similar PFC regions when compared to healthy controls (Figure 3.2). Given that ODPs expressing high cue-induced craving also displayed reward sensitivity in the left VL/DLPFC, one interpretation is that these areas are generally involved in salience attribution and reward assessment (O'Doherty, 2003; Volkow, 2011). As a way to validate these findings, we also examined whether this same region was correlated with drug-cue induced neural response and craving. Unpublished data from our lab (both Huhn and Harris) have shown that processing drug and alcohol cues elicits less PFC activity in recently withdrawn ODPs and alcoholics. Indeed, reduced response to drug cues in the left VL/DLPFC was associated with increased baseline craving, as measured by reduced willingness to avoid drug use rather than desire to use (Figure 6.1). Although the dimension of craving was different i.e. reduced willingness to avoid drugs versus increased desire to use drugs, both are measurements of propensity to use drugs. It is possible that reduced baseline avoidance leaves ODPs susceptible to cue-induced cravings. At the same time, desire to use may be associated with reward sensitivity during the BART. Regardless, it appears that drug cues and monetary reward cues share a common neural substrate in regard to reward-related stimuli.

In addition, baseline craving was positively correlated with activity in the VM/DLPFC in response to a loss (Figure 6.1). We previously presented data that ODPs had higher activation in
this area compared to controls in the passive version of the BART (Figure 3.2). It is possible that increased baseline craving (which may be related to tonic craving) is either (a) indicative of preexisting diathesis, or (b) related to allostatic changes such as increased sensitivity to negative feedback. The latter point fits the framework of Koob’s model concerning the role of negative reinforcement in SUDs (Koob & LeMoal, 2001; Koob 2013). Previous studies have shown that methadone maintained individuals persist in risky decision making behaviors despite negative feedback (Ersch et al., 2005). We also found that reduced neural activity in response to drug cues was associated with reduced feelings of control over drug use (Figure 6.1). Once more, neural activity in response to pill cues validates the association between BART activity and craving, although the dimension of craving was different. Interestingly, neuroimaging studies using PET in abstinent polysubstance abusers have shown a relationship between risky-decision making and reward sensitivity; more specifically, abstinent drug users show a positive relationship between risky decision making and sensitivity to reward in the bilateral OFC and right DLPFC, and a negative relationship between risky-decision making and activity in the left ACC (Fishbein et al., 2005). However, this study is the first to show associations between drug craving and the neural substrates of risky decision-making in recently withdrawn ODPs.

This study has limitations, as craving was not predictive of relapse or behavioral measurements on the BART. Also, it is not possible to ascribe a causal relationship between craving and risky behaviors with the current research design. Different dimensions of craving were associated with neural activity during the BART and drug cue paradigm respectively. Whereas this may be representative of overlapping neural substrates that respond to craving and risky decision-making, BART activity was associated with desire to use and should not be thought of in terms of the reduced avoidance of drugs or control over drug use. In addition,
future research should examine ecological momentary assessments of craving to better determine the relationship between tonic craving and decision-making during early recovery from opioid dependence. Future work should also examine the relationship between risk taking and craving as risk factors when individuals are more proximal to environments where they can use drugs e.g. during outpatient treatment.
CHAPTER 7

