Mechanisms of reward circuit function:

Novel insights from neurological lesion patients and psychopathic criminals

by

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Dissertation Abstract

The brain's "reward circuit" has been widely implicated in the pathophysiology of mental illness. Two central nodes in the reward circuit – the ventromedial prefrontal cortex/orbitofrontal cortex (vmPFC/OFC) and the ventral striatum (VS) – are known to play key roles in value-based decision-making and reward processing. Although there has been significant progress in identifying the functional characteristics of these nodes and linking their dysfunction to various forms of psychopathology, there remain substantial gaps in understanding how variation in vmPFC/OFC and VS function influences decision-making and reward processing in humans. To address these gaps, the experiments presented here relate key aspects of decision-making and reward processing to vmPFC/OFC and VS through studies of two populations: (1) neurological patients with focal vmPFC/OFC damage and (2) psychopathic prison inmates. Three separate studies identify (1) a causal role for vmPFC/OFC in attenuating susceptibility to bias during decision-making involving potential financial gains and losses, (2) causal interactions between vmPFC/OFC and VS during anticipation of financial gains, and (3) increased VS activity to financial gains among psychopathic individuals, who typically demonstrate poor decision-making and diminished behavioral restraint in obtaining rewards. Together, these findings yield novel insights on the importance of vmPFC/OFC and VS in decision-making and reward processing. As the translation from basic neuroscience to psychiatric patient care continues to advance, the brain's reward circuit is playing a more prominent role in the treatment of psychiatric disorder symptoms related to reward processing and decision-making, such as major depressive disorder and substance use disorder. Progress in this area of research will therefore be critical for the development of neuropathophysiologically-based strategies for diagnosis and treatment in psychiatry.

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Chapter 1. Introduction

1.1 Significance

The brain's "reward" circuit—the network of regions encoding various aspects of pleasure, motivation, value, and decision-making—is a major focus of research on the pathophysiology of mental illness (Chau et al., 2004; Dichter et al., 2012a). Clinical neuroimaging studies have consistently identified abnormalities in reward circuit function across a range of psychiatric disorders, including substance use disorder (Balodis and Potenza, 2015), major depressive disorder (Eshel and Roiser, 2010; Russo and Nestler, 2013), schizophrenia (Ziauddeen and Murray, 2010), obsessive-compulsive disorder (Fineberg et al., 2010; Burguière et al., 2015), autism (Dichter and Adolphs, 2012), and attention deficit hyperactive disorder (Proal et al., 2013). The involvement of the reward circuit in these various disorders suggests that this circuit underlies some crucial domain (or domains) of function that cuts across traditional diagnostic categories (Insel et al., 2010). In order for psychiatric medicine to advance toward a more neuropathophysiologically-based system of diagnosis and treatment, it will be necessary to more fully elucidate how particular elements of social, cognitive, and affective dysfunction relate to disordered activity in key brain networks, such as the reward circuit. Although neuroscientific studies have made considerable progress in identifying functional characteristics of individual nodes of the reward circuit, there remain critical unanswered questions about how these brain areas function and interact, and how disordered function in this circuit may give rise to particular symptoms of psychiatric illness.

Two central nodes in the reward circuit – the ventromedial prefrontal cortex/orbitofrontal cortex (vmPFC/OFC) and the ventral striatum (VS) (**Figure 1**) – are known to play key roles in reward processing and value-based decision-making. However, much remains to be known about

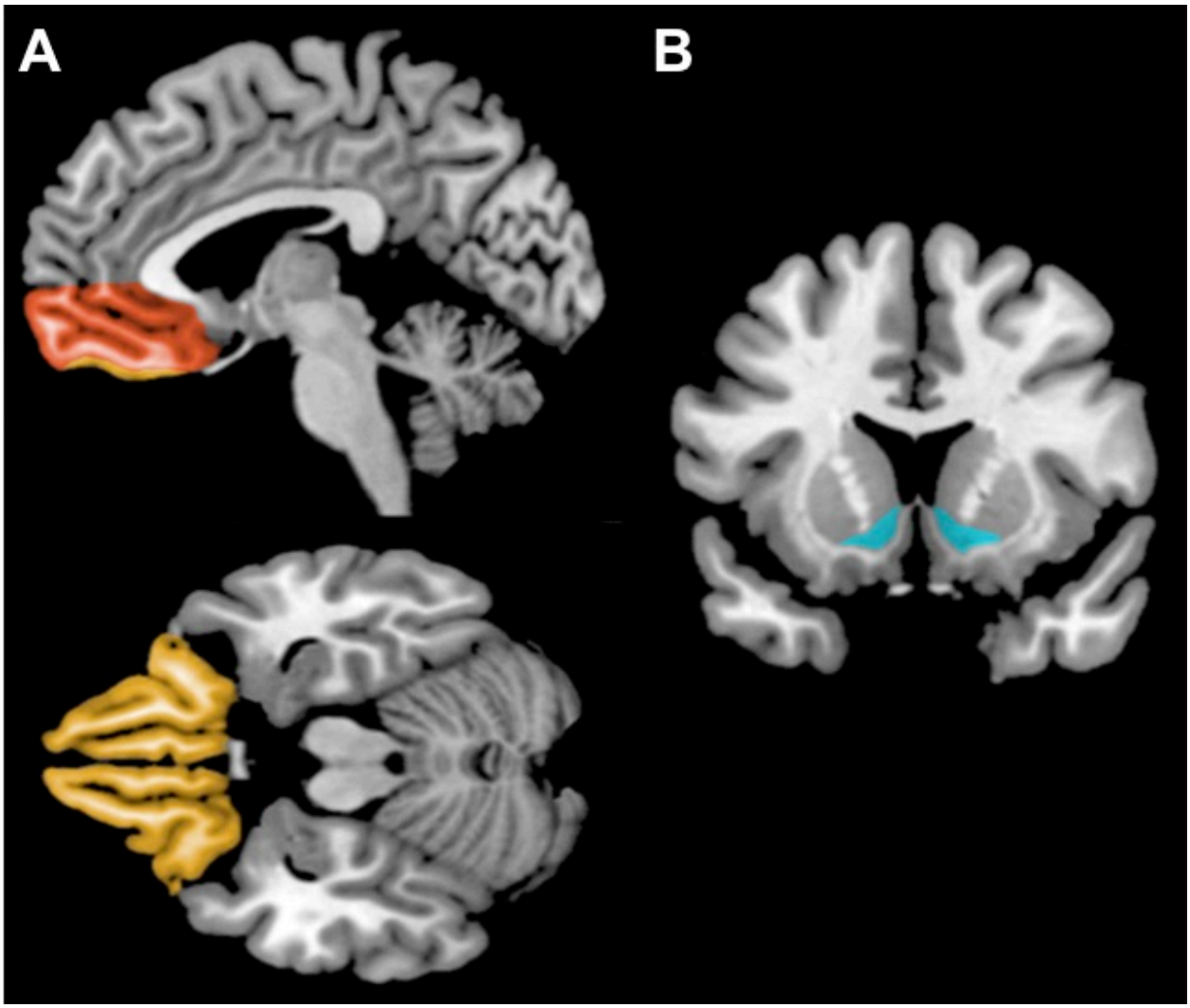

Figure 1. Illustration of ventromedial prefrontal cortex/orbitofrontal cortex and ventral striatum. (A) Sagittal (top panel) and axial (bottom panel) views depicting the ventromedial prefrontal cortex (vmPFC; in red) and orbitofrontal cortex (in orange). (B) Coronal view depicting the ventral striatum (in blue).

potential mechanisms by which these brain regions operate, both in isolation and in concert, during the process of value-based decision-making process in humans. A deeper understanding of the functional properties of this circuit will be a crucial step in identifying disordered reward-related decision-making processes that may be underlying a variety of mental illnesses. Using an integrative approach that combines functional magnetic resonance imaging (fMRI) with

complementary behavioral techniques, the work in this dissertation attempts to clarify the role of vmPFC/OFC and VS in modulating neural and behavioral responses during value-based decision-making and reward processing in a variety of subject populations: healthy individuals, neurological patients with focal brain damage, and prison inmates with psychopathy that exhibit significant decision-making impairments.

1.2 Background

1.2.1 The reward circuit

Identification of the brain's reward circuit can be traced back to the pioneering work of Olds and Milner (1954), who demonstrated that the placement of electrodes at particular areas of the brain in rats could elicit repetitive behavioral responses for electric self-stimulation. This seminal finding sparked a whole conceptual branch of neuroscience aimed at mapping the brain sites that underlie positive reinforcement. Today, various brain regions including the prefrontal cortex, striatum, ventral tegmental area, ventral pallidum, thalamus, hypothalamus, hippocampus, amygdala, and habenula (Haber and Knutson, 2010) interconnected by transmitter systems involving dopamine, serotonin, glutamate, GABA, and opioids (Koob et al., 1994) have been incorporated into a conceptual "reward circuit," which mediates aspects of value representation and behavioral reinforcement. Two key nodes of the reward circuit are thought to play critical roles in human social affective function, and, by extension, psychiatric illness: the ventromedial prefrontal cortex (vmPFC)/orbitofrontal cortex (OFC) and the ventral striatum (VS). Findings from animal and human research demonstrate the importance of each of these areas for various aspects of reward processing.

1.2.2 The role of Ventromedial Prefrontal Cortex/Orbitofrontal Cortex (vmPFC/OFC) in outcome anticipation and value-based decision-making

The vmPFC and OFC are two overlapping subregions of PFC that together comprise the lower medial wall and ventral surface of the frontal lobe, respectively (**Figure 1A**). Although there may be important differences in the functions of these PFC subregions (Rudebeck and Murray, 2011), vmPFC and OFC are densely interconnected, subserve related processes and representations, and are functionally and structurally distinct from other regions of the PFC (Ongur and Price, 2000; Grabenhorst and Rolls, 2011; Wallis, 2012). Moreover, in human research methodologies, such as neurological lesion studies and functional magnetic resonance imaging (fMRI), the inherent limitations in spatial resolution and adequate signal coverage often do not permit clear distinctions between the two areas. I will thus refer to this region of PFC collectively as vmPFC/OFC. Studies of focal brain lesions offered the first evidence that vmPFC/OFC is critical for certain aspects of value-based decision-making. Dating back to the landmark case of Phineas Gage (Harlow, 1868) and corroborated by a series of subsequent neurological case reports throughout the twentieth century (Blumer and Benson, 1975; Eslinger and Damasio, 1985), it has been well-established that damage to the vmPFC/OFC precipitates significant impairments in processing risk, reward, and punishment.

The essence of the real-world decision-making deficits observed in vmPFC/OFC lesion patients was first captured in the laboratory with the Iowa Gambling Task (IGT). In the IGT, subjects play cards from four decks that vary with respect to the relative frequency and amount of monetary gain or loss. Through trial-and-error, subjects must learn to adapt their card choices to enact advantageous selections in their subsequent turns. In the first-ever demonstration of performance on the IGT following vmPFC/OFC damage, Bechara et al. (1994) report a so-called

"myopia for the future," wherein lesion patients base their choices on risky (and ultimately disadvantageous) prospects of large, immediate payouts, as opposed to more modest but consistent payouts that are advantageous in the long-term. Since this initial finding, impairments in the IGT and related gambling tasks as a function of vmPFC/OFC damage have been replicated in rodents (Jentsch et al., 2010; Rivalan et al., 2011; Zeeb and Winstanley, 2011; Paine et al., 2013) and humans (Fellows and Farah, 2005; Hsu et al., 2005; Naccache et al., 2005; Waters-Wood et al., 2012). In a related line of work, the vmPFC/OFC has also been shown to be crucial in inhibiting prepotent responses to immediate, small rewards in favor of delayed, larger rewards—a decision-making phenomenon referred to as temporal discounting—in rodents (Cardinal et al., 2001; Mobini et al., 2002; Kheramin et al., 2004) and humans (Sellitto et al., 2010).

A study by Jones and Mishkin (1972) provided key evidence in non-human primates suggesting that impairments following damage to the vmPFC/OFC may specifically reflect an inability to update new information due to changes in contingencies (reversal learning), as opposed to an inability to learn from initial action-outcome contingencies (discrimination learning). This deficit in reversal leaning has since been replicated in additional vmPFC/OFC lesion studies of primates (Dias et al., 1996; Chudasama et al., 2007; Man et al., 2009), rodents (McAlonan and Brown, 2003; Schoenbaum et al., 2003; Stalnaker et al., 2007; Bissonette et al., 2008; Churchwell et al., 2009; Izquierdo et al., 2013), and humans (Fellows and Farah, 2003, 2005; Tsuchida et al., 2010). The robustness of these effects indicates a role for the vmPFC/OFC in updating information regarding the value of an outcome in order to adjust for changes in stimulus-outcome associations.

Yet another way to assess the role of the vmPFC/OFC in updating outcome value is through learning tasks that use extinction trials following post-training alterations in the relative value of an outcome. Outcome or reinforcer devaluation involves initial discrimination learning using cues that predict at least two separate rewarding stimuli, one of which is subsequently devalued through either satiation or induced aversion via pairing with a noxious stimulus. Devaluation impairments occur following vmPFC/OFC lesion in rodents (Gallagher et al., 1999; Pickens et al., 2003; West et al., 2013) and non-human primates (Izquierdo et al., 2004; Machado and Bachevalier, 2007; West et al., 2011). Although there are not yet any human vmPFC/OFC lesion data on reinforcer devaluation task performance, human fMRI studies show that OFC activity tracks outcome devaluation (specifically, of the cue that predicts a devalued outcome) (Gottfried et al., 2003; Valentin et al., 2007). vmPFC/OFC has also been implicated in other tasks that require integrating new information about previously learned stimulus-outcome contingencies. Takashi et al. (2009) used a Pavlovian overexpectation task to show that OFC lesions in rats impair the ability to adjust response behaviors based on violations of expected reward magnitudes. Similarly, contributions of the OFC in related reinforcement tasks such as the 'blocking' effect have been demonstrated in work with rodents (Burke et al., 2007) and humans (Tobler et al., 2006) [For a detailed review of these studies, see (Schoenbaum et al., 2011)].

Together, these lesion studies of reinforcement learning and decision-making that involve updating information of previously learned associations demonstrate a clear role for the vmPFC/OFC in integrating information about the magnitude or value of a specific outcome to guide future actions. This conclusion is further supported by human functional imaging work, which has shown that, across a wide variety of contexts, stimuli, and outcomes, vmPFC/OFC

activity commonly represents reward value (Grabenhorst and Rolls, 2011; Liu et al., 2011; Diekhof et al., 2012; Levy and Glimcher, 2012). A bulk of the work characterizing the effects of vmPFC/OFC damage on decision-making has been done in the context of value-based decisions made during active engagement in learning-dependent tasks (Schoenbaum et al., 2011). Such work suggests that vmPFC/OFC integrates information about the magnitude or value of a specific outcome to guide future actions during learning. However, less work has been done to evaluate decision-making impairments following vmPFC/OFC damage using learning-independent decision-making tasks. Establishing a causal role for the vmPFC/OFC in adaptive decision-making on a learning-independent paradigm forms the basis of **Chapter 2**.

1.2.3 The role of the ventral striatum (VS) in reward processing and decision-making

Whereas studies of focal brain lesions offered the first evidence that vmPFC/OFC is critical for certain aspects of value-based decision-making, electrophysiological recording and stimulation techniques provided the initial insight into the reward processing characteristics of the ventral striatum (VS). Because of its connections to limbic and cortical brain regions, the VS serves as a "limbic-motor" interface that integrates affective and cognitive information to influence motor output (Mogenson et al., 1980) (**Figure 1B**). Functional mapping studies have linked behavioral reward responses to a smaller subregion within the VS known as the nucleus accumbens (NAc) (Robbins and Everitt, 1996; Voorn et al., 2004). Early electrophysiological work demonstrated that dopaminergic projections from the ventral tegmental area of the midbrain signal the availability of a reward to the NAc (Schultz, 1998). The link between the neuromodulatory effects of dopamine on the NAc in relation to an animal's behavior was not established until seminal work by Salamone (1994), showing that dopamine depletion from the NAc drives an animal away from a state of motivation for reward-seeking, without affecting the

consumption of freely available but less appetitive food. Extracellular NAc dopamine levels are also enhanced during anticipatory or 'wanting' phases of reward learning (Robbins and Everitt, 1996). Therefore, it may be the case that the predictability of a rewarding outcome, as signaled by dopaminergic VTA neurons, influences VS activity to increase motivation for the rewarding outcome.

Studies involving loss-of-function following NAc lesions have established crucial roles for NAc (and its subregions, the NAc "core" and the NAc "shell") in performance on value-based tasks. Whereas control rats are able to suppress approach responses to odor cues that predict aversive outcomes and increase their responses to odor cues that predict positive outcomes, rats with NAc lesions fail to discriminate between positive and negative odor cues (Schoenbaum and Setlow, 2003). Rats with NAc core lesions also tend to favor smaller, immediate rewards over larger, delayed rewards (Cardinal et al., 2001; Cardinal and Howes, 2005), ascribing a role for the NAc core in withholding impulsive responses. NAc lesions in rodents cause greater activity in dorsal striatum (DS) and reliance on stimulus-response (i.e., habitual) behaviors in an odor-guided choice task, indicating that reward signals generated in VS are important for guiding flexible, goal-directed behaviors in the initial stages of learning (Burton et al., 2014). More broadly, the NAc seems to be crucial for guiding approach/avoidance behaviors based on salient features of an outcome (such as probability and valence).

Most of what is currently known about the role of the VS in reward in humans comes from functional neuroimaging studies. Due to the limited spatial resolution of fMRI, subregional NAc specificity is difficult to attain. Thus, in the context of fMRI, the NAc is referred to as the VS, which is more inclusive of a larger swathe of the basal ganglia to include the NAc in addition to the ventral medial caudate, and the rostroventral putamen (Haber and Knutson, 2010).

The VS in fMRI studies has been reliably activated by stimuli predicting rewards (Knutson et al., 2001a; Knutson and Cooper, 2005). The VS has also shown increased activation during the consumption of a reward (O'Doherty et al., 2002; Yacubian et al., 2006), especially when a reward is unpredicted or of a higher magnitude than expected (Berns et al., 2001; Yacubian et al., 2006). In accord with the animal electrophysiology results, human neuroimaging studies have shown that activity in the VS correlates with reward prediction (McClure et al., 2003; O'Doherty et al., 2003; Pessiglione et al., 2006; Tobler et al., 2006). The human fMRI data demonstrating associations between reward-related behaviors and VS activity align closely with animal evidence of the role of the VS in reward. Convergence from the neuroimaging literature seems to indicate that the VS is important for responses to reward sub-processes (e.g., pleasure, motivation) that are critical for guiding adaptive decision-making.

1.2.4 Interactions between vmPFC/OFC and VS

Collectively, the extant data on the functions of vmPFC/OFC and VS in reward processing provides evidence for complementary roles in reward processing that may be crucial for the control and execution of value-based decisions. A critical unresolved question, which serves as the motivation for the study presented in **Chapter 3**, is how these two areas interact to mediate the observed functions in humans.

Anatomical and functional connectivity data from animals and humans are consistent with putative interactions between vmPFC/OFC and VS. Rodent studies have demonstrated direct glutamatergic projections from vmPFC/OFC to VS (Sesack et al., 1989; Voorn et al., 2004; Gabbott et al., 2005), while human fMRI studies indicate that there are distinct structural connections from VS to vmPFC/OFC (Tziortzi et al., 2013), highly correlated activity between the vmPFC/OFC and VS at rest (Di Martino et al., 2008; Choi et al., 2012), and greater co-

activation in vmPFC/OFC and VS during tasks involving favorable outcomes or rewards (Cauda et al., 2011; Diekhof et al., 2012). While consistent with vmPFC/OFC modulation of VS activity, these circumstantial and correlational findings do not provide evidence of causality. Evidence corroborating the exact causal functional dynamics between the VS/NAc and vmPFC/OFC has only recently begun to emerge as a result of novel technological advances, which, at present, comes from non-human animal studies.

Prior to any non-human animal studies of vmPFC-VS interactions, Frank and Claus (2006) provided a computational mechanistic model of fronto-striatal interactions derived from theories of reward and reinforcement learning. In this model, a striatal system receives dopaminergic inputs from the midbrain, which monitors the frequency of positive and negative decision outcomes via go and no-go ('trial-and-error') learning to refine motor actions. The OFC receives information about these positive and negative decision outcomes from the midbrain and constitutively integrates this information with information about the value of an outcome to facilitate subsequent action selection. Taking the OFC 'off-line' in this OFC-striatal neural network model resulted in deficits in decision-making much like the effects seen in these tasks following lesions to the vmPFC/OFC across species. This model thus proposes that the expression of fast, flexible, and adaptive decision-making relies on intact interaction between the OFC and striatum. More specifically, it indicates a role for the OFC in the top-down biasing of striatal activity for action selection, wherein information about the magnitude or value of an outcome becomes integrated with information about simple frequencies of positive and negative outcomes to quickly and efficiently influence differentiation between 'go' and 'no-go' responses. This intriguing computational model preceded direct, *in vivo* tests of vmPFC/OFC-VS interactions by several years, owed to the recent emergence of novel applications of multimodal

techniques to test the behavioral consequences of causal interactions between these two brain regions.

Novel combinations of techniques have only recently been used to relate the causal interactions between vmPFC/OFC and VS to animal behavior. Ghazizadeh et al. (2012) did this for the first time by combining electrophysiological recording of neurons in the NAc shell (NAcS) with concurrent inactivation of the vmPFC in rodents during performance on a reward-learning task. Whereas control animals were able to make successful responses to obtain a reward, animals with inactivated vmPFCs were unable to discriminate between rewarded and unrewarded cues. These behavioral data were linked to have neural effects in the NAc – as expected, vmPFC inactivation resulted in direct modulation of NAcS neuronal activity and corresponded with disinhibited responding to unrewarded cues. vmPFC was specifically responsible for controlling at least two distinct populations of neurons in the NAcS to mediate appropriate responding: (1) one population, which facilitates actions ("go"), and (2) one population that inhibits responses ("no-go"). The dual nature of this modulation suggests a process of summation or integration of opposing signals to guide adaptive behavioral responses during reward learning.

In a parallel effort to characterize the importance of the VS-vmPFC/OFC neural pathway on value-based decision-making, St. Onge and colleagues (2012) performed concurrent inactivation of both brain regions and assessed the effects of this functional disconnection on rodent performance in a probabilistic discounting task. In this task, larger, uncertain rewards were pitted against smaller, sure rewards. Rats learned that pressing the lever that corresponded to large/risky outcomes was disadvantageous over time as the probability of obtaining a reward decreased over the course of the task. Although disconnection of the vmPFC and NAc did not

impair the acquisition of probabilistic reward learning, the animals were less accurate and had slower response times and reduced locomotor activity. The authors suggest that these findings reflect impaired attention or vigilance. This interpretation finds support in an earlier study showing that mPFC and NAc inactivation or disconnection resulted in attentional impairments in a five-choice serial reaction time task (Christakou et al., 2004). However, re-evaluating these findings in the context of the previously described computational model of vmPFC/OFC-VS interactions provides an alternative interpretation of the data. If both vmPFC/OFC and VS are taken 'off-line,' there is no information from vmPFC/OFC about value to integrate with dopamine signals from the midbrain to influence and efficiently guide discrimination of 'go' or 'no go' responding. In effect, the most efficient (and perhaps most direct) pathway involved in guiding value-based decision-making has been "wiped out," and it could be the case that other brain regions (i.e., amygdala, hippocampus, thalamus, dorsolateral PFC) are processing these reward-outcome associations, but to a much less efficient degree. This would explain these congruent findings, wherein learning is still acquired but occurs at a much slower rate and is subject to error, or perseveration (Christakou et al., 2004; St Onge et al., 2012).

Recent work combining optogenetics with fMRI (ofMRI) in awake rodents directly tests causal dynamics of a prefrontal-striatal-midbrain circuit (Ferenczi et al., 2016). The authors show that dopaminergic neuronal excitation causes an increase in striatal BOLD, which is associated with increased reward-seeking behavior. Sustained elevated mPFC activity decreases striatal BOLD responses to dopaminergic cell signaling, resulting in decreased dopamine neuron self-stimulation. This work corroborates the computational model presented by Frank and Claus (2006), where the striatum acts as the intersecting target of both midbrain dopaminergic and prefrontal cortical projections to influence reward-related processes. Resting-state connectivity

findings suggest that sustained or elevated mPFC activity results in greater connectivity with the ventral striatum, diminishing the modulatory influence of midbrain dopaminergic signals.

Despite these promising findings in rodents, virtually no human studies have been done to characterize the behavioral relevance of interactions within the vmPFC/OFC-VS circuit. Cohen et al. (2012) recorded NAc activity simultaneously with surface EEG in patients with obsessive-compulsive disorder undergoing NAc deep brain stimulation during performance on a task of reward anticipation and motivation. Granger causality analyses showed that "top-down" frontal cortical to NAc synchrony was stronger when rewards were being anticipated during NAc DBS, suggesting that these regions are dependent on each other during reward processing in humans. In order to further address this gap in the literature, the study described in **Chapter 3** combines fMRI with the lesion method to establish a causal role for vmPFC/OFC in modulating VS activity during reward anticipation. Establishing the normative behavioral outcomes of this circuit's causal dynamics, as well as the consequences of "top-down" prefrontal dysfunction, will lead to a better understanding of the pathophysiological mechanisms at play in adaptive and maladaptive reward processing. Dysfunction within the vmPFC/OFC-VS circuitry may be a key neuropathophysiological mechanism underlying certain symptoms of mental illness. If adaptive value-based learning and decision-making depend critically on efficient integration of reward-related information within the vmPFC/OFC-VS pathway, then variation in the integrity of this circuit should be associated with variation in reward processing.

1.2.5 Evidence of abnormal vmPFC/OFC and VS activity and structure in psychopathy

Clinical research findings have associated dysfunction in reward processing with abnormal structural and/or functional characteristics of vmPFC/OFC and VS in a number of mental health disorders, including psychopathy. Psychopathy is a mental health disorder

characterized by callous and impulsive antisocial behavior. Present in roughly a quarter of adult prison inmates, psychopathy is associated with a disproportionately high incidence of violent crime, substance abuse, and recidivism (Smith and Newman, 1990; Hare, 2003). Based on these personality and behavioral characteristics, vmPFC/OFC dysfunction is thought to be a key facet underlying the development of psychopathy. Psychopathic personality traits share striking similarities to personality changes that follow vmPFC/OFC damage, including lack of empathy, impulsivity, and poor decision-making. "Pseudopsychopathy" (Blumer and Benson, 1975) or "acquired sociopathy" (Eslinger and Damasio, 1985) following vmPFC/OFC damage have led researchers to test theories of vmPFC/OFC dysfunction in psychopathy (Kiehl, 2006; Blair, 2008). Numerous neuroimaging studies have identified reduced gray matter volumes in frontal cortex, particularly OFC, frontopolar cortex, anterior rostral PFC, and right inferior frontal gyrus (Yang et al., 2005; de Oliveira-Souza et al., 2008; Muller et al., 2008; Yang et al., 2010; Boccardi et al., 2011; Yang et al., 2011; Ermer et al., 2012; Gregory et al., 2012; Ly et al., 2012) and vmPFC/OFC dysfunction across various tasks ranging from cognitive control to moral decision-making [for a review of PFC dysfunction in psychopathy, see Koenigs (2012)].

It has long been postulated that psychopathy may be linked to abnormalities in processing reward and punishment (Cleckley, 1941; Lykken, 1957; Fowles, 1980; Gorenstein and Newman, 1980; Blair, 2008). In a seminal clinical description of psychopathy, *The Mask of Sanity*, Dr. Hervey Cleckley explains how abnormal reward and punishment processing manifests in psychopathic individuals:

> "Even weak impulses, petty and fleeting gratifications, are sufficient to produce in [the psychopath] injudicious, distasteful, and even outlandish misbehavior. Major positive attractions are not present to compete successfully with whims, and the major negative deterrents (hot, persistent shame, profound regret) do not loom ahead to influence him." (p. 389)

Gorenstein and Newman (1980) describe psychopathy as an extreme form of disinhibition, in which individuals act impulsively to (1) obtain immediate rewards, at the cost of achieving long-term goals and (2) avoid punishment. Over several decades, a host of behavioral and psychophysiological studies have offered support for these observations (Lykken, 1957; Schmauk, 1970; Newman et al., 1985; Arnett et al., 1997; Baskin-Sommers et al., 2010). Psychopathic individuals are unable to withhold responses to a rewarded stimulus, even when this error results in a loss of reward (Newman et al., 1985). In a reinforcement learning test of both rewards and punishments, psychopathic individuals show impairments in discriminating between stimuli associated with varying levels of punishment (Blair et al., 2006). These data corroborate clinical observations that psychopathic individuals simultaneously have a pronounced sensitivity to rewarded outcomes and insensitivity to aversive outcomes.

Functional brain imaging has been used to investigate whether psychopathic traits are associated with hypersensitivity to reward (Buckholtz et al., 2010; Bjork et al., 2012). These studies of psychopathy and reward have associated psychopathic personality characteristics with heightened reward sensitivity in VS. However, both of these studies were conducted with non-forensic community participants, among whom few, if any, would meet criteria for the categorical diagnosis of psychopathy as defined for pathologically antisocial individuals (Hare, 2003). To date, no studies have linked aberrant vmPFC/OFC-VS function to criminal psychopathy and relevant behavioral measures in a reward-focused framework. Therefore, **Chapter 4** addresses the question of whether or not vmPFC/OFC and VS activity is different between criminal psychopaths vs. non-psychopaths during reward processing.

1.3 Objectives

In the following two chapters, I use the lesion method with a neurosurgical patient population to establish a causal role for the vmPFC in a behavioral test of learning-independent decision-making under risk (**Chapter 2**) and to examine how vmPFC damage affects VS MRI-BOLD activity during reward anticipation (**Chapter 3**). The striking similarities between acquired behavioral dysfunction following vmPFC damage and psychopathic traits provide the rationale for the study described in **Chapter 4**, which focuses on VS dysfunction in a group of criminal inmates with psychopathy. I conclude with a summary and integration of the research findings.

Chapter 2: Ventromedial prefrontal cortex damage alters relative risk tolerance for prospective gains and losses

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2.1 Introduction

According to "rational actor" models of economic choice, in a cost-benefit analysis between two options with different expected payouts, people would be expected to choose the option that produces the maximum payout in the long run. In situations where two options provide the same expected payout, a person would be perfectly ambivalent about the choice. Daniel Kahneman and Amos Tversky (1979) were the first to test a proposed theory in social and behavioral economics known as Prospect Theory, which describes the way people are *actually* expected to choose between probabilistic options involving risk. They provided empirical evidence that human decision-making is susceptible to influence by a number of cognitive and affective biases that yield systematic deviations from ostensibly rational (i.e., financially optimal) choices. Kahneman received the Nobel Memorial Prize in Economic Sciences in 2002 for this work.

Tests of Prospect Theory show that people's decisions can be biased based on the way two options are worded or "framed." Individuals are more likely to gamble when the choices are framed as prospective losses, as compared to when mathematically equivalent choices are framed as prospective gains. For example, if asked to choose between a "sure" option of, say, a $20 gain or a gamble for a 50% chance of winning $40 (with a 50% chance of winning nothing), people are more likely to secure the "sure" gain instead of incurring a risky gamble. The inverse

is true in the loss domain, such that, if given the option between a "sure" loss of $20 versus a 50% chance of losing $40 (with a 50% of losing nothing), people are more likely to choose the risky gamble over incurring a certain loss. This bias towards risk aversion in the gain domain and risk-seeking in the loss domain was shown to exist on a utility curve along a range of expected value differences between the sure option and the gamble, until a "break point" (i.e., a point at which choices are made with deference to the expected utility of an outcome rather than by influence of the affective frame) for rational decision-making is met.

This difference in risk tolerance for gains versus losses (risk aversion for positive prospects in a "gain" condition but risk seeking for negative prospects in a "loss" condition) is called the "reflection effect" or "framing bias" because the preference reverses around zero, as a mirror image or reflection (Kahneman and Tversky, 1979). This pattern of choices violates "expected utility" models of decision-making and demonstrates that economic prospects are evaluated differently when conceived as gains versus losses. The reflection effect has been invoked to explain real-world choices deviating from expected utility, as commonly observed in casino gambling, financial investing, and insurance markets (Camerer, 2001). Identifying the brain region or regions responsible for biased decision-making in tests of the reflection effect would thus help illuminate the neuropsychological mechanisms governing pivotal aspects of human choice behavior, such as the susceptibility to bias when the probability of an outcome is unknown.

Human neuroimaging studies suggest that vmPFC/OFC seems to be encoding the value representation of an anticipated outcome, likely one that is rooted in the anticipated utility of the outcome (Grabenhorst and Rolls, 2011; Liu et al., 2011; Diekhof et al., 2012; Levy and Glimcher, 2012). Although functional imaging studies have correlated vmPFC/OFC activity with

the degree of rationality across individuals on tests of the reflection effect or framing (Deppe et al., 2005; De Martino et al., 2006), there has not yet been any demonstration that vmPFC/OFC plays a *causal* role in mediating biases in decision-making under risk. In this chapter, I investigate this causal brain–behavior relationship through the study of neurological lesion patients with vmPFC/OFC damage using a behavioral test of the reflection effect. vmPFC/OFC lesion patients' performances on this task are expected to differ from neurologically normal comparison and brain-damaged comparison groups, such that they would be expected to endorse choices with greater influence to bias within each condition.

2.2 Methods

Participants

The target lesion group consisted of five neurosurgical patients with extensive bilateral parenchymal changes, largely confined to the vmPFC, where vmPFC is defined as Brodmann areas 11, 25, 32, and the medial portion of 10 below the level of the genu of the corpus callosum (Mackey and Petrides, 2014) (**Figure 2**). All five patients had large anterior cranial fossa meningiomas with vasogenic edema. Their clinical presentations were subtle or obvious personality changes over at least several months preceding surgery. Each patient underwent gross total tumor resection without any intraoperative or postoperative complications. On post-surgical MRI, although vasogenic edema largely resolved, there were persistent circumscribed bilateral vmPFC lesions in each patient.

Five neurosurgical patients who had focal lesions outside of vmPFC comprised a brain-damaged comparison (BDC) group, which included n=2 patients who had undergone tumor resections and n=3 patients who had undergone surgery for aneurysm clipping following subarachnoid hemorrhage. Lesions in the BDC group involved anterior and

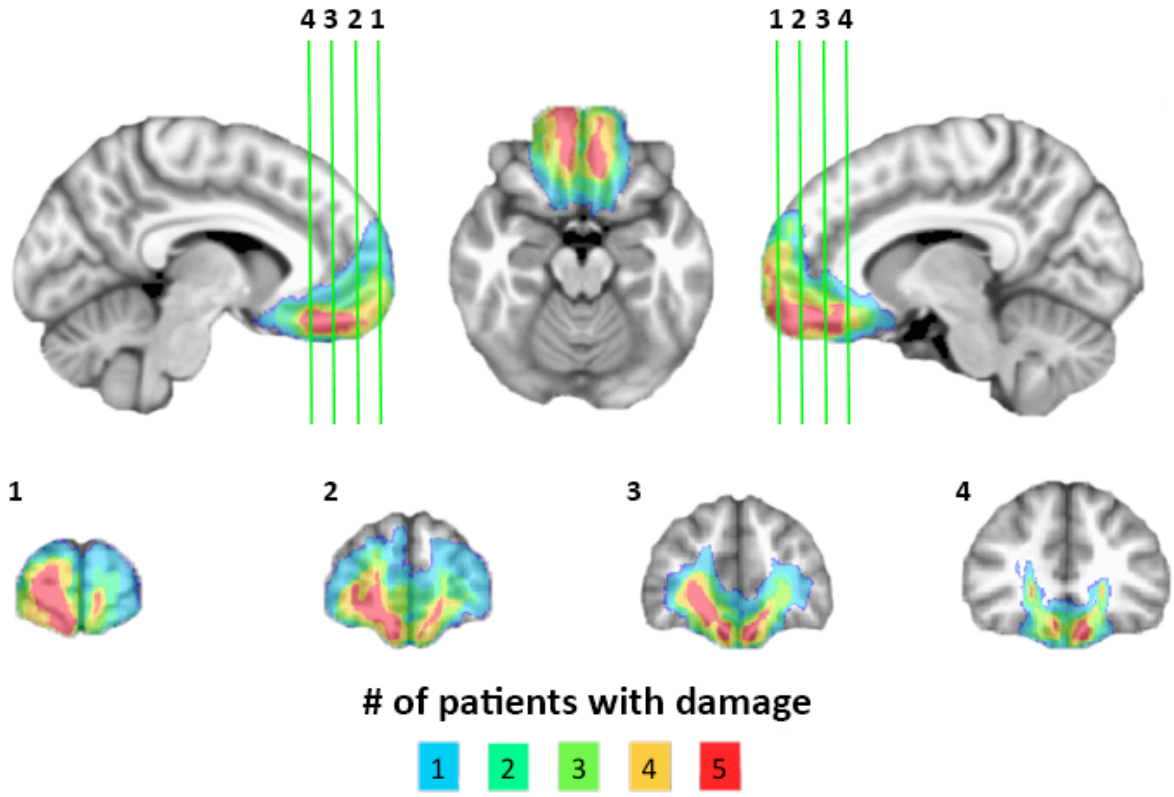

Figure 2. Lesion overlap of vmPFC patients. Color indicates the number of overlapping lesions at each voxel. For axial and coronal views, the left side of the brain is displayed on the reader's right.

lateral temporal cortex (*n*=3) and dorsal frontal cortex (*n*=2). All vmPFC and BDC patients' neurosurgeries were performed in adulthood, and all experimental data were collected at least three months after surgery, during the chronic phase of recovery (vmPFC range: 31.9–74.8 months). The inclusion of these BDC patients allowed me to rule out the possibility that the pattern of choices observed in the vmPFC lesion group could be due to anatomically non-specific effects of brain damage or history of related medical issues (e.g., craniotomy, edema, seizure, past medications, etc.). At the time of testing, one BDC patient and two vmPFC lesion patients were on psychoactive medications (one vmPFC patient on SSRI, one vmPFC patient and one BDC patient on anti-seizure medication). All neurosurgical patients (vmPFC and BDC) were

recruited through a patient registry established through the University of Wisconsin Department of Neurological Surgery.

Thirty neurologically healthy adults also participated as a normal comparison (NC) group. NC participants had no history of brain injury, neurological or psychiatric illness, or current use of psychoactive medication. NC participants were between the ages of 54 and 70, matched to the ages of the lesion groups (see **Table 1** for group demographic and neuropsychological data). NC participants were recruited through community advertisement. All participants had normal or corrected to normal vision.

Lesion segmentation and image normalization

vmPFC patients' lesions were visually identified and manually segmented on a high-resolution (1 mm^3) T1-weighted anatomical MRI image. Lesion boundaries were drawn to include areas with evidence of gross tissue damage or abnormal signal characteristics. A T2*-weighted FLAIR anatomical image was used to identify additional damage surrounding the core lesion area not apparent on the T1-weighted image (tissue with signal characteristics differing from healthy gray or white matter, e.g., hyperintensity). All structural MRI data were obtained at least three months after surgery (range: 13.6–55.5 months). T1-weighted anatomical images were preprocessed with AFNI (Cox, 1996) to remove non-brain tissue. The resulting skull-stripped anatomical images were diffeomorphically aligned to the Montreal Neurological Institute (MNI) coordinate system using a Symmetric Normalization algorithm (Avants and Gee, 2004) with constrained cost-function masking to prevent warping of tissue within the lesion mask (Brett et al., 2001). A lesion overlap map was created by computing the sum of lesion masks for all subjects in MNI template space (**Figure 2**).

Table 1. Subject Characteristics: Lesion Study 1

	Age	Sex	Edu.	IQ (Reading)	IQ (Arithmetic)	IQ (Avg.)	WMI	Digit Span	Arithmetic
vmPFC (n=5)	59.8 (5.2)	3 M / 2 F	15.6 (3.6)	105.2 (11.2)	92.6* (10.4)	98.9* (10.1)	107.0 (16.1)	13.0 (3.2)	9.6 (2.9)
BDC (n=5)	60.0 (7.0)	3 M/ 2 F	14.8 (1.8)	101.2* (8.1)	100.4 (5.6)	100.8 (3.5)	N/A	N/A	N/A
NC (n=30)	62.0 (4.1)	17 M/ 13 F	17.1 (2.6)	112.5 (6.0)	106.0 (9.8)	109.2 (6.4)	N/A	N/A	N/A

Age=age of participant at time of testing (years); Education=years of education completed; IQ (Reading)=IQ estimated by the Wide Range Achievement Test 4 (Wilkinson and Robertson, 2006), Blue Reading subtest; IQ (Arithmetic)=IQ estimated by the Wide Range Achievement Test 4 (Wilkinson and Robertson, 2006), Blue Arithmetic subtest; WMI=Working Memory Index from the WAIS (Wechsler, 2008) (standardized mean=100, SD=15); Digit Span=scaled score for subject's age group on the digit span subtest of the WAIS (standardized mean=10, SD=3); Arithmetic=scaled score for subject's age group on the arithmetic subtest of the WAIS (standardized mean=10, SD=3). For group data, means are presented with SD in parentheses. *Significant difference from normal comparison group (P<0.05). vmPFC=ventromedial PFC; BDC=brain-damaged comparison; NC=normal comparison.