GENERAL DISCUSSION
Clinical Relevance

The long term goal of this line of research is to determine whether PFC activity during a risky decision-making task is indicative of relapse risk in treatment seeking prescription opioid dependent patients. Our further goal is to develop both a model and a measure that have high clinical utility, i.e., an objective measure than not only advances our knowledge about addiction and potential directions for research, but one that also provides a useful tool for clinical decisions. To this end, the current study assessed the utility of the BART, a paradigm that models real-world risky decision-making, coupled with fNIRS, a neuroimaging modality which can be readily deployed in residential treatment facilities, to evaluate the impact of risky decision-making on three month relapse rates in prescription opioid dependent patients. We found that activity in the VM/DLPFC during the BART accurately differentiated patients who relapsed from those who abstained from drug use over the first three months post discharge (see Chapter 3). Using discriminant function analysis with a conservative leave-one-out cross-validation, we were able to differentiate relapse to opioid use with 81.3% specificity and 82.4% sensitivity in this sample. Binary logistic regression models showed that the neuroimaging data correctly classified relapse to opioids at 87.8%, and within this group, classify individuals with a home placement at 87.5% and individuals with a placement in sober living environments (SLEs) at 80%. In addition, neuroimaging results correctly classified return to any substance use at 78.9%, and, within this group, classified individuals with a home placement at 84.6% and individuals with a placement in SLEs at 71%. The predictive value of fNIR-BART paradigm also predicted time to relapse, as evidenced by Cox regression models including survival analysis. Overall, a combination of activity in the DLPFC and VMPFC during the BART appears to be a clinically relevant, objective, brain-based measure that has the potential to aid clinicians
in making empirically-based decisions regarding next-level of care following residential treatment.

Investigating predictive models of relapse risk also led to observations concerning disparity in relapse rates between individuals discharged to outpatient treatment versus SLEs. Relapse to opioid rates were much higher in those returning home for outpatient therapy (54.2%) than those entering SLEs (16%; Chapter 3). Whereas it may seem like common sense that those who went on to SLEs after 30 days of treatment relapsed at a lower rate following discharge to the community, it is important to note that these individuals also had access to the community, and thus, opportunity to relapse. It is also possible that these individuals had, to some degree, greater motivation to remain abstinent as they elected to enter SLEs. Our predictive model was not significant in this group. This is potentially due to the lower relapse rates among those who went on to SLEs, but could also be explained by lower sensitivity of the measures in this group, i.e., it was more difficult to correctly identify individuals that relapsed. Lower sensitivity could be indicative of individuals that should have relapsed in our model, but remained abstinent because the environmental factors associated with SLEs overcame the biological factors that predisposed to relapse. Unfortunately, the current study does not have the power to answer these questions, but future studies should consider evaluating social support as a factor that may ameliorate the biological drivers of relapse.

In addition to neuroimaging, we initially postulated that biological correlates of stress (salivary cortisol) would be indicative of risk for relapse based on previous work that found stress-induced craving predicted relapse (Sinha 2006; 2008). In cocaine dependent patients, stress-induced ACTH and cortisol levels are associated with elevated cocaine consumption
during relapse (Sinha et al., 2006). Furthermore, in alcohol dependent patients, stress induced cortisol/ACTH ratios predict *time to relapse* (Sinha, 2011). Nonetheless, we did not find diurnal salivary cortisol, measured directly following opioid withdrawal, to have predictive value at 90-day treatment outcome; though patients showed significantly higher cortisol levels compared to controls (Figure 5.1). Diurnal cortisol levels did appear to reregulate over 4 months of residential treatment; however, our study had to rely on a cross-sectional design on the larger cohort, and a marginal finding on the smaller cohort staying for 90 days of extended care (n=6). Thus, we were not able to determine reregulation with certainty in this population. We also aimed to use reregulation of the HPA-axis as a predictor of treatment outcome, but again were stymied by the low number of individuals completing all three data bursts.