Decision-making task

Participants performed a financial decision-making test adapted from original tests of Prospect Theory (Kahneman and Tversky, 1979; Tversky and Kahneman, 1981) (**Figure 3A**). At the beginning of each trial, participants saw a fixation cross (+) in the center of the screen for two seconds followed by the question "Which would you prefer?". Underneath this question, two hypothetical options were presented: a sure option and a gamble. Sure options ranged from gains or losses of $5 to $95, in increments of $5. Each sure value was presented twice for both the gain and loss conditions, for a total of 76 trials. The sure value was presented next to a gamble for a 50% chance to win or lose $100, depending on the condition (i.e., sure gains presented alongside a gamble to win $0 or $100 and sure losses presented alongside a gamble to lose $0 or $100). To ensure that all participants understood the task structure and the stakes of the gambles, practice trials involving the $5 and $95 sure values were presented for each gain/loss condition for a total

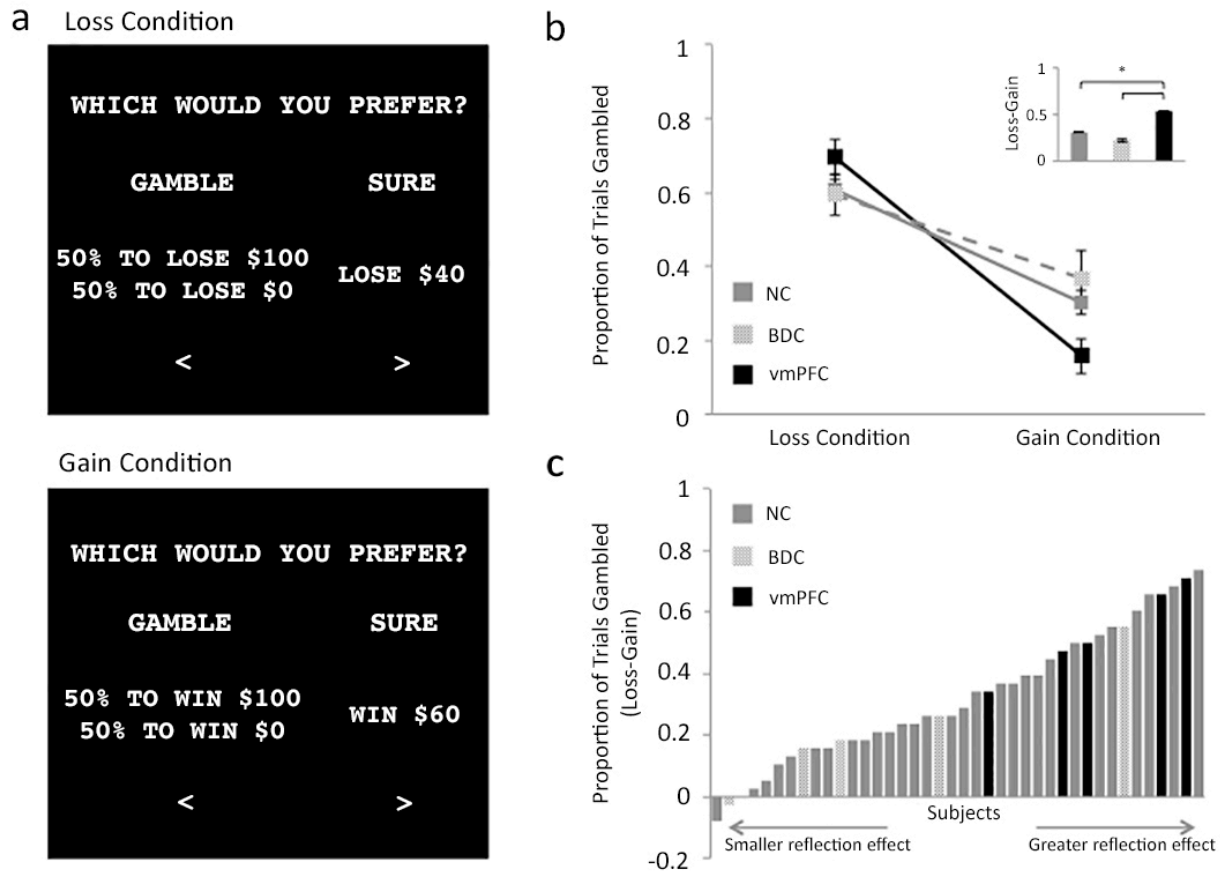

Figure 3. Example trials and summary data. (A) Examples of trials from the loss condition (top panel) and gain condition (bottom panel). In both examples, the difference between the gamble and the sure option is mathematically equivalent. The reflection effect is demonstrated by a greater likelihood to choose the gamble in the loss condition than in the gain condition. (B) Comparison of gamble frequency for the loss condition and gain condition, for each group. Error bars indicate standard error. The bar graph inset shows the difference in gamble frequency between the loss and gain conditions for each group. *P<0.05. (C) Each vertical bar represents the magnitude of reflection effect for an individual subject.

of four practice trials. Participants were instructed to press the left or right arrow keys to choose one of the two options and to treat each trial independently of the other trials. There was no limit on decision time. Participants did not see feedback of their gains and losses following their choice. Trial presentation was pseudorandomized such that all participants saw the same randomized trial order. The position of the sure option (left or right side of screen) was counterbalanced across trials.

Supplementary cognitive tasks

All vmPFC patients completed several neuropsychological tests to ensure intact basic elements of cognitive function germane to the demands of the decision-making task. vmPFC patients completed the Wechsler Adult Intelligence Scale-IV (WAIS) Working Memory Index (Wechsler, 2008), which consists of Digit Span and Arithmetic subtests to measure attention, concentration, mental control, and concentration while performing math problems. All participants completed the Wide Range Achievement Test (WRAT) 4 blue arithmetic test (Wilkinson and Robertson, 2006), a measure of basic arithmetic abilities. All vmPFC patients exhibited normal performance on each of these tests (**Table 1**).

Statistical analysis

I performed non-parametric statistical tests because of the small sample sizes of vmPFC lesion patients (n=5) and BDC patients (n=5) using SPSS. I used a two-tailed Wilcoxon signed-rank test for paired data to compare the proportion of gambles selected for the loss condition as compared to the gain condition, within each group. For between-group analyses I used a two-tailed Kruskal–Wallis test along with two-tailed Mann–Whitney U tests for pairwise comparisons. Because these tests collapse across all sure amount values, they are extremely conservative estimates of within- and between-group reflection effects. I therefore also ran a mixed effects logistic regression using the R statistical package (https://www.R-project.org) that allowed me to test for an overall interaction of group (vmPFC, NC, BDC) and condition (gain, loss), controlling for the effect of different levels of sure value (e.g., $5–$95), with respect to the subject's preference for the gamble versus the sure option.

2.3 Results

As expected, the NC subjects exhibited a significant difference between conditions (reflection effect), selecting the gamble more frequently overall in the loss condition (61.0%; SD: 15.5%) than in the gain condition (30.3%; SD: 17.5%) (Wilcoxon Z=−4.64, P=3×10^{-6}) (**Figure 3B**). As the key test of the study hypothesis, I compared the strength of the reflection effect (i.e., the difference between the proportion of trials gambled in the loss condition and the gain condition) between groups. Collapsing across all trials within each condition, the vmPFC patients exhibited a significantly stronger reflection effect (69.5% gamble frequency in loss condition; SD: 10.6%, 15.8% gamble frequency in gain condition; SD: 10.9%) than the NC subjects (Mann–Whitney U=29.50, P=0.032) (**Figure 3B and C**). This enhanced reflection effect cannot be attributed to non-specific effects of brain damage, as the BDC group exhibited a similar magnitude reflection effect to the NC group (59.5% gamble frequency in loss condition; SD: 12.6%, 36.8% gamble frequency in gain condition; SD: 16.4%) (Mann–Whitney U=57.50, P=0.41) but a significantly smaller reflection effect than the vmPFC group (Mann–Whitney U=3.0, P=0.05). Nor can the group differences in the reflection effect be attributed to overall differences in gambling rates (Kruskal–Wallis χ^2=0.61, P=0.74) or reaction times (Kruskal–Wallis χ^2=1.77, P=0.41).

I confirmed the significant group difference in reflection effect using a mixed effects logistic regression that accounted for variable non-independent choices across the different levels of sure values and group differences in standardized WRAT arithmetic scores (**Figure 4**). This analysis demonstrated a significant overall group by condition interaction (χ^2=31.22, P=1.66×10^{-7}), which held for specific comparisons between the NC and vmPFC groups (Z=3.28, P=8.00×10^{-7}) as well as between the BDC and vmPFC groups (Z=4.83, P=1.02×10^{-6}).

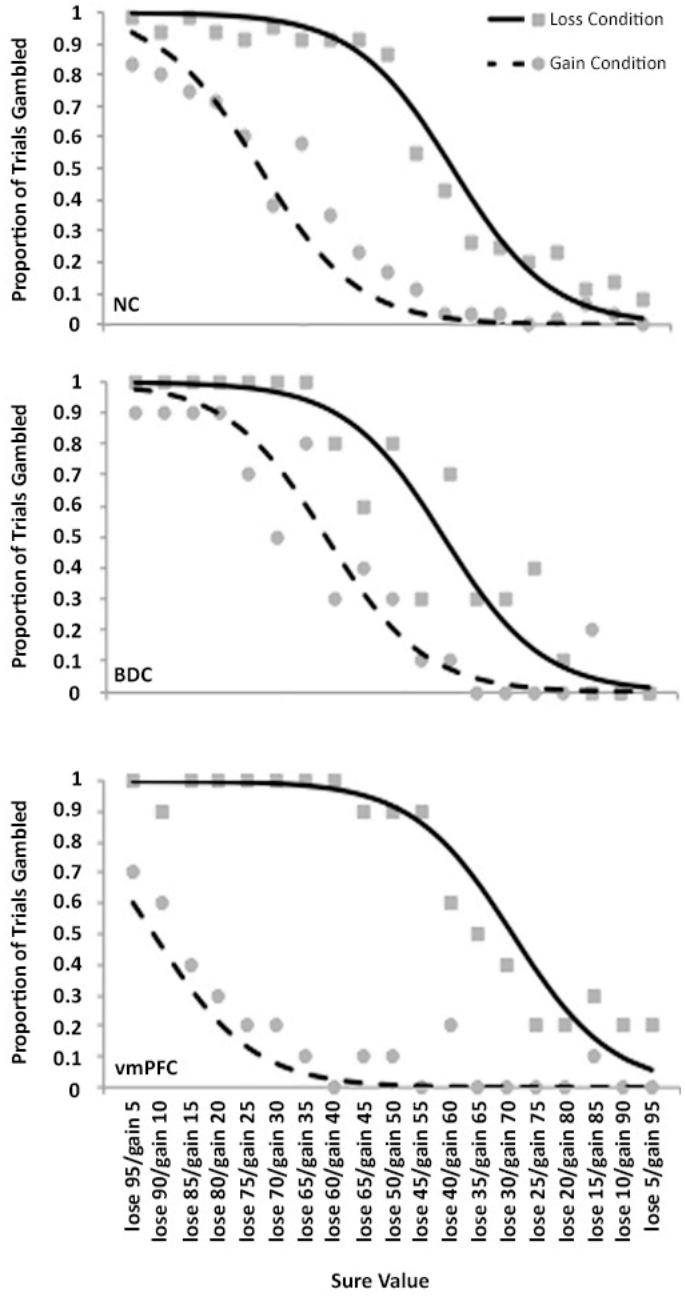

Figure 4. Reflection effect data across each sure option amount within each group. Each data point represents the overall proportion of selected gambles for each condition, for a given sure value amount. The *x*-axis indicates the sure value amounts (each column represents mathematically equivalent choices as either gains or losses). The lines represent the smoothed estimated probability of gambling for each condition, corresponding to the logistic regression analysis.

I conducted post-hoc Mann–Whitney *U* and logistic regression analyses to examine choices for the gain and loss conditions separately. Between the NC and vmPFC groups, there was no significant difference in gambling for the loss condition (Mann–Whitney U=41.5, P=0.11; logistic regression: Z=−1.01, P=0.78) but a trending significant difference for the gain condition (Mann–Whitney U=36.5, P=0.07; logistic regression: Z=2.26, P=0.11). Between the BDC and vmPFC group, there was no significant difference in gambling for the loss condition (Mann–Whitney U=7.0, P=0.25; logistic regression: Z=1.34, P=0.73) but a significant difference for the gain condition (Mann–Whitney U=3.5, P=0.06; logistic regression: Z=−3.49, P=0.03). Between the NC and BDC groups, there was no difference in gambling for the loss condition (Mann–Whitney U=70.5, P=0.83; logistic regression: Z=0.32, P=0.99) or for the gain condition (Mann–Whitney U=63.0, P=0.57; logistic regression: Z=−1.22, P=0.76).

To examine the vmPFC patients' pattern of choices in relation to “rational” choice, I calculated the average cumulative hypothetical earnings for each group across all trials. For this calculation I used the expected value of the gamble for any trial in which the gamble was selected (i.e., the product of the potential outcome and the probability of that outcome; $50 for the gain condition or −$50 for the loss condition). A purely “rational” actor who always selects the greater (or less negative) option between the expected value of the gamble and the sure amount would finish this task with a net balance of $900. The average hypothetical ending balance for the vmPFC group ($480.00, SD: $190.53) trended toward a significantly lower value than the NC group ($638.50, SD: $207.49; Mann–Whitney U=37.5, P=0.08) and the BDC group ($718.00, SD: $125.62; Mann–Whitney U=4.0, P=0.10). There was no significant difference between the NC and BDC groups (Mann–Whitney U=64.5, P=0.63).

To further examine the choice behavior of each group, I calculated the sure value amounts at which the choice probability for each group was equal to 0.5. These values serve as an index of subjective equality (indifference) between the sure and gamble options. In the gain condition, the indifference point for the vmPFC lesion group ($8.25) was lower than either comparison group (NC: $27.73; BDC: $38.30), consistent with the selection of fewer gambles. In the loss condition, the indifference point for the vmPFC lesion group was less negative (−$29.60) than either comparison group (NC: −$38.31; BDC: −$41.08), consistent with the selection of more gambles.

Finally, I found no significant group by condition interaction for reaction times (χ^2=2.25, P=0.32**; Figure 5**).

2.4 Discussion

The difference in risk-taking for prospective gains relative to losses is one of the seminal demonstrations of irrational bias in human decision-making. This study is the first to identify a brain region that plays a causal role in moderating this effect. Furthermore, this study provides novel evidence regarding the function of vmPFC, which is a key node in the brain network underlying value-based decision-making. Human functional imaging research has shown that, across a wide variety of experimental stimuli, tasks, and outcomes, vmPFC activity is commonly linked to reward and subjective value (Knutson et al., 2003; Grabenhorst and Rolls, 2011; Liu et al., 2011; Levy and Glimcher, 2012). Moreover, vmPFC damage has been associated with impairments in real-world decision-making (Blumer and Benson, 1975; Eslinger and Damasio, 1985; Barrash et al., 2000), as well as in laboratory paradigms involving risky gambles (Bechara et al., 1997; Camille et al., 2004), moral judgment (Ciaramelli et al., 2007; Koenigs et al., 2007; Young et al., 2010), economic exchange (Koenigs and Tranel, 2007; Krajbich et al., 2009),

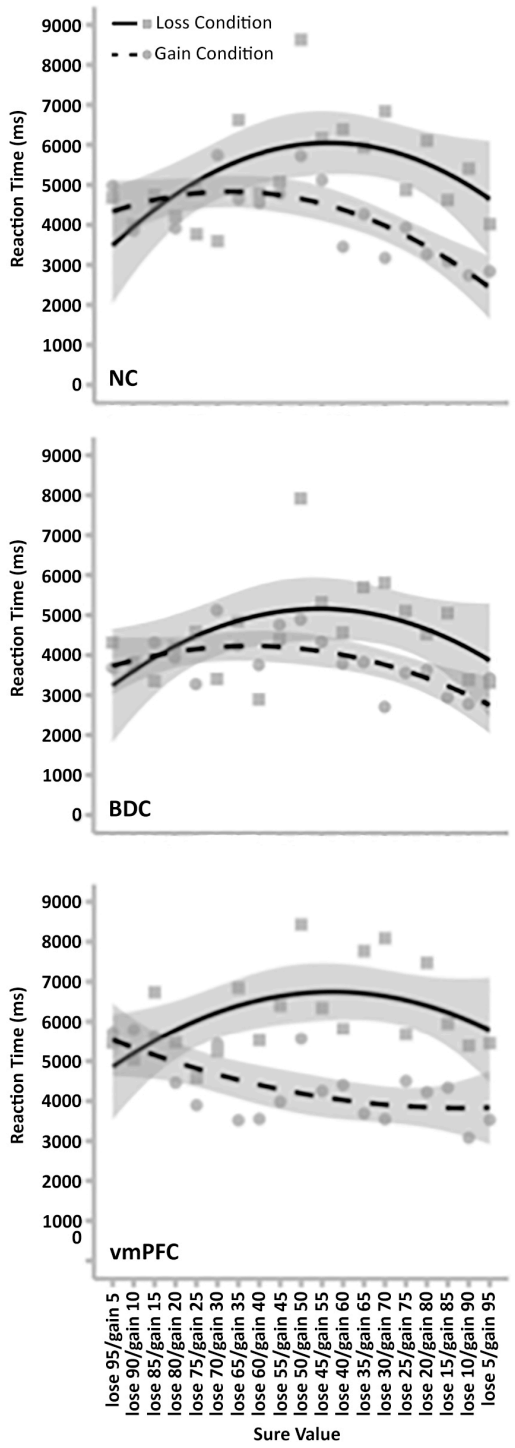

Figure 5. Reaction time data across each sure option amount within each group. Each data point represents the average reaction time for each condition, for a given sure value amount. The *x*-axis indicates the sure value amounts (each column represents mathematically equivalent choices as either gains or losses). The lines represent the smoothed estimated reaction time for each condition, corresponding to the logistic regression analysis.

probabilistic reinforcement learning (Fellows and Farah, 2003; Wheeler and Fellows, 2008), and simple binary item preference (Henri-Bhargava et al., 2012). Despite the well-established role for vmPFC in value-based decision-making, the specific cognitive and affective functions subserved by this brain area are still a matter of debate and inquiry.

The reflection effect can be interpreted in terms of a dual-process model of decision-making, where one process is intuitive, affective, fast, heuristic, and automatic, whereas the other process is deliberative, effortful, slow, analytical, and based on conscious reasoning (Kahneman, 2003). It is assumed that the reflection effect is based on a relative predominance of the former process over the latter. Previous studies have suggested that vmPFC mediates the intuitive/affective contribution to value-based decision-making (Damasio et al., 1996; Bechara et al., 1997; Greene, 2007; Koenigs et al., 2007). The present results challenge this interpretation, as damage to the vmPFC resulted in a putatively less rational pattern of choices. It is important to note that the vmPFC patients' choices were not simply more erratic or less consistent, as has been shown in simple preference studies (Fellows and Farah, 2007; Henri-Bhargava et al., 2012). As can be seen in **Figure 4**, the vmPFC patients exhibited choice functions (proportions of trials gambled across different sure amounts) that were at least as "smooth" or consistent as the choice functions of the NC and BDC groups, in that the proportion of gambles for a given sure gain amount was almost always greater than or equal to the proportion of gambles for smaller sure gain amounts, and almost always less than or equal to the proportion of gambles for larger sure gain amounts (and vice versa for sure loss amounts). Nor were vmPFC patients simply more apt to gamble, regardless of condition. Rather, the vmPFC patients evinced a systematically enhanced reflection effect, indicating a more complicated, multi-faceted role for vmPFC in decision-making.

One possibility is that vmPFC plays a critical role in triggering emotional responses to imagined, hypothetical gambles. It has been proposed that affective responses to hypothetical outcomes are critical input during value-based decision-making (Damasio et al., 1996; Bechara et al., 1997). For example, imagining winning money in a gamble could engender a positive emotional response (thereby making the gamble an attractive option), whereas imagining losing money in a gamble could engender a negative emotional response (thereby making the gamble an unattractive option). A previous study found that vmPFC patients were emotionally insensitive (in terms of subjective ratings and skin conductance responses) to the results of hypothetical gambles that they could have (but did not) engage in (Camille et al., 2004). If the vmPFC patients in the present study were similarly insensitive to the hypothetical outcomes of the gamble options, then their choice behavior would be driven predominantly by their reactions to the sure options. That is, vmPFC patients would exhibit reduced attraction to the potential gamble gains relative to the sure gains (i.e., fewer gambles chosen in the gain condition) and reduced aversion to the potential gamble losses relative to the sure losses (i.e., more gambles chosen in the loss condition)—i.e., an abnormally large reflection effect. Indeed, I see that the results are consistent with the general idea that vmPFC contributes to value-based decision-making by triggering affective responses to hypothetical risks and rewards (Bechara et al., 2003). However, it should be noted that all options in the task (sure amounts and gambles) were hypothetical, so this interpretation presumes that the gamble options require one to compare and contrast multiple uncertain hypothetical outcomes in a way that the sure options do not. Future studies that compare responses for real, immediate gains/losses as opposed to hypothetical or distant gains/losses could more definitively test this interpretation.

The paradigm used in this study to examine the reflection effect is similar, conceptually and methodologically, to paradigms used to examine the framing effect. The framing effect and reflection effect were two key initial pillars of empirical support for prospect theory. Both paradigms involve a series of choices between a sure amount and a risky gamble; the main difference is that framing effects refer to a choice between options that have mathematically equivalent outcomes, but are framed differently (i.e., highlighting what may be lost in a particular transaction instead of what may be gained, or vice versa), whereas reflection effects refer to choices in conditions of potential gain versus potential loss. Regardless of this difference, both paradigms have shown that normal individuals are more likely to gamble when considering prospective losses as compared to prospective gains. Consistent with the current results, a previous neuroimaging study of the framing effect in healthy individuals showed that vmPFC activity correlated with the "rational" choice (i.e., lower levels of vmPFC activity were associated with larger framing effects) (De Martino et al., 2006).

One feature of the study design that warrants further discussion is the limited sample size of vmPFC lesion patients (n=5). For this study, I employed stringent selection criteria for the target group; lesions had to involve substantial portions of vmPFC bilaterally, but could not extend significantly outside vmPFC. This patient selection strategy is distinct from typical vmPFC lesion studies, which often include patients with lesions that are exclusively or primarily unilateral and/or lesions that extend beyond the boundaries of vmPFC (e.g., into adjacent dorsomedial PFC, lateral PFC, or anterior temporal lobe). Limiting the vmPFC lesion patient group to these more stringent criteria increases lesion homogeneity and reduces the likelihood of preservation of function by a single hemisphere. I believe the uniformity of lesion characteristics in this vmPFC patient sample likely contributes to the remarkable consistency of the individual

results. As can be seen in **Figure 3C**, the reflection effects for each vmPFC patient were similar to one another, and all well above the median of each comparison group ($median_{NC}$=0.26, $median_{BDC}$=0.18; $range_{vmPFC}$=0.34–0.71).

In this chapter, I present novel evidence that the vmPFC plays a critical role during human decision-making in a test of the reflection effect, when outcomes of choices are uncertain. As mentioned earlier, damage to vmPFC and/or adjacent white matter fibers may be resulting in an inability to imagine or anticipate what a choice's outcome or value *could be* in the future. Being able to anticipate an outcome's value may be crucial for the control and execution of adaptive value-based decisions. The extant data on the functions of both vmPFC/OFC and VS in reward processing provide evidence to support the hypothesis that these areas of the brain interact to mediate this anticipatory function for potentially rewarding outcomes. The nature of this interaction, however, remains a critical unresolved question in humans. In order to answer this question, the study described in the following chapter (**Chapter 3**) combines fMRI with the same sample of vmPFC lesion patients used in the current study (*n*=5) to establish a causal role for vmPFC/OFC in modulating VS activity during reward anticipation.

Chapter 3: Ventromedial prefrontal cortex damage is associated with decreased ventral striatum volume and response to reward

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3.1 Introduction

Previous human neuroimaging studies on reward processing have extensively used a task of reward processing called the Monetary Incentive Delay (MID) task. This paradigm has been shown to engage fronto-striatal circuitry during both reward anticipation and reward response (Knutson et al., 2001a; Knutson et al., 2001b; Knutson et al., 2008; Strohle et al., 2008; Nielsen et al., 2012; Stoy et al., 2012; Jung et al., 2013). In such tasks, vmPFC/OFC and VS activations co-occur most often during reward anticipation (Haber and Knutson, 2010). Although there is evidence from animals that vmPFC inactivation and sustained excitation alters VS activity (Ghazizadeh et al., 2012; Ferenczi et al., 2016) and human lesion work suggests impaired anticipatory physiological responses during value-based decision-making tasks (Bechara et al., 1997; Camille et al., 2004), there have been no demonstrations of the causal modulatory role of vmPFC/OFC on VS activity during reward anticipation in humans. In this chapter, I take the novel approach of combining fMRI with vmPFC/OFC lesion patient testing to inspect the modulatory role of vmPFC/OFC on VS activity during reward anticipation.

It is hypothesized that vmPFC/OFC damage will result in significantly lower VS responses to cues that indicate potential monetary gains, relative to no gains or potential losses, in a behavioral task of reward processing, compared to normal comparison subjects. This study also examines whether vmPFC/OFC damage results in structural reorganization of the reward circuit as measured by VS volume.

3.2 Methods

Participants

The target vmPFC lesion group consisted of five adult neurosurgical patients described in **Chapter 2** (**Figure 2)**. At the time of testing (range of time elapsed since surgery: 32-75 months), all patients had focal, stable MRI signal changes and resection cavities and were free of dementia and substance abuse. Seventeen healthy adults (*n*=10 males; *n*=7 females) with no history of brain injury, neurological or psychiatric illness, or current use of psychoactive medication were recruited as a normal comparison (NC) group. Demographic and neuropsychological data for the vmPFC and NC groups are summarized in **Table 2.**

fMRI task

To assess ventral striatum activity, I used an fMRI task involving the anticipation of monetary reward (Monetary Incentive Delay task), which has been used extensively to examine reward-related neural responses in healthy and patient populations (Knutson et al., 2008; Strohle et al., 2008; Beck et al., 2009; Khemiri et al., 2012; Nielsen et al., 2012; Stoy et al., 2012; Gleichgerrcht and Young, 2013). Previous fMRI research with this task has reliably demonstrated ventral striatum activity in response to cues indicating the potential gain of money (Khemiri et al., 2012; Gleichgerrcht and Young, 2013). Hence, this task provides a well-established fMRI measure of ventral striatum response to reward. Each trial consists of three periods. During the initial 2-second cue period, the subject views one of six different shapes (circles indicating potential gains, squares indicating potential losses) displaying the amount of money that could be gained or lost on that trial (+$0.00, +$1.00, +$5.00, -$0.00, -$1.00, -$5.00), followed by a 2-second fixation cross display (anticipation phase). During the following reaction-time task period (performance phase), the subject presses a button in response to a

Table 2. Subject characteristics: Lesion Study 2

	Age	Sex	Edu	IQ	BIS Total	BAS Total	BAS D	BAS FS	BAS RR	Pos Aff	Neg Aff	BDI-II	STAI-T
vmPFC (*n*=5)	59.8 (5.2)	3M/2F	15.6 (3.6)	105.2 (11.2)	16.4 (1.5)	38.6 (4.2)	11.0 (1.1)	11.6 (1.1)	16.0 (1.4)	37.6 (8.1)	16.2 (7.8)	6.2 (3.3)	33.4 (8.4)
NC (n=14)	62.6 (3.9)	9M/5F	17.1 (2.4)	113.0 (6.0)	18.9 (3.5)	38.1 (4.8)	10.6 (2.1)	11.4 (1.9)	16.1 (2.0)	39.9 (7.2)	13.9 (4.2)	3.7 (3.0)	29.6 (5.3)
P (vmPFC vs NC)	0.39	0.86	0.44	0.13	0.11	0.82	0.75	0.96	0.96	0.72	0.62	0.22	0.34

Means are presented with standard deviations in parentheses. Edu, years of education; IQ, intelligence quotient estimated by the Wide Range Achievement Test 4, Blue Reading subtest (Wilkinson and Robertson, 2006); BIS/BAS, scores from the Behavioral Inhibition System/Behavioral Approach System, with subtests for D=Drive, FS=Fun Seeking, and RR=Reward Responsiveness (Carver and White, 1994); Pos/Neg Aff, scores from the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988); BDI-II, Beck Depression Inventory-II (Beck et al., 1996); STAI-T, trait version of the Spielberger State Trait Anxiety Inventory (Spielberger et al., 1983).

visual prompt, a solid white triangle, as quickly as possible. If the subject responds quickly enough while the prompt is displayed, the subject either gains money or avoids losing money on that trial. The third task period (outcome phase) indicates the monetary result based on the response (e.g., "+$1.00" for a successful response during a gain trial or "-$5.00" for an unsuccessful response during a loss trial) for 2 seconds. The task difficulty for individual subjects was manipulated based on performance across the task, such that each subject successfully hit the target on approximately 66% of the trials for each cue type. The entire task consisted of one functional run of approximately 20 minutes, consisting of 90 8-second trials (15 trials for each of the 6 cue types) presented in pseudorandom order, followed by an inter-trial interval of 2, 4, or 6 seconds.

Before scanning, subjects were informed of all cue-outcome contingencies and completed a practice task consisting of 15 trials to ensure task comprehension and accurate reaction time calibration. Subjects completed the practice task twice outside the scanner and once inside the scanner during T1 acquisition, prior to the start of the full-length task. At the start of the scanning session, subjects were told that they would receive additional payment corresponding to their cumulative earnings on the full-length reward task.

After the scan, subjects were brought to a separate room and asked to rate their overall arousal and valence for each cue type using a scale ranging from 1 (arousal: "not at all aroused", valence: "very negative") to 7 (arousal: "highly aroused", valence: "very positive").

MRI data acquisition

All structural and functional MRI data were acquired using a 3.0 T GE Discovery MR750 scanner equipped with an 8-channel radio-frequency head coil array (General Electric Medical Systems; Waukesha, WI). High-resolution T_1-weighted anatomical images were acquired using an inversion-recovery spoiled GRASS [SPGR] sequence (TR=8.2ms, TE=3.2ms, α=12°, FOV=256x256mm, matrix=256x256, in-plane resolution=1x1mm^2, slice thickness=1mm, 1024 axial slices). To facilitate lesion segmentation, I collected a separate T_2-weighted FLAIR scan (TR=8650ms, TE=136ms, α=0°, FOV=220x220mm^2, matrix=512x512, in-plane resolution=0.43x0.43mm^2, slice thickness=5mm, gap 1mm, 25 axial slices).

Baseline resting cerebral blood flow (CBF) was estimated using a 3D fast spin echo spiral sequence with pseudocontinuous arterial spin labeling (pcASL) (Dai et al., 2008; Xu et al., 2010; Okonkwo et al., 2012) and background suppression for quantitative perfusion measurements (TR=4653ms, TE=10.5ms, post-labeling delay=1525ms, labeling duration=1450ms, eight

interleaved spiral arms with 512 samples at 62.5 kHz bandwidth and 38 4mm thick slices, number of excitations=3, scan duration=4.5min).

Whole-brain functional scans were acquired using a T_2*-weighted gradient-echo echoplanar imaging (EPI) sequence (TR=2000ms; TE=22ms; α=79°; FOV=224x224mm^2; matrix=64x64, in-plane resolution=3.5x3.5mm^2, slice thickness=3mm, gap=0.5mm, 38 interleaved axial oblique slices). Field maps were acquired using two separate acquisitions (TR=600ms, TE_1=7ms, TE_2=10ms, α=60°, FOV=240x240mm^2, matrix=256x128, slice thickness=4mm, 33 axial oblique slices). Resting-state functional images were collected while subjects lay still and awake, passively viewing a fixation cross for 5 minutes. Scans were acquired in the following order: pcASL, field map, rest, T1, task, T2-FLAIR.

Lesion segmentation and image normalization

Individual vmPFC lesions were visually identified and manually segmented on the T_1-weighted images. Lesion boundaries were drawn to include areas with gross tissue damage or abnormal signal characteristics on T_1 or T_2 FLAIR images. T_1-weighted images were skull-stripped, rigidly co-registered with a functional volume from each subject, then diffeomorphically aligned to the Montreal Neurological Institute (MNI) coordinate system using a Symmetric Normalization algorithm (Avants and Gee, 2004) with constrained cost-function masking to prevent warping of tissue within the lesion mask (Brett et al., 2001). I created the lesion overlap map by computing the sum of aligned binary lesion masks for all five vmPFC patients (**Figure 2**). Alignment parameters computed during this step were used in the subsequent normalization of all anatomical and functional data to MNI space.

fMRI task preprocessing and analysis

Data analysis was conducted using AFNI (Cox, 1996) and FSL (http://www.fmrib.ox.ac.uk/fsl) software. The task run was slice time corrected, field map corrected (Jezzard and Clare, 1999), motion corrected, smoothed with a 4mm full-width half-maximum (FWHM) Gaussian kernel, scaled to percent signal change, aligned to MNI space, and resampled to $3mm^3$ isotropic resolution. Anticipatory activity was modeled using a duration-modulated boxcar regressor, beginning at cue onset and spanning the 4-second anticipation phase (cue and fixation cross) prior to the presentation of the target. All six cue regressors were included in a general linear model (GLM) with six additional regressors for each outcome (gains of $0, $1, or $5; losses of $0, $1, or $5). The GLM also included several regressors of no interest: six motion covariates from rigid-body alignment (Johnstone et al., 2006) and a fourth-order polynomial to model baseline and slow signal drift. To avoid potential confounds introduced by subject motion, volumes in which more than 10% of voxels were time series outliers were censored prior to conducting the GLM.

One vmPFC lesion patient was re-scanned due to input device malfunction during the first scan. Three NC subjects (n=1 male; n=2 females) were excluded from task-based analyses due to excessive head motion [>2 mm] (Power et al., 2012), for a total sample size of n=14 NC subjects (n=9 males; n=5 females). There were no group differences in the percentage of censored volumes (W=60.5, P=0.84) or in mean framewise displacement (NC: 0.06±0.02mm, vmPFC: 0.07±0.03mm; W=134.0, P=0.31). Resulting whole-brain maps of voxelwise β-values for sustained BOLD responses, in MNI space at $3mm^3$ isotropic resolution, were used for second-level analyses.

To identify brain regions responsive to the anticipation of monetary gain, I first performed a whole brain, two-tailed paired-sample t test between responses to gain cues

(collapsed across magnitude) and the neutral gain cue (+$0) using only the n=14 NC subjects (Chen et al., 2013). All statistical maps were family-wise error (FWE) corrected for multiple comparisons across the whole brain at the cluster level (P_{FWE}<0.05), using a height threshold of P<0.001 (Forman et al., 1995b; Carp, 2012). A corrected P_{FWE}<0.05 was achieved using a cluster extent threshold of 20 voxels (594 mm^3), calculated using Monte Carlo simulations with 3dClustSim (updated December 2015 version) in AFNI.

Due to the small sample size of patients with vmPFC lesions, I used non-parametric Mann-Whitney U tests to evaluate the main *a priori* hypothesis regarding activity of the ventral striatum and behavioral differences between groups (percentage of hits by condition, post-scan valence and arousal ratings by condition, target duration by condition, and cumulative money earned from the task). Specifically, I focused the between-group analyses on percent signal change (PSC) estimates extracted from functionally derived right and left ventral striatum ROIs (ventral striatum clusters from the gain > neutral contrast in the NC group). I used functional ROIs to ensure that group comparisons were conducted within functionally-relevant regions within the ventral striatum (i.e., regions that responded strongly in anticipation of potential gains in healthy subjects) (Poldrack, 2007). However, to confirm that group comparisons within functionally derived ventral striatum ROIs reflected differences in ventral striatum activity, I conducted additional between-group tests using values extracted from ROIs in the right and left ventral striatum (number of voxels in masks: n_{right}=99; n_{left}=107), created from subregions in a striatal parcellation atlas derived from functional connectivity to 17 distinct cortical networks in 1,000 healthy adults (Choi et al., 2012). The chosen subregions, which correspond to regions #10 and #17 in the 17-network parcellation map (available at http://www.freesurfer.net/fswiki/StriatumParcellation_Choi2012), demonstrated functional

connectivity in the healthy adults to cortical areas corresponding to the region of damage in this vmPFC lesion patient sample.

To test the specificity of observed effects to the ventral striatum, I conducted follow-up analyses on PSC values extracted from the remaining functionally-derived regions outside the ventral striatum. All tests were considered significant at $P<0.05$.

Volumetric analysis

The averaged T1-weighted images were processed using FreeSurfer (Forman et al., 1995a; Fischl, 2012). The FreeSurfer tissue segmentation includes volume measurements (in mm^3) for four striatal subregions in each hemisphere. I used non-parametric Mann-Whitney *U* tests to calculate group differences in volumes of the following striatal subregions: left and right putamen, left and right caudate, left and right accumbens, and left and right pallidum. I also calculated group differences in volumes of two additional subcortical limbic structures—the amygdala and hippocampus—to further examine specificity. All regional volumes were corrected for estimated intracranial volume (Sanfilipo et al., 2004).

Cerebral perfusion analysis

Quantitative CBF images from pcASL were rigidly co-registered with a T_2*-weighted EPI volume from the task scan and normalized to MNI space. Normalized CBF volumes were scaled to whole-brain CBF (after masking out the lesion in vmPFC patients) and smoothed with a 6mm FWHM Gaussian kernel. To rule out differences in baseline cerebral perfusion, I examined group differences in mean whole-brain CBF and differences in scaled CBF for all functionally defined ROIs using non-parametric Mann-Whitney *U* tests.

3.3 Results

Behavioral data

Groups did not significantly differ with respect to task performance (percentage of hits by condition, post-scan valence and arousal ratings by condition, target duration by condition, and cumulative money earned from the task) (all comparisons $P>0.19$). These behavioral data for the vmPFC and NC groups are summarized in **Table 3.**

fMRI task data

Relative to the neutral cue, gain anticipation elicited robust bilateral striatum activity in the NC subjects (**Figure 6, Table 4**). To examine group differences in striatum activity, I extracted PSC estimates from these functionally-derived right and left striatum ROIs. In support of the main hypothesis, patients with vmPFC lesions exhibited significantly less activity in right striatum ($W=64.0$, $P=0.005$) and left striatum ($W=59.0$, $P=0.03$) during gain anticipation than did NC subjects (**Figure 6**). This effect was present for the high gain \$5 cue > \$0 cue contrast (right striatum: $W=64.0$, $P=0.005$; left striatum: $W=60.0$, $P=0.02$) but not the low gain \$1 cue > \$0 cue contrast (right striatum: $W=54.0$, $P=0.09$; left striatum: $W=47.0$, $P=0.30$). Consistent with the results based on functionally-derived ROIs, I observed a significant group difference for the \$5 cue > \$0 cue contrast for the *a priori* right ventral striatum ROI ($W=28.0$; $P=0.04$) and a trend-level group difference for the \$5 cue > \$0 cue contrast for the *a priori* left ventral striatum ROI ($W=30.0$; $P=0.07$).

To test the anatomical specificity of group differences in activity related to gain anticipation (**Table 4**), I conducted follow-up analyses in the three remaining functionally-derived ROIs from the gain > neutral cue contrast (e.g., left paracentral lobule/medial frontal gyrus (MFG), left inferior parietal lobule (IPL), and right caudate) and found similar group

Table 3. Behavioral data

		vmPFC group		NC group		
	Gain/Loss	mean	s.d.	mean	s.d.	p-value
% Hits	-$0	65.3	5.6	62.1	5.7	0.34
	-$1	53.3	19.4	59.0	10.5	0.92
	-$5	68.0	7.3	65.6	7.1	0.78
	+$0	62.3	7.6	61.5	10.2	0.99
	+$1	66.7	4.7	57.9	12.3	0.21
	+$5	64.0	3.7	60.5	11.0	0.70
Arousal Ratings	-$0	2.6	1.5	2.8	1.4	0.85
	-$1	2.8	1.6	3.3	1.5	0.63
	-$5	3.2	2.2	4.5	2.4	0.29
	+$0	3.0	1.6	2.9	1.3	0.92
	+$1	4.4	1.3	4.4	1.3	0.85
	+$5	6.0	0.7	6.0	1.2	0.78
Valence Ratings	-$0	3.4	1.3	4.2	0.9	0.34
	-$1	3.8	0.4	3.9	0.8	0.99
	-$5	3.6	2.4	2.7	1.5	0.50
	+$0	3.6	1.1	4.2	0.4	0.39
	+$1	4.6	1.1	4.9	0.6	0.63
	+$5	6.0	1.0	5.8	1.5	0.99
Target Duration (ms)	-$0	367	61	352	77	0.69
	-$1	345	77	333	83	0.56
	-$5	350	85	328	71	0.89
	+$0	352	71	354	56	0.96
	+$1	378	67	336	92	0.19
	+$5	334	82	322	84	0.82
Payment		$27.00	$8.06	$22.15	$12.49	0.50

Note: Due to a computer malfunction, the behavioral data for one NC subject was not available.

differences (left MFG: W=68.0, P=0.0007; left IPL: W=64.0, P=0.005; right caudate: W=63.0, P=0.007).

To ensure that the hypothesized group differences in the functionally-defined striatum regions were not due to baseline differences in perfusion after vmPFC damage, I estimated CBF using pcASL before the functional scan in all subjects. There were no significant differences

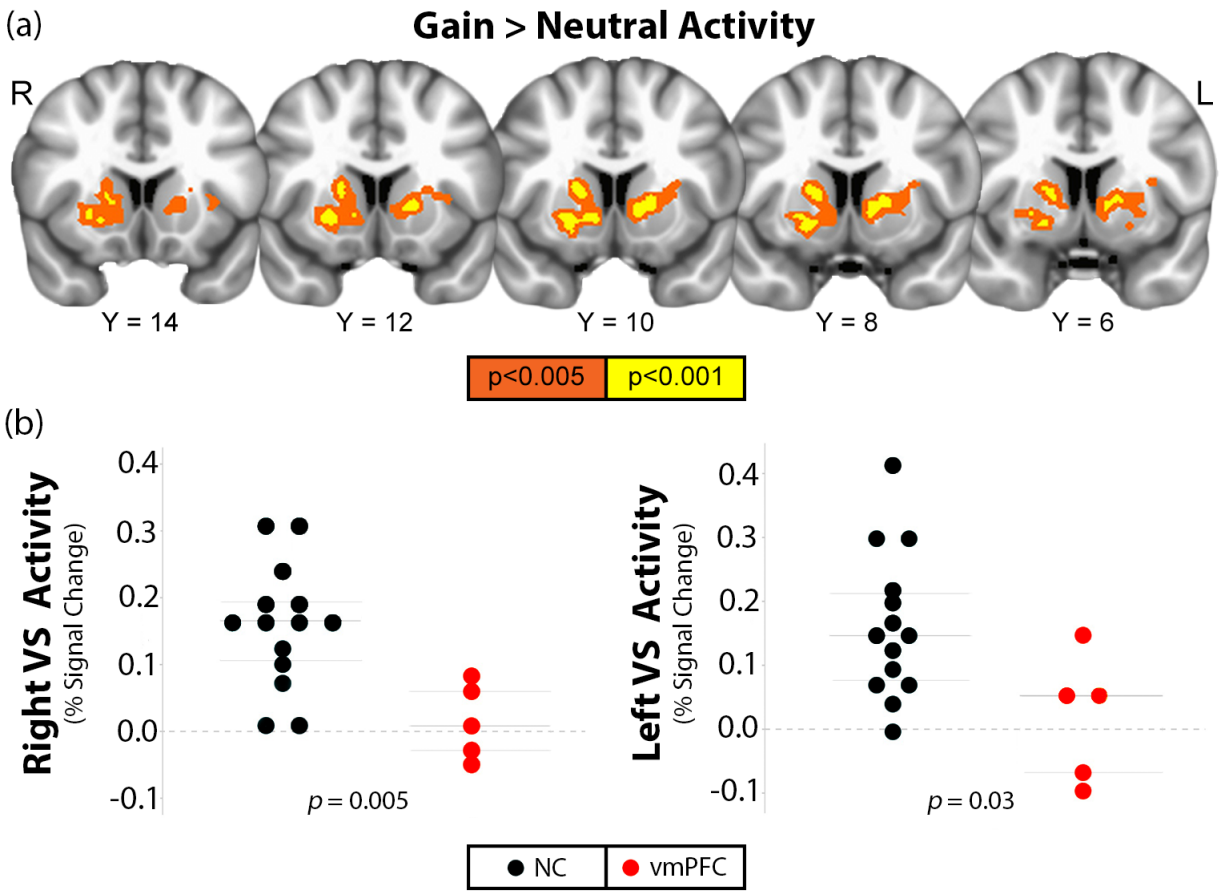

Figure 6. Activation data for gain anticipation. (a) Striatal regions with greater activation to gain, relative to neutral, cues in n=14 NC subjects. Significant striatum clusters from the gain > neutral contrast at P<0.005 uncorrected in orange and P<0.001 in yellow (P_{FWE}<0.05) for display. Slice coordinates (in mm) are presented in MNI template space. **(b)** Plots depict the distribution of individual PSC values for vmPFC lesion patients (red circles) and NC subjects (black circles) in response to gain (+$5, +$1) minus neutral (+$0) cues within each striatum cluster at P<0.001 uncorrected, P_{FWE}<0.05. Light gray horizontal lines on the plots represent the mean and the first and third quartiles of PSC values for each group.

between groups for whole-brain CBF (W=26, P=0.44) or for either of the functionally-defined striatum ROIs (right: W=50.0, P=0.19; left: W=41.0, P=0.62).