Based on evidence that opioid dependent individuals going through withdrawal display HPA-axis hypersensitivity (Culpepper-Morgan & Kreek, 1997), we postulated that high cortisol would be indicative of withdrawal severity, and by extension, be predictive of treatment outcome. Even though salivary cortisol did not add to the predictive model, current depressive symptoms measured by the Hamilton Depression Scale, which are likely attributable to withdrawal severity, were independently predictive of *time to relapse* (Chapter 3). In addition, adding self-reported depressive symptoms to neuroimaging results from the BART created a synergistic effect on the survival analysis in this population (but not the binary measurement of treatment outcome). Future research should aim to optimize combinations of variables (e.g. PFC activity, cortisol/ACTH ratios, depressive symptoms) in creating novel predictive models that accurately assess of relapse risk. This research direction could have high clinical utility and be applicable to personalized medical approaches in opioid dependent individuals.
The addiction treatment community is in need of a collaborative, sophisticated approach to improve treatment outcome for prescription opioid dependence. In order to move the field forward, we must account for biological, psychological, and social factors that predispose individuals to substance abuse and increase risk of relapse following treatment. This thesis explores data concerning the neural correlates of decision-making, stress, and emotion following withdrawal from prescription opioid dependence. Subsequently, we used this understanding to identify biological markers that predict relapse risk in treatment seeking opioid dependent patients. Currently, the field of substance abuse treatment lacks such biomarkers, relying entirely on patient self-report and subsequent clinician judgment. However, high relapse rates among treatment seeking individuals suggest that there is a need for empirical measurements and medical interventions to improve treatment outcomes (O’Brien & McClellan, 1996; McLellan et al., 2000). The current study found individuals entering SLEs to be at reduced risk for relapse. This could be due to increased motivation and/or commitment to sobriety, as well as higher level of supervision than outpatient therapies alone. Likewise, residential treatment has been shown to ameliorate cortical dysregulations in abstinent cocaine dependent individuals (Balodis et al., 2016; Bell et al., 2014; Moeller et al., 2012). Given that the cost of treatment and length of time away from the community is prohibitive for many treatment seeking individuals, making the system more efficacious could help in controlling costs while improving treatment outcome.

**Conceptual Understanding**

There are several behavioral and perceptual constructs that contribute to the decision-making process. Among these constructs, impulsivity, stress, affect, and personality traits converge to determine each individual’s appetite for risk given a specific reward. Neuroimaging
tools such as fMRI have increased our understanding of these factors; studies examining behavioral inhibition (Castelluccio et al., 2013; Miller & Cohen, 2001) and value calculation (Schonberg et al., 2011) have attributed propensity for risky decision-making to the DL/VMPFC. The BART is a naturalistic decision-making paradigm that measures value calculation and response to reward and/or loss of reward (Rao et al., 2008; Schonberg et al., 2012). To the author’s knowledge, these data are the first to use the BART paradigm to assess PFC function in recently withdrawn opioid dependent patients. Our version of the BART measures passive risk taking (i.e. the participant has no control over the paradigm) and active risk taking (i.e. the participant is actively engaging in progressive risk/reward propositions). Previous studies have shown that, during the passive version of the BART, there is increased activity in the parietal cortex of healthy individuals (Rao et al., 2008). Data from the current study found that ODPs display increased neural activity in the left PFC (see Figure 3.2); this activity is likely attributable to increased attention and reward sensitivity during involuntary risk taking. In real life, individuals may be involved in risky behaviors that they do not directly control. This may be especially true of addicted individuals that put themselves in harm’s way for the sake of obtaining and using drugs. Increased neural activity during the passive version of the BART may reflect a propensity to attend to risk/reward decision-making processes, even in the absence of direct control. As such, recently withdrawn ODPs may be drawn to risky decision-making in their environment, irrespective of their own risk-taking behaviors.

In the behavioral version of the BART, ODPs display increased activity in the right VLPFC while performing the decision-making task (Figure 3.2). Other BART neuroimaging studies have shown activity in the right DLPFC (directly superior to our findings) in healthy controls (Rao et al., 2008) and in methamphetamine dependent patients (Kohno et al., 2014),
although the latter study looked at this activity relative to connectivity with the striatum. It is possible that ODPs in our study are working harder to exert cognitive control during the decision-making process (e.g., Ayaz et al., 2012). In addition, compared to healthy controls, ODPs display altered sensitivity to reward and loss of reward in the right VMPFC and left DLPFC; both areas have been related to reward sensitivity in a similar fNIR-BART paradigm in healthy individuals (Cazzell et al., 2012). It is not surprising that recently withdrawn ODPs experience PFC alterations in the early stages of recovery; however, characterizing these alterations during a naturalistic decision-making paradigm helps us understand the link between addiction-related neurocognitive abnormalities and subsequent reward sensitivity in recently withdrawn ODPs.