Volumetric data

Compared to the NC group, the vmPFC group had significantly smaller volumes of the accumbens subregion of the left ventral striatum (W=57.0, P=0.04), and a trend-level difference for the right accumbens subregion of the ventral striatum (W= 54, P= 0.09) (**Figure 7**). There

Table 4. Brain regions sensitive to anticipatory cues in NC group

		Cluster		Peak Voxel			
Contrast	Structure	Size	P_{FWE}	T	x	y	z
Gain > Neutral	L Striatum	26	< 0.001	5.40	+15.5	-9.5	+3.5
	R Striatum #1	34	< 0.001	5.92	-20.5	-9.5	-5.5
	R Striatum #2	29	< 0.001	6.76	-17.5	-6.5	+9.5
	L MFG	218	< 0.001	7.21	+6.5	+20.5	+66.5
	L IPL	192	< 0.001	7.31	+27.5	+44.5	+39.5
	R Caudate	29	< 0.001	6.76	-17.5	-6.5	+9.5
Loss > Neutral	none						

Cluster size in number of voxels (3x3x3 mm^3). Corrected *P* thresholds indicate minimum FWE-corrected *P* value for each cluster. Peak voxel coordinates (mm) are presented in MNI space. BA, Brodmann area; FWE, familywise error; L, left; R, right.

were no significant group differences for any other region of the striatum (right putamen: *W*=33.0, *P*=0.49; left putamen: *W*=38.0, *P*=0.76; right caudate: *W*=29.0, *P*=0.32; left caudate: *W*=28.0, *P*=0.28; right pallidum: *W*=34.0, *P*=0.54; left pallidum: *W*= 46.0, *P*=0.82), amygdala (right: *W*=44.0, *P*=0.93; left: *W*= 35.0, *P*=0.59), or hippocampus (right: *W*=52, *P*=0.49; left: *W*=45.0, *P*=0.88) (**Table 5)**.

3.4 Discussion

Through a novel application of fMRI in patients with bilateral vmPFC damage, this study demonstrates a critical role for the vmPFC in modulating the reward-related activity and structure of the ventral striatum. Specifically, I found that vmPFC lesions were associated with decreased ventral striatal activity during the anticipation of reward as well as decreased volumes of the accumbens subregion of the ventral striatum. These results are germane to neural circuitry models of reward processing and mental illness.

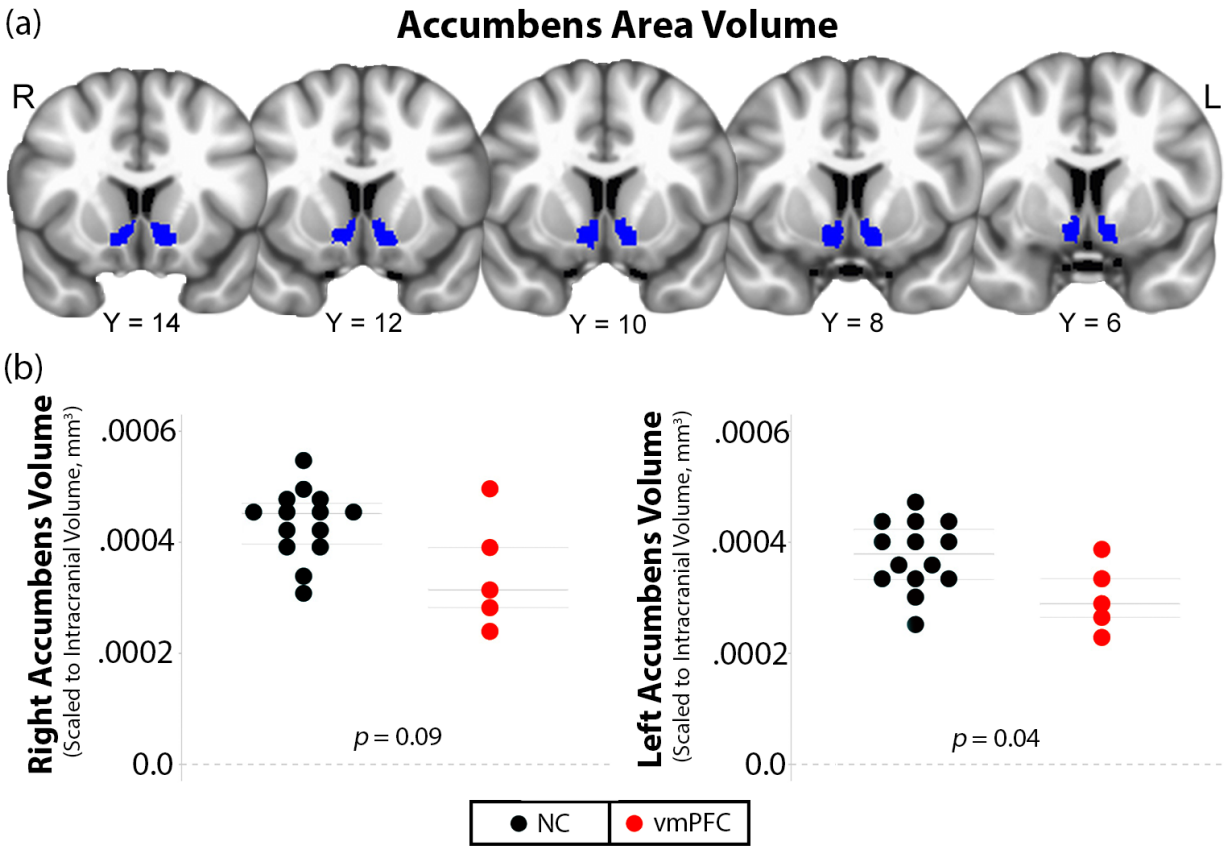

Figure 7. Accumbens area volume data. (a) Accumbens area (ventral striatum) subregions of a representative subject. **(b)** Plots depict the distribution of individual volume values (in mm^3) for vmPFC lesion patients (red circles) and NC subjects (black circles) for each accumbens area region of interest, scaled to total estimated intracranial volume. Light gray horizontal lines on the plots represent the mean and the first and third quartiles of volume values for each group.

First, with respect to neural circuitry models of reward processing, the study results fill an empirical gap between previous animal and human research findings. Human fMRI studies have consistently shown that vmPFC and ventral striatum exhibit coincident activity (Di Martino et al., 2008; Cauda et al., 2011; Choi et al., 2012). However, a fundamental limitation of this correlational approach is that it does not distinguish between cause and consequence within the network of observed activity. In other words, is the observed co-activation of vmPFC and ventral striatum during reward processing in these studies due to vmPFC activity modulating ventral

Table 5. Limbic subregion volume data

Region	NC mean	NC s.d.	vmPFC mean	vmPFC s.d.	W	*P*
Striatum						
L NAc	568.8	126.2	481.14	129.8	57.0	**0.04**
R NAc	658.5	121.4	549.9	184.1	54.0	0.09
L caudate	3397.1	573.4	3773.8	381.4	28.0	0.28
R caudate	3645.2	679.7	4059.6	641.7	29.0	0.32
L putamen	5248.1	724.0	5557.4	620.6	38.0	0.76
R putamen	5052.2	651.1	5427.2	502.9	33.0	0.49
L pallidum	1319.2	182.3	1407.9	260.6	46.0	0.82
R pallidum	1447.5	257.6	1527.9	190.0	34.0	0.54
Amygdala						
L amygdala	1527.7	260.2	1634.6	221.4	35.0	0.59
R amygdala	1680.1	272.0	1753.2	417.5	44.0	0.93
Hippocampus						
L hippocampus	3943.8	296.9	4199.2	486.8	45.0	0.88
R hippocampus	4138.6	324.3	4314.5	453.1	52.0	0.49
Total Estimated ICV	1507627.1	146862.7	1587332.61	145817.2	23.0	0.30

Significant group differences are in bold. L, left; R, right

striatum activity, or vice versa? Or are activity changes in these areas just parallel, coincidental downstream effects triggered by activity elsewhere in the brain? Animal research suggests a causal effect of vmPFC activity on ventral striatum activity. Rodent studies have shown that vmPFC has direct glutamatergic projections to the ventral striatum (Sesack et al., 1989; Voorn et al., 2004; Gabbott et al., 2005) and that inactivation of vmPFC alters neuronal activity in ventral striatum (Ghazizadeh et al., 2012). Lesioning or inactivating both vmPFC and ventral striatum/accumbens disrupts behavioral responding during reward learning and reaction time tasks, indicating that adaptive decision-making depends on concurrent activation of both regions (Christakou et al., 2004; Peters et al., 2008; Bossert et al., 2012; St Onge et al., 2012; Richard

and Berridge, 2013; Smith and Graybiel, 2013; Feja and Koch, 2015). The present study yields the first human evidence suggesting that vmPFC does in fact have a causal influence on modulating ventral striatum activity, in that deprivation of vmPFC input (via focal lesion) results in reduced ventral striatum activity during the anticipation of reward. This finding accords with human lesion studies that demonstrate impairments in value-based decision-making following vmPFC damage (Zald and Andreotti, 2010; Fellows, 2011). In the context of these behavioral effects, the fMRI data from this study suggest a critical role for vmPFC in modulating anticipatory ventral striatal responses to potential rewards.

The present findings may also help inform neural circuitry models of mental illness. Clinical neuroimaging studies have consistently identified abnormalities in reward circuit function and decision-making across a range of psychiatric disorders, including major depression (Tremblay et al., 2005; Epstein et al., 2006; Robinson et al., 2012), schizophrenia (Waltz et al., 2009; Morris et al., 2012; Nielsen et al., 2012), substance use disorders (Kalivas and Volkow, 2005; Koob and Volkow, 2010), attention-deficit hyperactivity disorder (Scheres et al., 2007; Plichta et al., 2009), obsessive-compulsive disorder (Harrison et al., 2009; Figee et al., 2011; Jung et al., 2011), and autism (Scott-Van Zeeland et al., 2010; Dichter et al., 2012b). Clarifying the functional architecture of this circuit is thus an important step in advancing the neuropathophysiological understanding of mental illness. The present results suggest that vmPFC dysfunction may contribute to psychopathology by disrupting ventral striatal activity.

In addition to the diminished reward-related activity in ventral striatum, I also observed reduced ventral striatum volumes in the vmPFC lesion patients. Importantly, this volume reduction was specific to the accumbens subregion of the striatum; the volumes of all other striatal subregions (caudate, putamen, pallidum) and other limbic subregions (amygdala,

hippocampus) did not significantly differ between groups. The specificity of this finding mirrors known anatomical connections between vmPFC and striatum, which share a particularly high density of reciprocal axonal connections (Haber and Knutson, 2010; Rigoard et al., 2011). It is possible that the ventral striatum volume reduction among vmPFC lesion patients is due to diminished input from vmPFC and/or retrograde degeneration from damaged axonal connections. Regardless, the complementary fMRI and volumetric findings underscore the tight link between structure and function in this brain circuit.

Although the study hypothesis focused on the ventral striatum, I also observed activity related to gain anticipation in the lateral parietal cortex. This finding accords with electrophysiological studies of non-human primates, which have consistently demonstrated reward-related neuronal activity in lateral parietal cortex during decision-making and reinforcement learning (Platt and Glimcher, 1999; Dorris and Glimcher, 2004; Sugrue et al., 2004; Peck et al., 2009; Seo et al., 2009; Louie and Glimcher, 2010). The finding that reward-related activity in parietal cortex was significantly reduced in the vmPFC lesion patients suggests that vmPFC damage may attenuate reward-related signals outside the striatum.

One limitation of the present study is the inability to determine whether vmPFC was engaged in response to reward cues in normal subjects. Unfortunately, the area of vmPFC damage in this patient sample corresponds almost exactly to the area of maximal fMRI signal dropout due to magnetic field inhomogeneities. In addition, the lesions almost certainly involved damage to white matter pathways in and around the vmPFC. Hence, I was unable to determine whether vmPFC damage disrupted local processing during the task, or perhaps impaired communication between striatum and other cortical areas via damage to underlying white matter. To account for the absence of a lesion control group, I assessed baseline cerebral perfusion.

Since ASL data indicated no gross alterations of perfusion in the vmPFC patients (either globally or in ventral striatum), the observed group differences in task activation cannot be readily explained by group differences in cerebral perfusion. Another limitation of this study is that the MID fMRI paradigm does not provide a sensitive behavioral measure of reward processing. To more conclusively determine the behavioral relevance of the observed abnormalities in ventral striatum structure and function, future studies could examine the link between striatal neurobiology and established behavioral measures of reward-learning or value-based decision-making.

One feature of this study that warrants consideration is the limited sample size of vmPFC lesion patients (n=5). For this study, I employed extremely stringent selection criteria for this target group; lesions had to involve substantial portions of vmPFC bilaterally, but could not extend significantly outside vmPFC. Furthermore, because the study involved fMRI, I could not include patients with metallic implants, such as aneurysm clips. To meet these criteria, I selected a group of patients who had all undergone surgical resection of large orbital meningiomas. So, although the sample size may be small by conventional vmPFC lesion patient standards (which typically feature n=5 to n=12 vmPFC lesion patients), it is unique with respect to the homogeneity of etiology, uniformity and selectivity of bilateral vmPFC lesions, and compatibility with fMRI.

In sum, these findings indicate a role for vmPFC in contributing to reward-related activity of the ventral striatum. The results offer new insight into the functional and structural interactions between vmPFC and ventral striatum, two key components of the brain circuitry underlying human affective function and decision-making. Dysfunction in these nodes has

implications for a range of neuropsychiatric disorders characterized by aberrant reward processing, which is the focus of the following chapter.

Chapter 4: Neural correlates of reward and loss sensitivity in psychopathy

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4.1 Introduction

Psychopathy is a mental health disorder characterized by callous and impulsive antisocial behavior. Present in roughly a quarter of adult prison inmates, psychopathy is associated with a disproportionately high incidence of violent crime, substance abuse and recidivism (Smith and Newman, 1990; Hare, 2003). Based on these personality and behavioral characteristics, it has long been postulated that psychopathy may be linked to abnormalities in processing reward and punishment (Cleckley, 1941; Lykken, 1957; Fowles, 1980; Gorenstein and Newman, 1980; Blair, 2008). Over several decades, a host of behavioral and psychophysiological studies have offered qualified support for this theory (Lykken, 1957; Schmauk, 1970; Newman et al., 1985; Arnett et al., 1997; Baskin-Sommers et al., 2010). More recently, functional brain imaging has been used to address this question at the neural-systems level (Buckholtz et al., 2010; Bjork et al., 2012). These functional magnetic resonance imaging (fMRI) studies have focused primarily on the ventral striatum (VS), a major subcortical target of mesolimbic dopamine neurons, which have been shown to signal the receipt and prediction of pleasurable rewarding stimuli (Schultz et al., 1997; Drevets et al., 2001; Schultz, 2010).

Human functional imaging studies have reliably demonstrated VS activation in response to innately pleasurable stimuli, as well as to abstract stimuli predicting their occurrence (McClure et al., 2004; O'Doherty, 2004). Two fMRI studies of reward processing and psychopathy have associated certain psychopathic personality characteristics with heightened VS activity during the anticipation of monetary gain (Buckholtz et al., 2010; Bjork et al., 2012).

These intriguing initial results raise a number of important questions. Although these findings associate psychopathy with hypersensitive neural responses in anticipation of monetary gains, to date, no study has examined the relationship between psychopathy and neural responses related to monetary loss. Moreover, both of the aforementioned reward-processing studies were conducted with non-forensic community participants, among whom few (if any) would meet criteria for the categorical diagnosis of psychopathy as defined for pathologically antisocial and criminal individuals (Hare, 2003). Although there are ample clinical and behavioral data suggesting that psychopathic traits fall along a continuum—with psychopaths representing a quantitatively greater manifestation of the traits rather than a qualitatively distinct category (Marcus et al., 2004; Edens et al., 2006; Walters et al., 2007; Walters et al., 2008)—there is not yet strong evidence to support the assumption that the neurobiological correlates of the disorder are similarly continuous (Koenigs et al., 2011). In other words, it may be the case that VS reward activity correlates with certain social and affective personality traits among individuals with overall low levels of psychopathy, as has been previously reported (Buckholtz et al., 2010; Bjork et al., 2012), but among actual psychopathic individuals, the relationship between psychopathic trait severity and VS reward-related activity may be notably different.

This study will thus address two distinct but related questions on the neural basis of psychopathy: (i) Do psychopathic offenders have significantly altered reward and/or loss sensitivity in VS? (ii) Is the relationship between psychopathy severity and VS reward/loss sensitivity consistent across the entire spectrum of psychopathy severity, or does the relationship differ depending on whether one exhibits low or high levels of psychopathic traits?

4.2 Methods

Participants—Magnetic Resonance Imaging study

Participants were adult male inmates recruited from a medium-security Wisconsin correctional institution. Inmates were eligible if they met the following criteria: <45 years of age, IQ >70, no history of psychosis or bipolar disorder, no history of significant head injury or post-concussion symptoms and not currently taking psychotropic medications. Nine subjects (*n*=6 non-psychopathic and *n*=3 psychopathic) were excluded owing to a lack of button responses during the task (instruction non-compliance; see 'fMRI task' later in the text), leaving a final sample of 41 inmates (*n*=18 psychopathic and *n*=23 non-psychopathic).

The Psychopathy Checklist-Revised (PCL-R) (Hare, 2003) was used to assess psychopathy. The PCL-R assessment involves a 60- to 90-min interview and file review to obtain information used to rate 20 psychopathy-related items as 0, 1 or 2. Participants were assessed for substance use disorder with the Structured Clinical Interview for DSM-IV Disorders (First, 2002) (**Table 6**).

Participant groups

Participants were recruited based on their PCL-R scores. Psychopathic inmates had PCL-R scores of ≥30, whereas non-psychopathic inmates had PCL-R scores of ≤20 (Hare, 2003). Group characteristics for the magnetic resonance imaging (MRI) study are presented in **Table 6.** The psychopathic and non-psychopathic groups did not significantly differ with respect to age, race or intelligence. Importantly, the groups also did not differ with respect to lifetime diagnosis of substance use disorder (abuse or dependence) for any of the following substances: alcohol, cannabis, cocaine, opioids, stimulants, sedatives or hallucinogens.

Table 6. Subject characteristics: Psychopathy Study

Variable	Non-psychopathic (*n*=23)	Psychopathic (*n*=18)	*P*
Demographic			
Age	32.4 (8.0)	32.2 (6.5)	0.94
Race (Cauc/Afr Am)	21/2	13/5	0.21
Neuropsychological			
IQ[a]	100.7 (11.9)	100.1 (11.2)	0.87
Digit Span Back	6.9 (2.7)	6.5 (3.3)	0.69
Anxiety/Neg Affect[b]	10.7 (8.1)	13.3 (9.0)	0.33
Psychopathy			
PCL-R total	14.1 (3.5)	31.7 (1.7)	<0.001
Factor 1	4.8 (2.2)	11.7 (1.8)	<0.001
Factor 2	7.3 (3.3)	17.2 (1.4)	<0.001
Substance Abuse[c]			
Alcohol			
Prevalence	10/23	9/18	0.76
Age of onset	21.5 (3.3)	18.6 (2.0)	
Cannabis			
Prevalence	6/23	8/18	0.32
Age of onset	19.3 (4.5)	19.5 (8.0)	
Cocaine			
Prevalence	4/23	6/18	0.29
Age of onset	20.5 (2.9)	20.5 (5.3)	
Stimulants			
Prevalence	1/23	2/18	0.57
Age of onset	18	15,23	
Opioids			
Prevalence	3/23	5/18	0.27
Age of onset	20.7 (5.1)	18.8 (3.3)	
Sedatives			
Prevalence	1/23	2/18	0.57
Age of onset	27	20/22	
Hallucinogens			
Prevalence	1/23	4/18	0.15
Age of onset	20	18.3 (2.8)	

[a]based on Shipley Institute of Living Scale (Zachary, 1986), [b]based on Welsh Anxiety Scale, [c]based on diagnosis of abuse or dependence in the Structured Clinical Interview for DSM-IV Disorders (SCID) (First, 2002). *P*-values for race distribution and substance abuse prevalence were computed with Fisher's Exact Test. All other *p*-values are based on *t*-tests (means presented followed by standard deviations in parentheses). *P*-values were not calculated for substance abuse age of onset due to relatively small sample sizes of abusers for most substances.

Participants—Follow-up Behavioral Activation System study

As a follow-up to the MRI results, I analyzed data from a separate group of inmates. These inmates are a subset of individuals who had all previously completed a self-report measure of Behavioral Inhibition System (BIS) and Behavioral Activation System (BAS) traits (Newman et al., 2005; Wallace et al., 2009). To mirror the group analysis scheme for the functional and structural MRI data, I analyzed BIS/BAS data from only those inmates who were classified as psychopathic (PCL-R ≥30; *n*=93) or non-psychopathic (PCL-R ≤20; *n*=117) in the previous studies. These adult Caucasian male inmates met the same eligibility criteria as the participants in the MRI study (<45 years of age, IQ >70, no history of psychosis or bipolar disorder, no history of significant head injury or post-concussion symptoms and not currently taking psychotropic medications). The BIS/BAS scale (Carver and White, 1994) is a 20-item questionnaire based on Gray's reinforcement sensitivity theory (Gray, 1970). The BIS subscale (seven items) primarily assesses worry and anxiety, whereas the BAS subscale (13 items) measures sensitivity to anticipated/acquired rewards, motivation to achieve desired goals and willingness to approach new appetitive stimuli.

fMRI task

While in the scanner, participants completed a task involving the passive gain or loss of money. Each trial consisted of three phases (**Figure 8**). The first phase (3 s) was a cue stimulus (one of five white shapes on a black background). The second phase (3 s) was a slot machine (one of six colored slot machines). The third phase (2 s) was an indication of monetary outcome (win $1, win $0 or lose $1). A fixation cross was shown during the inter-trial intervals (mean duration 4 s, range 2–6 s). A total of 76 trials were divided into two runs of 38 trials each. Each cue was associated with a fixed probability of being followed by each slot machine, and each slot

Figure 8: **Schematic of the fMRI task**. Trials lasted 8 seconds and were separated by jittered intervals of 2-6 seconds. Participants were instructed to indicate by a button press during the presentation of the cue which slot machine they thought was most likely to follow. They were instructed to be as accurate as possible, but their responses were not related to any monetary reward. Subjects passively gained $1 ("gain"), gained $0 ("neutral"), or lost $1 ("loss"). There were 76 total trials (29 "gain" trials, 34 "neutral" trials, and 13 "loss" trials).

machine was associated with a fixed probability of winning, losing or breaking even. Three of the slot machines delivered monetary gains (66% chance of winning $1), two of the slot machines always yielded $0 and one slot machine delivered monetary loss (66% chance of losing

$1). All participants received the same predetermined order of cues, slot machines and monetary outcomes. To keep participants engaged during the task and allow monitoring of the participants' attention to the task, participants were instructed to indicate by a button press during the presentation of the cue which slot machine they thought was most likely to follow. Subjects who failed to respond to at least a third of all trials (within the 3-s window) were excluded from the final analysis. In the final subject sample, there was no significant between-group difference in the number of button responses (t=0.50, P=0.63). To heighten the psychological impact of gaining and losing money, the monetary outcome of one trial chosen randomly from the task was added or subtracted to the subject's compensation for participating in the study.

MRI data collection

All MRI data were acquired using the Mind Research Network's mobile Siemens 1.5 T Avanto MRI System on correctional facility grounds. Gradient echo T2*-weighted echoplanar images (EPIs) were acquired with the following parameters: TR=2800 ms, TE=39 ms, flip angle=75°, FOV=24 × 24 cm^2, matrix=64 × 64, slice thickness=4.0 mm, gap=1 mm, voxel size=3.8 × 3.8 × 4.0 mm^3, 38 interleaved axial oblique slices per volume and total of 240 volumes. A high-resolution T1-weighted structural image was acquired for each subject using a four-echo magnetization-prepared rapid gradient-echo sequence (TR=2530 ms; TE=1.64, 3.5, 5.36 and 7.22 ms; flip angle=7°, FOV=256 × 256 mm^2, matrix=128 × 128, slice thickness=1.33 mm, no gap, voxel size=1 × 1 × 1.33 mm^3 and 128 interleaved sagittal slices). All four echoes were averaged into a single high-resolution image.

MRI data analysis

All fMRI data analyses were performed using AFNI (Cox, 1996). EPI volumes were slice-time corrected using the fourth slice of the first session as a reference (interleaved

ascending, Fourier interpolation) and motion corrected by rigid body alignment to the fourth EPI acquisition. The data were spatially smoothed with a 4-mm full-width at half-maximum Gaussian kernel. The averaged T1-weighted images were processed using FreeSurfer v5.0, as previously described (Fischl, 2012). EPI time series data and high-resolution T1 images skull-stripped in FreeSurfer were normalized to the MNI coordinate system using a 12-parameter linear warp. The time series of both runs were scaled and concatenated before being modeled with canonical gammavariate hemodynamic response functions time-locked to the onsets of monetary outcome stimuli, as well as to the onsets of the cue and slot stimuli. In addition to modeling these stimuli onsets as regressors of interest, residual head motion after volume correction was also entered into the model as a covariate of no interest. The resulting statistical maps were resampled to 3 mm cubic voxels and registered to the same coordinate space as the normalized T1 images for subsequent analyses.

To compare responses related to gains and losses, I performed a linear contrast between gain (+$1), loss (−$1) and neutral ($0) trials. Group differences were considered significant at a corrected $P < 0.05$ (cluster size >41 voxels at uncorrected $P < 0.005$). Cluster extents were computed using Monte Carlo simulations implemented in the 3dClustSim program (AFNI).

Measurement of Striatal Volumes

The averaged T1-weighted images were processed using FreeSurfer (Fischl, 2012). The FreeSurfer tissue segmentation includes volume measurements (in mm^3) for four striatal subregions in each hemisphere. I computed correlations between PCL-R scores and volumes of the following striatal subregions: left and right putamen, left and right caudate, left and right accumbens area and left and right pallidum. The accumbens area most closely corresponds to the task-defined VS region-of-interest (ROI).

4.3 Results

Here I address each of the two main study questions in turn. The first question is whether psychopathic offenders exhibit significantly altered sensitivity to reward or loss in VS. To address this question, I examined BOLD activity in response to stimuli indicating monetary gain, loss and no change (neutral). Across the entire sample, I observed greater activation bilaterally in the VS for gain relative to loss trials at $P < 0.005$ uncorrected (**Figure 9A**). Activation in the left VS remained significant after whole-brain correction for multiple comparisons ($P < 0.05$ corrected, t=5.94, 48 voxels; **Figure 9B** and **Table 7)**. Activity in the left VS was greater for gain relative to neutral but lower for loss relative to neutral (**Figure 9C**). An outlier test (Grubbs' test) revealed that one non-psychopathic subject was an outlier for the gain–loss contrast, and that a separate non-psychopathic subject was an outlier for the loss–neutral contrast. After the exclusion of these two subjects, I observed no significant difference in VS response magnitude between psychopathic and non-psychopathic groups for the gain–neutral contrast (t=1.08, P=0.29), loss–neutral contrast (t=1.20, P=0.20) or gain–loss contrast (t=0.85, P=0.40). These results indicate that psychopathic and non-psychopathic offenders do not exhibit significant overall differences in reward- or loss-related activity in VS.

The second question is whether the relationship between psychopathy severity and VS reward/loss sensitivity is consistent across the entire spectrum of psychopathy severity, or if the relationship differs depending on whether one exhibits low or high levels of psychopathic traits. To address this question, I calculated the correlation between overall psychopathy severity (total PCL-R score) and reward-related VS activity (gain-loss in left VS), separately for the psychopathic and non-psychopathic groups. Non-psychopathic offenders exhibited no significant correlation between left VS activation for gain–loss and total PCL-R score (r=−0.04, P=0.85).

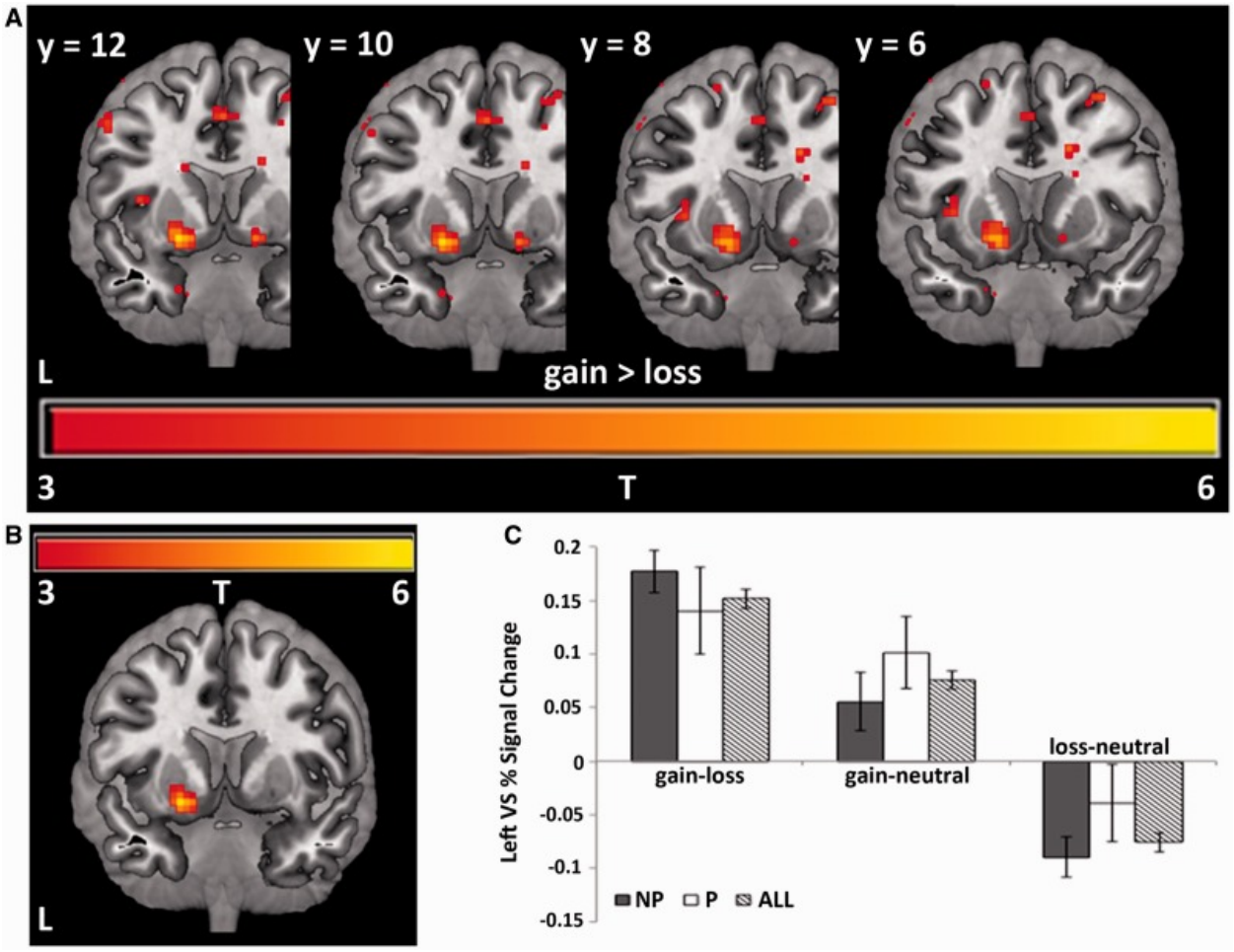

Figure 9. Activation data for gain > loss response. (**A**) Bilateral activation in VS in response to gains relative to losses, displayed at $P < 0.005$ uncorrected. (**B**) Activation in left VS in response to gains relative to losses, corrected for multiple comparisons. Peak activation at MNI coordinates: $x=-21$, $y=9$, $z=-9$; 48 voxels, $P < 0.005$ uncorrected, $\alpha=0.05$. (**C**) Bar graph showing the average percent signal change across all 48 voxels of the task-activated region of left VS for non-psychopathic offenders (NP), psychopathic offenders (P) and across all subjects (All). Error bars indicate S.E.M.

In contrast, psychopathic offenders exhibited a strong and significant positive correlation between left VS gain–loss activity and total PCL-R score ($r=0.74$, $P=0.0004$; **Figure 10A**). A direct test comparing the total PCL-R score/VS gain–loss activity correlations indicates a highly significant difference between non-psychopathic and psychopathic groups ($Z=-2.87$, $P=$

Table 7. Areas of significant activation for gain > loss response

Description	Cluster Size	*t*-value (peak)	*x*	*y*	*z*
Ventral striatum	**48**	**5.94**	**-21**	**9**	**-9**
Precuneus	43	4.37	-12	-66	60
Dorsolateral prefrontal cortex	63	4.27	-36	42	39
Middle frontal gyrus	77	3.95	-39	57	15
Occipital cortex	91	-4.30	-45	-66	6

All foci are corrected for multiple comparisons using the Monte Carlo simulations implemented in the 3dClustSim program (AFNI). Foci with cluster size >41 (corrected $p<0.05$) are reported, along with peak *t*-values and MNI coordinates (mm).

0.004). These results indicate that the relationship between reward/loss-related VS activity and psychopathy severity is significantly different for psychopathic and non-psychopathic offenders.

I next examined whether the observed group difference in correlation between VS gain–loss activity and PCL-R score could be due primarily to either the VS response to gain or loss, individually, or if it is due to the combination of the two. To address this question, I computed separate within-group correlations between PCL-R score and VS activity for the gain–neutral and loss–neutral contrasts, respectively (**Figure 10B and C**). Among non-psychopathic offenders, there was no significant correlation between PCL-R score and VS activity for either contrast (gain–neutral: $r=-0.14$, $P= 0.54$; loss–neutral: $r=0.02$, $P=0.93$). Among psychopathic offenders, there was a non-significant correlation for gain–neutral ($r=0.23$, $P=0.36$) and a significantly negative correlation for loss–neutral ($r=-0.61$; $P=0.007$). A direct test comparing the total PCL-R score/VS reward-activity correlations shows no significant difference between non-psychopathic and psychopathic groups for the gain–neutral contrast ($Z=-1.09$, $P=0.28$) and a marginally significant difference between groups for the loss–neutral contrast ($Z=-1.99$; $P=0.05$). In neither the gain–neutral nor loss–neutral contrast was the correlation with

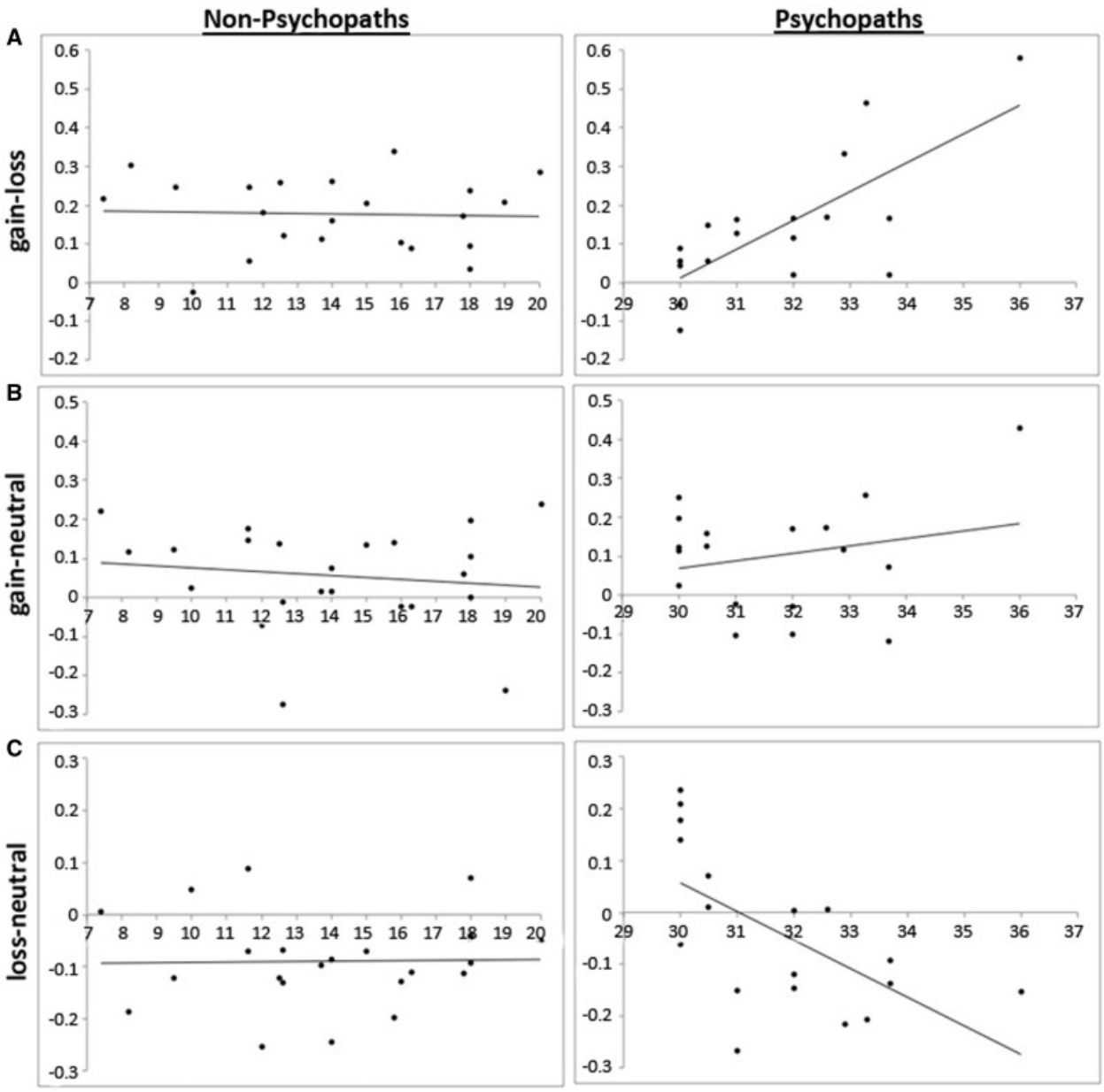

Figure 10. Correlation of percent signal change across the gain > loss task-activated region (left VS; see Figure 9B; 48 voxels) **and PCL-R scores** for (**A**) gain–loss: activity in left VS had no correlation with PCL-R score for non-psychopathic offenders (r=−0.04, P=0.85) but positive correlation with PCL-R score for psychopathic offenders (r=0.74, P=0.0004); (**B**) gain–neutral: activity in left VS had no correlation with PCL-R for non-psychopathic offenders (r=−0.14, P=0.54) but slight positive correlation with PCL-R score for psychopathic offenders (r=0.23, P=0.36); (**C**) loss–neutral: activity in left VS had no correlation with PCL-R score for non-psychopathic offenders (r=0.02, P=0.93) but negative correlation with PCL-R score for psychopathic offenders (r=−0.61, P=0.007).

PCL-R score among psychopaths as strong as in the gain–loss contrast (r=0.72, P=0.0004); hence, the significant positive correlation between PCL-R score and gain–loss VS activity can be viewed as a combination of positive correlation with gain–neutral activity and negative correlation with loss–neutral activity. However, given that the loss–neutral correlation was much stronger than the gain–neutral correlation, this finding appears to be driven primarily by the loss–neutral VS activity.

As a follow-up to the VS activity finding, I examined structural characteristics of VS to determine whether I could observe similar differences between psychopathic and non-psychopathic offenders. Specifically, I computed volumes of striatal subregions for each group (**Table 8)**. There were no significant between-group differences in mean volume for any of the subregions (all $P > 0.28$). However, like the VS activity results described previously, there was a significant difference between groups in the correlation between VS volume and PCL-R score (**Figure 11)**. Volume of the right accumbens area was not significantly correlated with PCL-R score among non-psychopathic offenders (r=−0.13, P=0.55) but significantly positively correlated with PCL-R score among psychopathic offenders (r=0.56, P=0.02). Again these within-group correlations were significantly different between psychopathic and non-psychopathic offenders (Z= 2.24, P=0.03).