Even though comparisons of opioid dependent and healthy individuals are informative, studies examining executive function in SUDs compared to healthy controls have almost become superfluous. It is well established that addicted individuals have a higher propensity for risk and struggle with inhibiting maladaptive behaviors (for review see Bechara, 2005; Goldstein & Volkow, 2011); on the other hand, measuring these traits in ODPs that are known to have relapsed following treatment offers new information on risk factors for relapse and may help further our understanding of allostatic and iRISA models of addiction. In the Caron study, differences between relapsers and abstainers during the BART were relegated to the right VMPFC and left dIPFC (Figure 3.3), and may reflect altered value calculation and reward sensitivity as neuroadaptations indicative of relapse risk. Previous neurocognitive studies have attributed VMPFC function to cognitive branching (handling complex tasks) and value calculation (Rushworth et al., 2011; Schonberg et al., 2012). Given that the VMPFC has been predictive of relapse risk in other neuroimaging studies of SUDs, (e.g., Seo et al., 2013)
continued focus on the VMPFC is likely to yield clinically translatable results. In addition, PFC activity during the BART has been associated with decreased striatal D2/D3 receptor binding (Kohno et al., 2015), which builds on preclinical and human neuroimaging studies that have attributed reduced D2/D3 receptor availability to impulsivity and propensity to self-administer drugs (Everitt et al., 2008; Lee et al., 2009; Volkow et al., 2012). Finally, Kohno et al. (2016) notes that dopamine pathways moderate PFC activity during the BART. Overall, risky decision paradigms such as the BART may capture real-world, reward related decision-making processes in a way that is highly useful in clinical populations.

In addition to risky decision-making, we also presented data in this thesis regarding anhedonia in the early stages of recovery from prescription opioid dependence. A combination of ASMR (Figure 4.1), fNIR (Figure 4.2 and 4.3), and self-report via the SHPS (Figure 4.3) offer evidence that ODPs have a tendency to experience post-withdrawal anhedonia, although there is variation within the group. As a group, ODPs endorsed higher levels of self-reported anhedonia compared to controls on the day of neurophysiological testing; although not all patients reported significant levels of anhedonia. ODPs were also found to have increased AMSR to positive hedonic stimuli relative to controls. These results suggest that, on average, ODPs attribute less positive hedonic value to (some) naturally rewarding stimuli. Interestingly, this is the first study in ODPs to measure PFC response to specific natural rewards such visual depictions of highly palatable food, positive social interactions, and emotionally intimate interactions. Compared to controls, ODPs displayed reduced neural activity in the left DLPFC in response to positive social stimuli, and reduced neural activity in the right VLPFC, left RPF, and left lateral PFC in response to food stimuli. Within the patient population, patients endorsing anhedonic traits displayed reduced neural activity in response to food and social stimuli in areas of bilateral
RPFC, which was consistent with findings from an fMRI study in recovering heroin dependent individuals (Zijlstra et al., 2009). The area of RPFC activated by social stimuli has been shown to be involved in the retrieval of episodic memories, and to a lesser degree, emotional material (Gilbert et al., 2006). One interpretation of our data is that reduced RPFC activity may be associated with diminished ability to link episodic memories to natural rewards. In this case, anhedonic ODPs may experience a deficit in retrieving or connecting these memories. In addition, anhedonic patients also had elevated morning cortisol levels on the day of testing; a finding that suggests depressive symptoms such as anhedonia are also related to dysregulation of the HPA-axis. Whether HPA dysregulation and PFC deficits are synergistic is not clear in this study, but would be an interesting avenue for future work.