As another follow-up, I examined the relationship between psychopathy severity and a widely used self-report measure of behavioral motivation (BIS/BAS) in a much larger sample of inmates (n=93 psychopathic and n=117 non-psychopathic offenders). BIS scores indicate anxiety and behavioral inhibition, whereas BAS scores indicate sensitivity to appetitive stimuli and reward. The BAS results closely mirrored the VS functional and structural imaging findings. Among non-psychopathic offenders, there was no significant correlation between PCL-R score

Table 8. Striatal subregion volume correlations with PCL-R scores

	Non-Psychopathic (*n*=24)			Psychopathic (*n*=18)			Between-group test of correlations
Striatal Subregion	Mean Volume (mm^3)	Correlation (*r*) with PCL-R	*p*	Mean Volume (mm^3)	Correlation (*r*) with PCL-R	*p*	*Z*, *p*
L Putamen	5765.43	-0.03	0.88	5946.28	0.22	0.38	-0.74, 0.50
R Putamen	5480.17	-0.02	0.94	5545.72	0.18	0.47	-0.59, 0.56
L Caudate	3750.30	0.10	0.65	3580.94	-0.11	0.67	0.62, 0.54
R Caudate	3848.96	0.10	0.65	3726.72	-0.03	0.90	0.38, 0.70
L Accumbens	662.74	-0.14	0.52	664.61	0.29	0.24	-1.29, 0.20
R Accumbens	650.09	-0.13	0.55	612.28	0.56	**0.02**	**-2.24, 0.03**
L Pallidum	1872.57	0.18	0.42	1887.28	0.18	0.48	0.00, 1.00
R Pallidum	1632.30	0.31	0.15	1697.28	0.27	0.29	0.13, 0.90
L TOTAL	12051.04	0.04	0.86	12078.11	0.14	0.60	-0.3, 0.76
R TOTAL	11611.52	0.06	0.77	11582.00	0.20	0.44	-0.42, 0.67
TOTAL	23662.57	0.05	0.81	23660.11	0.17	0.50	-0.36, 0.72

Significant group differences are in bold. L, left; R, right

and BAS score (r=−0.06, P=0.51), but among psychopathic offenders, there was a significant positive correlation between PCL-R score and BAS score (r=0.26, P=0.01; **Figure 12**). These correlations were significantly different between groups (Z=2.31, P=0.02). I observed no such group difference for BIS scores; both psychopathic and non-psychopathic offenders exhibited no significant correlation between BIS score and PCL-R score (r=−0.19 and r=−0.05, respectively; Z=1.01, P=0.31).

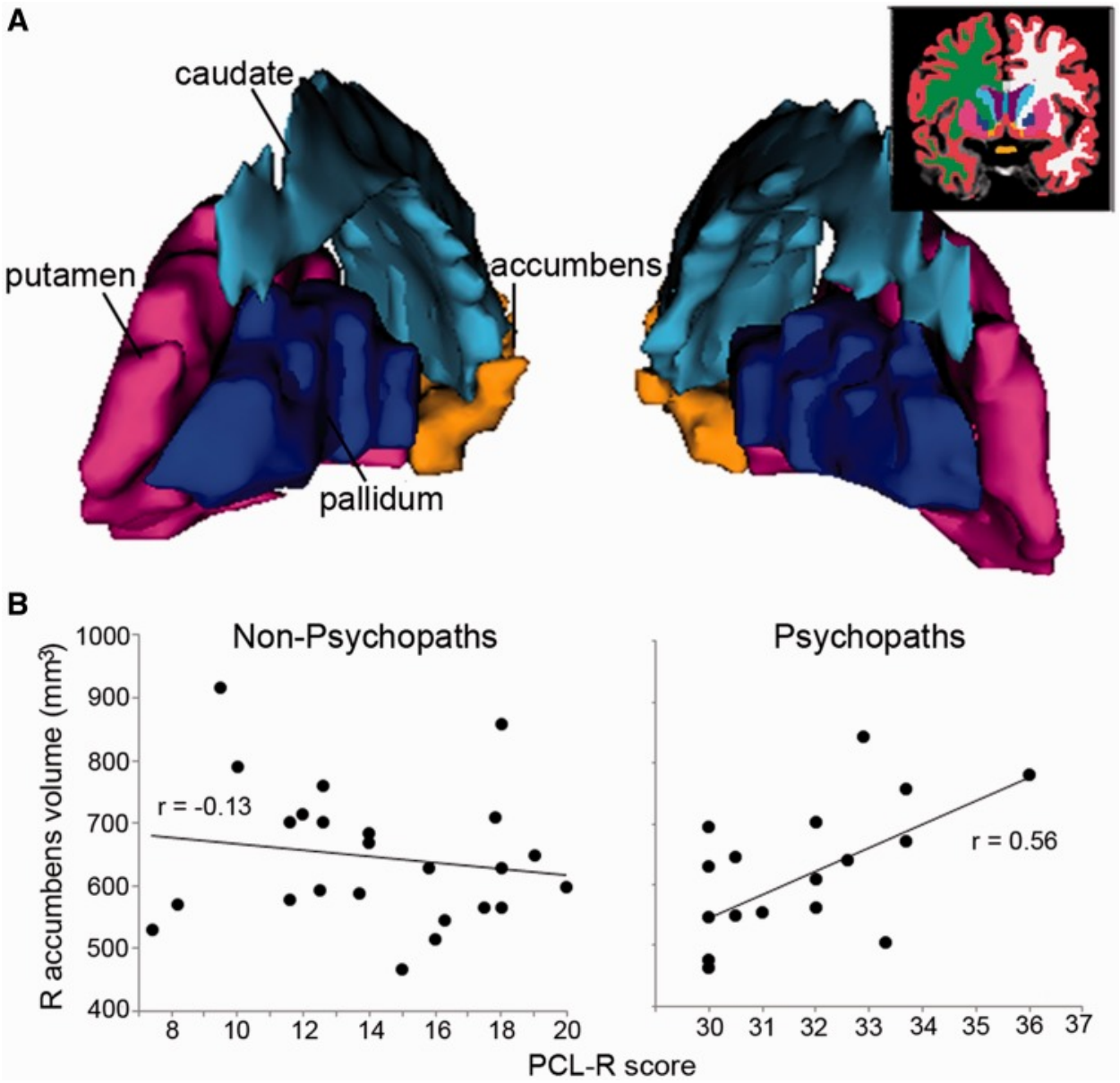

Figure 11. Accumbens area volume in psychopathy (A) Three-dimensional-rendered striatal subregions of a representative subject. Inset: coronal slice illustrates the segmentation. (B**)** Correlation of right accumbens area volume (mm^3) and PCL-R score. Volume in this region of VS had no correlation with PCL-R score for non-psychopathic offenders (r=−0.13, P=0.55) but positive correlation with PCL-R score for psychopathic offenders (r=0.56, P= 0.02). See Table 8 for group mean volumes.

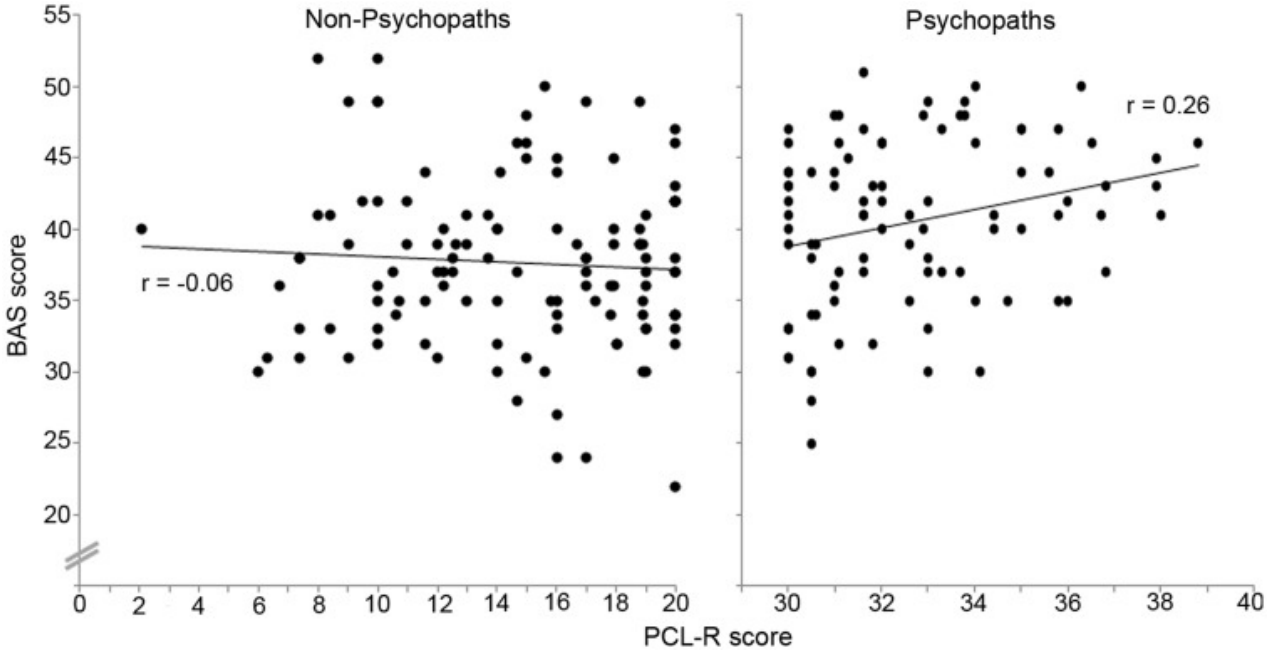

Figure 12. Correlation of Behavioral Approach System scores and PCL-R scores. BAS scores and PCL-R scores had no correlation for non-psychopathic offenders (r=−0.06, P=0.51) but positive correlation for psychopathic offenders (r=0.26, P= 0.01).

4.4 Discussion

The aim of this study was to evaluate the neural substrates of reward and loss sensitivity in psychopathic criminals. For decades, psychopathy researchers have theorized that deficits in processing reward and punishment may underlie the impulsive and remorseless behavior of criminal psychopaths (Cleckley, 1941; Lykken, 1957; Fowles, 1980; Gorenstein and Newman, 1980; Blair, 2008). Although I found no overall differences in the mean level of VS activity in response to reward or loss between psychopathic and non-psychopathic offenders, I did observe a marked difference in the relationship between VS activity to reward vs. loss and psychopathy severity between the two groups, with non-psychopathic offenders exhibiting no significant correlation and psychopathic offenders exhibiting a strong positive correlation. This positive

correlation with gain–loss VS activity in psychopathic offenders appeared to be driven primarily by a negative correlation with loss–neutral VS activity. Volume of the accumbens area of right VS also correlated positively with psychopathy severity among psychopathic, but not non-psychopathic, offenders. Moreover, in an analysis of self-reported reward sensitivity and appetitive motivation, I again observed a similar pattern (i.e. no significant correlation with psychopathy severity among non-psychopathic offenders, but a strong positive correlation among psychopathic offenders). These convergent neurofunctional, neurostructural and psychological results provide novel evidence that reward and loss processing may play a key role in psychopathic behavior.

These results may indicate a potentially important interaction between psychopathy severity and sensitivity to rewards relative to losses. Among non-psychopathic offenders, neither reward nor loss sensitivity (as measured by VS response and BAS self-report) had a significant relationship with psychopathy severity. I propose that this is because greater levels of reward sensitivity in non-psychopathic offenders may be adequately tempered by intact behavioral control mechanisms, ultimately yielding no significant relationship between reward/loss sensitivity and overtly reckless behavior. Psychopathic offenders, on the other hand, notoriously lack such behavioral restraints. Thus, greater differences in VS activity to rewards relative to losses and greater levels of appetitive motivation in psychopathic offenders may directly correspond to greater levels of impulsive, careless and irresponsible (‘psychopathic’) behavior.

This study features several methodological strengths. This is the first fMRI study of reward and loss processing in a group of stringently classified psychopathic offenders (PCL-R ≥30). In addition, the combination of functional and structural MRI analyses in a study of

criminal psychopathy is unique to the Koenigs research group (Motzkin et al., 2011; Ly et al., 2012) and offers convergent support for the study conclusions.

One potential limitation worth considering is the range of PCL-R scores of participants in the MRI correlation analyses, particularly for the psychopathic inmates. For the VS fMRI and volumetric data (**Figures 9-11**), the psychopathic group had PCL-R scores that ranged from 30 to 36 (out of a maximum possible range of 30–40). Although this relatively narrow range of psychopathic PCL-R scores yielded highly significant *P*-values (e.g. $P=0.0007$ for correlation with VS gain–loss fMRI data and $P=0.02$ for correlation with VS volumetric data), I was nonetheless concerned that the observed relationship may not hold for larger numbers of psychopathic inmates with a greater range of psychopathy severity. To address this concern, I analyzed previously collected BAS data from a much larger group of inmates (Newman et al., 2005; Wallace et al., 2009). The BAS scale is a widely used measure of reward sensitivity in psychological research (Bijttebier et al., 2009). I reasoned that if greater differences in VS activation in response to monetary gains relative to monetary losses are related to approach-related motivation at the psychological level, then I should observe a similar relationship between BAS score and PCL-R score. Indeed, this is what I found: no significant correlation among non-psychopathic offenders but a significant positive correlation among psychopathic offenders (**Figure 12)**. Importantly, the $n=93$ psychopaths in this follow-up study spanned nearly the full range of PCL-R scores (30–39). Hence, I believe that the fMRI and BAS data provide convergent support for my interpretation.

At first glance, these results may not appear to be entirely consistent with previous fMRI studies correlating psychopathic traits with increased reward-related VS activity (Buckholtz et al., 2010; Bjork et al., 2012). I see two possible reasons for this apparent discrepancy. One is the

difference in task paradigms. The previous studies examined VS responses during the anticipation of monetary gain (relative to no gain), whereas this study examined VS responses to the receipt of monetary gain, monetary loss and no gain. A second important difference is the participant sample. The previous studies used community samples, which were likely composed entirely of non-psychopathic individuals, as the prevalence of psychopathy in the general U.S. adult population is believed to be <1% (Hare, 2003), and likely even lower among subjects screened for substance use history. In fact, the severity of 'psychopathy' in these non-incarcerated community samples is almost certain to be dramatically lower than even the current sample of non-psychopathic criminal offenders, who had PCL-R scores ranging from 7 to 20 (mean of 14.1; **Table 6**). Given these considerable differences between study designs and subject populations, I believe that this study has generated unique standalone data on the neural substrates of reward and loss processing in patently psychopathic individuals.

The results of this study may inform a broader discourse on categorical (i.e. qualitatively distinct type of individual) vs. dimensional (i.e. quantitatively greater degree of certain traits or characteristics) perspectives on psychiatric disorders (Chabernaud et al., 2012). Despite ample empirical support for the dimensional conception of psychopathy (Marcus et al., 2004; Edens et al., 2006; Walters et al., 2007; Walters et al., 2008), there are at least two previous studies indicating categorical effects (Patrick et al., 1993; Young et al., 2012). The present neurobiological data join these previous psychophysiological and behavioral findings in demonstrating categorically distinct features of psychopathy. To address this issue more definitively from a neuroscientific standpoint, future brain imaging studies using larger samples that include individuals spanning the entire range of psychopathy severity will be necessary to

determine whether there are indeed certain neurobiological correlates of psychopathy that appear to be non-dimensional in nature.

Overall, this study yields unique and novel data on the neurobiology of reward and loss processing and psychopathy. The functional and structural neuroimaging data presented here converge to demonstrate that brain–behavior relationships among criminal psychopaths differ significantly from non-psychopathic offenders. The next chapter presents a summary and integration of the research findings from **Chapters 2**, **3**, and **4**.

Chapter 5: General Discussion

The overarching question of this dissertation is whether variation in the functional and structural integrity of this frontostriatal neural circuit contributes to variation in reward processing and decision-making. The findings from the series of experiments presented in the previous chapters relate key aspects of decision-making and reward processing to a common neural "reward" circuit through tests of two populations: (1) neurological patients with focal vmPFC/OFC damage and (2) psychopathic prison inmates. The study in **Chapter 2** demonstrates that vmPFC/OFC damage results in an enhanced reflection effect – that is, the difference in risk-taking for prospective monetary gains relative to prospective monetary losses. This finding lends support for the vmPFC/OFC's role in processing information about the magnitude or value of an anticipated outcome. Results from **Chapter 3** on the same patients with vmPFC/OFC damage suggest that the vmPFC/OFC modulates both VS volume and VS activity during reward anticipation for prospective monetary rewards, suggesting that interactions between these two regions during reward anticipation may be a key neurobiological mechanism for adaptive decision-making. The findings in **Chapter 4** demonstrate a relationship between VS activity during the passive receipt and loss of reward and the severity of psychopathy for a group of psychopathic prison inmates, relative to non-psychopathic inmates. Within the psychopathic group, there was also a relationship between VS volume and psychopathy severity, and a similar relationship between a self-report measure of reward sensitivity and psychopathy severity. The data from this experiment support a role for VS in the reward-related processing deficits that are characteristic of psychopathic criminals.

Taken together, the work presented here links a key dimension of psychological and behavioral function—reward processing and value-based decision-making—with a discrete

neural circuit—vmPFC/OFC-VS. As outlined in the National Institute of Mental Health's Research Domain Criteria (RDoC; https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml) (Insel et al., 2010), the elucidation of such brain-behavior linkages may ultimately help clinicians derive neuropathophysiologically-based interventions to treat symptoms that are common across several mental health diagnostic categories. To consider my findings in the context of this broad mental health initiative, I will first describe evidence-based interventions and treatments focused on the reward circuit, specifically on vmPFC/OFC and VS dysfunction in major depressive disorder and substance use disorder. I will then acknowledge the limitations and discrepancies among the studies presented in this dissertation that, if addressed in future research, could advance psychiatry towards more precise neuropathophysiologically-based diagnostics and treatments.

5.1 vmPFC/OFC-VS Dysfunction in Major Depressive Disorder and Substance Use Disorder

The symptoms of major depressive disorder (MDD) and substance use disorder (SUD) are particularly germane to reward circuit function. One of the core symptoms of MDD is anhedonia—the loss of interest or pleasure in most, if not all, activities (Der-Avakian and Markou, 2012). In patients with SUD, abuse and dependence on drugs and alcohol is defined by compulsive drug use, diminished impulse control, maladaptive decision-making, and increased negative affect (Koob and Volkow, 2010). Both disorders are highly prevalent in the United States: in 2014, an estimated 15.7 million adults suffered a depressive episode, and an estimated 21.5 million people had some form of SUD (Hedden et al., 2015). These disorders are also highly co-morbid (Davis et al., 2008), which suggests that common biological substrates may underlie their etiologies. Decades of basic research on reward neural circuitry have yielded evidence-based interventions that target specific nodes of the reward circuit to alleviate

symptoms of MDD and SUD. In the following sections, I will review abnormal function and structure in vmPFC/OFC and VS and the clinical efficacy of considering the vmPFC/OFC-VS circuit in clinical treatments of MDD and SUD symptoms.

5.1.1 Major Depressive Disorder

Anhedonia is a key symptom for reward circuit studies of MDD because of its relationship with impaired emotional and motivational responses to positively valenced stimuli. MDD patients display differences in vmPFC/OFC engagement when processing money and other rewards (Knutson et al., 2008; McCabe et al., 2009; Smoski et al., 2009; Smoski et al., 2011) and positively valenced stimuli (Johnstone et al., 2007; Heller et al., 2009; Keedwell et al., 2009) compared with controls. Studies of OFC gray matter volume report gray matter reductions in MDD patients compared with controls (Bremner et al., 2002; Lee et al., 2003; Lacerda et al., 2004). Interestingly, Koenigs et al. (2008) report markedly low levels of depression in patients with bilateral vmPFC lesions. When compared with healthy controls, patients with MDD show markedly different VS activity in response to money and other rewarding or pleasant stimuli, with the majority of these studies implicating VS hypo-activity (Kumar et al., 2008; Heller et al., 2009; McCabe et al., 2009; Diener et al., 2012; Robinson et al., 2012; Stoy et al., 2012; Greening et al., 2013). Taken together, converging evidence of structural and functional impairments of vmPFC/OFC and VS in MDD provides the basis for targeting vmPFC/OFC-VS pathways for clinical treatments.

Deep brain stimulation (DBS) has gained traction in the past ten years as a promising therapy for treatment-resistant depression (Widge et al., 2016). DBS is a favorable alternative to destructive clinical procedures such as cingulotomy, capsulotomy, and leukotomy, since implanted stimulating electrodes can reversibly modulate activity in a brain site that may be

dysfunctional in psychiatric patients (Cleary et al., 2015). Reward frontostriatal circuitry has been most commonly targeted for treatment-resistant depression using DBS (Taghva et al., 2012). Early DBS clinical trials stimulated the subcallosal cingulate gyrus (CG25) of the prefrontal cortex because of its metabolic hyperactivity in patients with treatment-resistant MDD (Mayberg et al., 2005; Cleary et al., 2015). Ventral capsule/ventral striatum stimulation has also more recently shown to be effective in treating symptoms of depression in treatment-resistant patients (Schlaepfer et al., 2007; Malone Jr et al., 2009; Taghva et al., 2012; Dougherty et al., 2015). Interestingly, patients who respond to suballosal cingulate white matter DBS show increased white matter connectivity from the stimulation site to medial prefrontal cortex, rostral cingulate cortex, and subcortical nuclei including the ventral striatum (Riva-Posse et al., 2014). The most recent target for treating anhedonia in patients with MDD is the median forebrain bundle – the white matter fibers that connect midbrain subnuclei to striatal and prefrontal regions (Schlaepfer et al., 2013). Though there is converging evidence on the efficacy of DBS target placement within this circuit, response rates with DBS are still only about 50% in patients with treatment-resistant depression (Widge et al., 2016). Therefore, a better understanding of how the functional dynamics and structural connections within this circuit relate to behavioral outcomes could yield more optimal electrode target implantation and patient selection strategies for future DBS clinical trials.