Taken together, the evidence from Chapter 4 supports the hypothesis that ODPs experience varying levels of anhedonia post-withdrawal that may reduce their capacity to derive gratification from natural rewards. The early stages of abstinence from opioids are marked by depressive symptoms (e.g., Garfield et al., 2014, Hatzigiakoumis et al., 2011 and Janiri et al., 2005), and as such, future research should focus on characterizing and alleviating symptoms of depression in recovering ODPs. Given that we, like other investigators (e.g., Dodge et al., 2005; Greenfield et al., 1998) also found depressive symptoms to be predictive of time to relapse (Chapter 3), there is a pressing need to better understand and alleviate the mechanisms by which depression affects individuals in recovery from prescription opioid dependence.

Many of the same factors that predispose individuals to initiate drug use double as risk factors for relapse. Notably, the dynamics of decision-making are mediated by a balance between executive function and motivational drive, which, if imbalanced, results in impulsivity.
Consequently, proclivity for risky decision-making is a key factor in initiating, maintaining, and recovering from SUDs (Bechara, 2005; Kreek et al., 2005). Although we are not able to discern whether individuals in this study had an abnormal appetite for risk prior to initiation, or during the maintenance phase of drug dependence, we were able to correlate brain activity with self-reported impulsive traits. In brief, we found that ODPs endorsed higher levels of self-reported impulsivity and ADHD symptomatology relative to controls, and these self-report measures (Barratt Impulsivity Scale) were associated with increased reward sensitivity in the bilateral DLPFC (Chapter 3). Previous studies have found that more impulsive individuals show deactivation of the DLPFC in response to delayed reward (this pattern was found in our healthy controls; Ballard & Knuston, 2009). ODPs in this study show the opposite pattern, suggesting that impulsivity leads to increased reward sensitivity post-withdrawal. It is possible that reward sensitivity plays a unique role in certain opioid dependence individuals based on behavioral phenotype. Whereas our study yielded interesting results regarding ODPs with trait impulsivity, future research could extend these findings by examining reward sensitivity relative to stress reactivity and/or depressive symptoms.

The allostatic model of addiction predicts long-term dysregulation of the balance between neural stress and reward systems (Diana et al., 1996; Koob, 2010). Because of this, neuroendocrine factors associated with the HPA-axis have been a focal point of research on the biology of addiction (Koob and LeMoal, 2001; Kreek, 2005; Sinha, 2006). Our study indicates that ODPs in residential treatment display probable reregulation of the HPA-axis over a four month period. In addition, even though stress reactivity has been shown to predict time to relapse in other SUDs such as cocaine dependence (Sinha, 2006), our study failed to show predictive value in diurnal cortisol. It may be that cue-induced or stress-induced cortisol levels are
indicative of relapse risk in ODPs, however further research is needed to elucidate these phenomena in opioid dependence.

Total mean cortisol levels were correlated neural activity in the DLPFC in response to winning trials during the BART. Similar to trait impulsivity, high cortisol may affect reward sensitivity in recently withdrawn ODPs, although the direction of this association cannot be determined from data in our study. In addition, mean cortisol was also correlated with increased activity in the area straddling the VM/DLPFC in response to losing trials. Interestingly, the VMPFC has previously been associated with valence in response to monetary outcomes in a similar cognitive paradigm (O'Doherty et al., 2003). Initially, we postulated that high stress exacerbates risky decision-making, however the data in Chapter 5 suggest that high stress is associated with response to reward/loss in recently withdrawn ODPs. In Chapter 4 we found that anhedonic ODPs also display high cortisol levels; future studies should seek to delineate the relationship between stress, anhedonia, and reward sensitivity in this population.

In addition to stress and trait impulsivity, we also found that drug craving correlated to PFC activity during the BART. The construct of craving can be broken down into tonic craving, cue-induced craving, and stress induced craving. In our paradigm, we assume that baseline craving is indicative of tonic craving, although future studies using EMA can better characterize tonic craving in this population. Drug-cue induced craving scores were obtained after the presentation of visual stimuli featuring prescription opioids. We found a positive association between neural activity in the left VL/DLPFC in response to a win (during the passive version of the BART) and cue-induced craving (Figure 6.1). In Chapter 3 we showed that ODPs display elevated PFC response to passive wins compared to controls (Figure 3.2), and it is possible that
cue-induced craving (which is also passive) and reward sensitivity have overlapping neural substrates. This was further validated by correlations between neural activity in response to pill cues during the cue reactivity paradigm and self-reported craving, although the dimension of craving used for this correlation differed from that in the BART-craving correlation. Our results suggest that the left VL/DLPFC plays a role in response to drug cue and response to monetary reward. Previous studies have found that similar brain regions are involved in reward assessment and salience attribution (O’Doherty, 2003; Volkow, 2011). In addition, baseline craving, which is likely closer to tonic craving, was correlated with activity in the VM/DLPFC in response to a loss during active trials of the BART, which was again validated by pill cue reactivity (Figure 6.1). It is possible that high tonic craving increases sensitivity to negative feedback in ODPs, in line with Koob’s model stating that negative reinforcement is a primary driver in relapse (Koob & LeMoal, 2001; Koob 2013). While this is an interesting perspective, more work should be done to examine whether high tonic craving is associated with risky decision-making and sensitivity to positive and/or negative reinforcers.

There are several limitations to the current study. First, the sample size that completed two and three data bursts was relatively small. Whereas we used the first data burst to identify neural correlates of purported risky decision-making and anhedonia, we have yet to elucidate the time-course of reregulation (if any) of the PFC. Second, it cannot be determined from these data whether risky decision-making and anhedonia are functions of new homeostatic set points related to developing drug dependence (e.g., Koob & Le Moal, 2001; Pettorruso et al., 2014), or pre-existing conditions that may have played a role in the onset of addiction (e.g., Blum et al., 2000 and Loas, 1996). In either case, the neural substrates of risky decision-making do have predictive value in evaluating relapse risk. Efforts to improve treatment in addiction will benefit from
continued refinement of understanding of the etiology and, more importantly, the amelioration of these risk factors in substance use disorders. Third, there are a number of different measures of risky decision-making (Kohno et al., 2014), impulsivity (Passetti et al., 2008), and anhedonia (Franken et al., 2007 and Garfield et al., 2014), which might produce different results. As in much of psychiatry, there is currently no gold standard for these assessments, although continuing to develop biological markers indicative of relapse risk will increase reliability in determining next level of care decisions for ODPs. Fourth, this thesis presents data that implies associations between risky decision-making and craving, stress, and/or trait impulsivity. This data was not causal, and should not be interpreted, for example, as stress or craving lead to risky decision-making. Fifth, as fNIR does not have the same spatial resolution as fMRI, our study focused on rather large sections of the PFC to categorize differences between groups and predict treatment outcome. Also, we used a priori regions of interest to control for family-wise error, and therefore may be subject to reverse inference (Poldrack, 2006). Future research could replicate many of these findings in more precise neuroimaging modalities; in this way, we may gain better understanding of cortical and subcortical contributions to the constructs examined in this thesis, and validate fNIR as a clinically viable technology in assessing relapse risk in opioid dependent patients.

Conclusion

The multifaceted nature of this study represents a novel approach in the assessment of relapse risk in prescription opioid dependent individuals. Our results suggest that several methods show promise in predicting treatment outcome, including central nervous system measurements of impulsivity, risky decision-making, reward deficiency, and stress reactivity.
Although this study makes important strides in improving our conceptual understanding of opioid use disorders, further longitudinal research is necessary to fully elucidate the clinical utility of our findings. Further research is also needed to determine the nature and time-course of the potential reversal of allostatic processes in substance use disorders. In closing, addiction is a disease that has devastating consequences; it breaks down individuals, tears apart families, and shatters entire communities. Understanding the biological factors that drive this disease is crucial in determining appropriate treatment for individuals with substance use disorders. At the same time, it is in everyone’s interest to connect our neurobiological understanding of addiction to social factors and environmental influences. In doing this, we can develop novel methods to prevent the onset of substance abuse, reduce the stigma attached to addictive disorders, and improve patient care for treatment seeking individuals.


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