Compared to DBS, repetitive Transcranial Magnetic Stimulation (rTMS) is a relatively less invasive neuromodulatory technique that also has potential for treating the symptoms of several psychiatric disorders. Such studies have been conducted in patient samples with major depressive disorder, schizophrenia, obsessive-compulsive disorders, post-traumatic stress disorder, panic disorder, and substance use disorder (Machado et al., 2013; Gorelick et al., 2014).

rTMS involves delivering short, rapidly changing magnetic field pulses on a focal region of the scalp to modulate activity in the underlying cortical tissues (Burt et al., 2002). Though direct stimulation of the deep cortical and subcortical structures described above is not possible with rTMS, stimulation of surface cortical structures likely modulates the activity of connected cortical and subcortical structures (Eldaief et al., 2013). The dorsolateral prefrontal cortex (dlPFC) is a frequently targeted region for rTMS stimulation in studies of depression because of its accessibility and connectivity to other regions implicated in the pathophysiology of the disorder (Fox et al., 2012b; Noda et al., 2015). Recent work in treatment-resistant MDD patients highlights the importance of studying reward circuit dynamics to assess response outcomes following dlPFC rTMS. In one study, the antidepressant efficacy of left dlPFC rTMS was related to the degree of anticorrelation of the chosen dlPFC site with the subgenual cingulate (Fox et al., 2012b). In another study, depressed individuals who did not show any symptom improvement after dmPFC rTMS showed lower connectivity within a network that included vmPFC, striatum, and ventral tegmental area, relative to rTMS responders (Downar et al., 2014). Observing reward circuit dynamics may therefore be useful for clinicians who wish to identify subject-specific rTMS targets and/or patient subtypes that would respond to rTMS treatment.

DBS and rTMS have demonstrated potential as treatments for psychiatric patients with extreme symptom expression. These interventions may therefore be effective and accessible for a small percentage of people who suffer from problems of mental health. Basic research on how pharmacological or behavioral interventions can alter the brain and behavior may be more useful for developing widely applicable evidence-based treatments. It may be likely that antidepressant medication and cognitive therapies mitigate symptoms of depression through similar neural circuits (DeRubeis et al., 2008; Hayley and Litteljohn, 2013). A major focus of this work has

centered on prefrontal-amygdala circuitry, given its prominent role in regulating negative affect (Quidé et al., 2012). Only recently has attention been given to the link between increased positive affect following pharmacological and psychotherapeutic interventions and changes in reward circuit function. Patients with depression who underwent two months of fluoxetine or venlafaxine treatment reported increased post-treatment positive affect, which was associated with greater connectivity between the vmPFC and nucleus accumbens at rest (Heller et al., 2013). Pharmacological intervention studies have also shown normalization of VS activity to monetary rewards (Stoy et al., 2012) and vmPFC/subgenual anterior cingulate cortex activity to emotionally salient pictures (Keedwell et al., 2010; Rosenblau et al., 2012). Patients with depression who received between 8 and 14 weeks of Behavioral Activation Therapy, designed specifically to increase reward-seeking behaviors and reduce avoidance behaviors, showed greater activity in prefrontal and striatal regions during a monetary reward task relative to a healthy control group (Dichter et al., 2009). Work in this area suggests that normalization of frontostriatal activity may be a therapeutic target and/or marker of psychotherapeutic or behavioral therapy treatment efficacy.

5.1.2 Substance Use Disorder

Perhaps not surprisingly, vmPFC/OFC and VS structure and function are also altered in individuals with SUD (Kravitz et al., 2015). Many human neuroimaging studies of SUD patients have implicated the PFC, specifically the OFC, as a region showing reward-related impairments (London et al., 2000; Goldstein and Volkow, 2011). For instance, cocaine administration was shown to induce activations in the OFC along with other PFC regions (Kufahl et al., 2005). SUD subjects also show reduced gray matter volumes of the vmPFC/OFC (Tanabe et al., 2009; Durazzo et al., 2011; Ersche et al., 2011; Konova et al., 2012). VS activity in response to rewards

and reward-predicting cues is dysfunctional in SUD for a number of substances, including cocaine (Jia et al., 2011; Hyatt et al., 2012; Konova et al., 2012), nicotine (David et al., 2005; Franklin et al., 2007; Peters et al., 2011; Rose et al., 2012), alcohol (Braus et al., 2001; Volkow et al., 2007; Wrase et al., 2007; Beck et al., 2009; Schacht et al., 2011), and other drugs (Bjork et al., 2008; Nestor et al., 2010). Non-normative VS activity across substance use groups appears to reflect the marked changes in appetitive and hedonic experiences of SUD patients. There are indications that interactions between vmPFC/OFC and VS may be important for the development of SUD. OFC activity is negatively associated with methylphenidate-induced dopamine (DA) increases in the VS, whereas low DA D2 receptor availability was associated with increased mPFC responses to rewards (Asensio et al., 2010). Furthermore, decreased functional connectivity between the NAc and OFC is associated with duration of opioid dependence (Upadhyay et al., 2010). Such work suggests that these nodes may be critical neural substrates for SUD symptoms.

Interventions similar to those undertaken for MDD have been applied to treat symptoms of SUD. The use of DBS for SUD has targeted the nucleus accumbens/VS and resulted in spontaneous smoking cessation (Kuhn et al., 2009; Mantione et al., 2010), decreased alcohol intake and remission (Kuhn et al., 2007; Müller et al., 2009; Kuhn et al., 2011), and remission from heroin abuse (Zhou et al., 2011; Valencia-Alfonso et al., 2012; Kuhn et al., 2014). While the PFC is not yet considered a viable target for DBS for SUD treatment, emerging evidence suggests that reduced drug use following accumbens/VS stimulation occurs by antidromic activation of cortico-striatal white matter pathways. Inhibition of the pathway between infralimbic cortex (the rodent homologue of vmPFC) and nucleus accumbens pathway abolishes cocaine-induced locomotor sensitization (Pascoli et al., 2012). Deep brain stimulation of the

accumbens in a patient with severe alcoholism resulted in less risky, more careful choices during accumbens stimulation, with recruitment of a region of vmPFC (Heldmann et al., 2012). rTMS is also beginning to show promise in modulating brain activity to treat SUD symptoms (Gorelick et al., 2014; IB Protasio et al., 2015). High frequency dlPFC rTMS reduces craving for nicotine (Eichhammer et al., 2003; Johann et al., 2003; Amiaz et al., 2009; Pripfl et al., 2014), cocaine (Camprodon et al., 2007; Politi et al., 2008), and alcohol (Mishra et al., 2010; De Ridder et al., 2011). The acute effects of rTMS to cortical sites are more transient compared to DBS of the accumbens, and it is still unclear how fronto-striatal circuitry might be mediating the effects of rTMS in SUD subjects. However, the nucleus accumbens and dopamine have been implicated in mediating drug-triggered relapse, perhaps through the mesolimbic pathway connecting cortical and striatal regions (Gardner, 2011). A pharmacological PET study shows that enhancing dopamine signaling with methylphenidate can reduce orbitofrontal and striatal activity in response to cocaine-related cues in active cocaine users (Volkow et al., 2010). G-protein-coupled receptor (GPCR) heteromer-selective ligands are now being used to target distinct subpopulations of receptors and may soon tease apart the molecular mechanisms by which fronto-striatal interactions mediate these effects (Kravitz et al., 2015). Overall, this collection of findings provides promising avenues for treating SUD symptoms.

5.1.3 Considerations for treatments and interventions

Advancements in neuropathophysiologically-based diagnostics and treatments will require a greater knowledge of the fundamental neurobiological mechanisms underlying mental health disorder symptoms across multiple diagnostic categories. A number of considerations should be taken into account in order to achieve a greater degree of precision in future clinical studies. Human neuroimaging research done in the past several decades has resulted in tens of

thousands of studies identifying neural correlates for cognition and behavior in patient and healthy samples (Downar et al., 2016). While evidence from these studies has been useful for identifying brain target sites for DBS or rTMS in humans, there are two limitations of this approach: (1) fMRI allows for correlative inferences of brain activity and behavior and does not establish a causal role for a brain region or several regions for a given function, nor does it establish directionality of influence between two or more co-active or functionally connected brain regions (Logothetis, 2008); (2) fMRI provides coarse spatial resolution, so uncovering information about the involvement of smaller subnuclei is less likely at the whole-brain level, especially with the magnetic field strength of MRI scanners currently used (1.5 and 3.0 Tesla) (Logothetis, 2008; Wardlaw et al., 2012). As several lines of evidence converge to support the existence of discrete neural networks, combinatorial methods such as optogenetics and fMRI in animals (Lee, 2012), rTMS and fMRI (Fox et al., 2012a), DBS and fMRI (Lang et al., 2014), and brain-injured patient studies with fMRI (Gillebert and Mantini, 2013) will be crucial for addressing causal brain circuit dynamics and their role in behavior. As stronger magnetic fields for neuroimaging technologies become accessible to more research groups, resolving midbrain subnuclei of the brain's reward circuit, such as the ventral tegmental area and the lateral habenula – both of which have been implicated in the pathophysiology of MDD and SUD (Lecca, 2014; Polter and Kauer, 2014) – may lead to an expansion in the number of accessible DBS target sites (Abosch et al., 2010).

Another methodological consideration is the comparison of patient samples identified strictly by diagnostic categories to a psychiatrically healthy sample. More work is now being done to address this. As part of the RDoC initiative, researchers are now encouraged to include individuals who fall short of meeting a formal diagnosis as well as patients with Not Otherwise

Specified (NOS) diagnosis, with the ultimate goal of parsing heterogeneous syndromes into homogenous clusters (Insel et al., 2010; Insel and Cuthbert, 2015). Performing continuous statistical analyses between a neurobiological outcome variable (e.g., BOLD percent signal change in ventral striatum) and a behavioral index of a symptom or set of symptoms (e.g., "anhedonia") that cut(s) across several disorders is another strategy that will be critical for increasing the chances of successful response outcomes to the clinical interventions described in the previous section, including DBS (Widge et al., 2016) and rTMS (Janicak and Dokucu, 2015). In the following sections, I will highlight the methodological strengths, limitations, and discrepancies of the work presented in this dissertation, as well as future directions for research to address these gaps and establish the vmPFC/OFC-VS circuit as a relevant treatment target.

5.2 Limitations, Discrepancies, and Future Directions

Findings from human behavioral, pharmacological, and neuroimaging studies have clearly played a major role in guiding evidence-based psychiatric interventions involving major depressive disorder and substance use disorder. The series of experiments presented in Chapters 2-4 of this dissertation offer unique methodological strengths in building upon this body of work. In **Chapters 2** and **3**, I utilized the lesion method, which offers the unique opportunity to observe *causal* shifts or deviations in human behavior and neural function and structure (when combined with MRI) following focal brain damage. The experiment described in **Chapter 4** featured a stringently classified group of psychopathic offenders (PCL-R $\geq$ 30) and a group of incarcerated non-psychopathic offenders that served as a more closely matched comparison group than a healthy community sample. These studies contribute to a growing body of neuroscientific evidence that may one day help clinicians meet the more realistic goal of treating clusters of symptoms, rather than a given disorder as a whole. Despite these strengths, the studies presented

also have a number of methodological limitations and discrepancies that need to be addressed in future research.

5.2.1 Limitations

The samples characterized in all three studies limit the generalizability of results, which merits consideration for future work. In **Chapters 2** and **3**, the vmPFC lesion patient sample consisted of 5 individuals. The criteria employed were extremely stringent for this target group in order to recruit patients who had extensive bilateral vmPFC damage that did not extend into other prefrontal or temporal regions. Patients with metallic implants, such as aneurysm clips that would not be MRI-compatible, were only included in the brain damaged comparison group for the behavioral study described in **Chapter 2**, but not for the fMRI study described in **Chapter 3**. Only patients who had undergone surgical resection of large orbital meningiomas were recruited for the vmPFC/OFC lesion group described in **Chapters 2** and **3**, since anterior skull base meningiomas frequently result in damage restricted to the vmPFC/OFC following surgical resection (Abel et al., 2015). Therefore, although the sample size may be small by conventional vmPFC lesion patient standards (which typically feature n=5 to n=12 vmPFC lesion patients), it is unique with respect to the homogeneity of etiology, uniformity and selectivity of bilateral vmPFC lesions, and compatibility with fMRI. Of note, people tend to develop intracranial meningiomas later in life, peaking in the 60-69 year age group among men and in the 70-79 age group among women (Prabhu et al., 2014). Therefore, the vmPFC/OFC lesion sample in the current studies was older (average age at time of testing: mean=59.8; SD=5.2). Though we recruited age-matched comparison groups for both studies, we cannot make generalizations about populations beyond the age range of the groups. In the sections below, I will address the implications that the age of the lesion sample has for **Chapter 2** and **3** study results and any

comparisons that can be drawn between behavioral deficits following vmPFC damage and behavioral deficits in criminal psychopathy.

As described in **Chapter 4**, criminal inmates who scored in the intermediate range of PCL-R scores (between 20 and 30) were excluded from the study. Identifying extreme scoring groups has been a common methodological approach for assessing differences between psychopathic individuals and non-psychopathic individuals (Koenigs et al., 2011). While this was one of the few neuroimaging studies published in its time that adhered to the recommended cutoffs for characterizing these groups (Pujara et al., 2013), a couple of critical questions were left unanswered following this approach. In our sample, we could only speculate on whether the observed brain-behavior relationships with respect to VS function and structure were continuous across the full spectrum of psychopathy severity. The inclusion of the intermediate group would help identify the exact inflection point at which neural and psychological outcome measures change as a function of psychopathy score. Another question is whether VS function and structure relates to any specific subset(s) of psychopathic traits. Symptoms of psychopathy can be disaggregated into two main "factors," or dimensions, of traits. Factor 1 corresponds to the unique interpersonal/affective traits of psychopathy (e.g., callousness, egocentrism, pathological lying), whereas Factor 2 corresponds to more general lifestyle/antisocial features (e.g., impulsivity, irresponsibility, criminal versatility) that are shared with other externalizing disorders (Hare, 2003). Given that the psychopathic and non-psychopathic groups differed significantly on both factors, we were unable to link VS function and structure to a particular factor of psychopathy (Pujara et al., 2013). For future directions, I will propose studies to test vmPFC/OFC-VS structure and function in a larger sample of incarcerated criminal offenders across a broad range of psychopathy severity. Another consideration in the study of psychopathy

in an incarcerated population is IQ, which is an important factor in selecting behavioral tasks. The reward-learning task described in **Chapter 4** involved probabilistic stimulus-response-outcome contingencies and was therefore too complex for most subjects to learn successfully (both groups had average IQs: psychopathic group=100.1; non-psychopathic group=100.7). In the section below, I will acknowledge the implications this has for **Chapter 4** study results.

5.2.2 Discrepancies

All three studies involved tasks that probed responses to monetary rewards and losses. However, each task was different with regard to the types of neural and behavioral outcomes that were tested. In the fMRI studies described in **Chapters 3** and **4**, there were two major task components that probed neural responses to rewards and losses: an "anticipation" phase and a "feedback" phase. In **Chapter 3**, I analyzed the anticipation phase of a task that required no new stimulus-outcome learning, since subjects already knew in real time which cues would result in which monetary outcome. In **Chapter 4**, however, I analyzed the feedback epoch of a reward-learning task involving probabilistic stimulus-response-outcome contingencies that did require subjects to update their responses based on new information. As I mentioned in the previous section, few of the subjects were able to learn the task successfully due to its complexity relative to subjects' IQ scores. To put this in context, a similar probabilistic reward learning task was administered to a sample of 20 above-average math-proficient undergraduate students, and even in this study, two subjects were excluded for not meeting criterion for minimal learning on the task (Gläscher et al., 2010). I therefore analyzed the feedback period to assess responses to gains and losses for all subjects who demonstrated active engagement with the task, despite a demonstrated inability to learn its contingencies. Though the anticipation period and the

feedback period in response to monetary gains resulted in heightened VS activity in both studies, it is important to note that this activity reflects distinct behavioral processes.

Influential work by Kent Berridge in rodent models distinguished between (1) motivational or "wanting" processes during the anticipation of reward, which correspond more closely to the "anticipation" phase, and (2) hedonic or "liking" processes associated with unconditioned responses on reward consumption, which correspond more closely to the "feedback" phase (Berridge and Kringelbach, 2008). Hedonic or "liking" responses are primarily mediated by opioid transmission within the nucleus accumbens shell (Peciña and Berridge, 2005), whereas motivational or "wanting" behaviors are mediated by opioids *and* dopamine in both the nucleus accumbens shell and core subregions (Peciña and Berridge, 2013). Differentiating between reward anticipation versus reward feedback in human studies will provide valuable insights for teasing apart the exact mechanisms of dysfunction in patient samples. For example, in SUD patients, there seems to be a general dissociative trend of either reduced or no detectable change in VS activity during reward anticipation (Wrase et al., 2007; Bjork et al., 2008; Beck et al., 2009; Jia et al., 2011; Peters et al., 2011; Rose et al., 2012) and increased VS activity during reward feedback (Braus et al., 2001; David et al., 2005; Franklin et al., 2007; Wrase et al., 2007; Bjork et al., 2008; Jia et al., 2011; Konova et al., 2012). The remarkable similarities in VS activation patterns during distinct stages of reward processing speak to a possible common underlying dysfunction for users of different substances. These patterns would not have been apparent if not for distinguishing between "wanting" and "liking" phases across experimental paradigms that probe neural responses to rewards.

As I mentioned in the previous section, I did not observe any significant whole-brain responses to anticipated losses in the healthy comparison group (**Chapter 3**). This seemed to run

counter to MID studies that show consistent activations in medial caudate and anterior insula bilaterally for loss anticipation (Knutson and Greer, 2008). However, a study of the MID task done in older adults also reports striatal activation for anticipated gains and null findings for the loss anticipation condition (Samanez-Larkin et al., 2007), which is attributed to a positivity bias seen in older age (Mather and Carstensen, 2005). In **Chapter 2**, I found a trending group difference between vmPFC lesion patients and the normal comparison groups and a significant group difference between the vmPFC lesion patients and the brain damaged comparison group for the gain condition (NC v. vmPFC: Mann–Whitney U=36.5, P=0.07; logistic regression: Z=2.26, P=0.11; NC v. vmPFC: Mann–Whitney U=3.5, P=0.06; logistic regression: Z=−3.49, P=0.03), but no significant difference between groups for the loss condition (NC v. vmPFC: Mann–Whitney U=41.5, P=0.11; logistic regression: Z=−1.01, P=0.78; BDC v. vmPFC: Mann–Whitney U=7.0, P=0.25; logistic regression: Z=1.34, P=0.73) (Pujara et al., 2015). Indeed, a recent meta-analysis comparing framing effects between younger and older adults found that younger adults are more likely than older adults to choose riskier choices in the loss frame (Best and Charness, 2015). Therefore, age of the lesion group and the comparison group may be important to consider in tasks where monetary losses are involved.

5.2.3 Future Directions

Acknowledging the limitations and discrepancies of the current work provides clearer avenues for exploration in future research. There are several hypothesized operations of vmPFC/OFC in value-based decision-making that could be tested with the lesion method. Psychophysiological research in normal subjects has shown that distinct, characteristic visual fixation patterns occur during the value comparison process between two food rewards, which can bias the relative value of the items and influence choice (Krajbich et al., 2010). This would

be like the real-world equivalent of shifting one's gaze back and forth between two equally preferred items at a grocery store. Ultimately, one item will be chosen over another—the results of Krajbich et al. (2010) indicate that the relative amount of visual allocation between items influences what item is ultimately chosen. Lim et al (2011) found that vmPFC in humans tracks the difference between attended versus unattended food rewards during a binary choice task in which attention was manipulated, as a way to control for any possible attentional biases that factor into the comparison process. A recent study that tracked the effects of prefrontal cortex damage on visual fixations during a binary choice task showed no impairment following vmPFC damage (Vaidya and Fellows, 2015). However, the vmPFC lesion group in this study had mostly unilateral, heterogeneous vmPFC damage. Utilizing the vmPFC lesion group with extensive bilateral vmPFC/OFC damage characterized in the Koenigs lab will establish a critical role for vmPFC/OFC in mediating the effect of attentional gaze on item selection.

Research on the neural underpinnings of a learning test called outcome devaluation implicates a role for the vmPFC/OFC in driving flexible, goal-directed responses during reward extinction (McDannald et al., 2014). Outcome or reinforcer devaluation involves initial discrimination learning using cues that predict at least two separate rewarding stimuli, one of which is subsequently devalued through either satiation or induced aversion via pairing with a noxious stimulus. Taking the vmPFC 'off-line' results in perseverative or habitually entrained responses to a devalued stimulus during the extinction period that tests responses to the devalued and non-devalued items in rodent (Gallagher et al., 1999; Pickens et al., 2003; West et al., 2013) and non-human primate studies (Izquierdo et al., 2004; Machado and Bachevalier, 2007; West et al., 2011). Human fMRI studies show that OFC activity tracks the value of the cue that predicts a devalued reward (Gottfried et al., 2003; Valentin et al., 2007). Outcome devaluation is one of

many learning tests that can be employed to elucidate a critical role for vmPFC/OFC in encoding relative value and mediating response inhibition according to new stimulus-outcome contingencies [for review of other tasks, see (McDannald et al., 2014)]. Performing these tasks in a study of patients with vmPFC/OFC damage would be a way to establish a critical role for vmPFC/OFC in what is referred to in computational neuroscience as model-based, rather than model-free, learning (McDannald et al., 2012). These systems represent distinct processes for guiding decision-making: whereas model-based learning reflects flexible, goal-oriented/deliberate behaviors, model-free learning involves automatic, habitually entrained responses to previously learned stimulus-outcome contingencies (Lee et al., 2014). A better understanding of vmPFC/OFC's critical role in guiding flexible decision-making has considerable implications for understanding how persistent, habitually entrained behavioral repertoires – such as anhedonia and negative affect in MDD (Chen et al., 2015) and compulsive drug-seeking and drug-taking in SUD (Lucantonio et al., 2014) – can develop.

To better characterize the role of vmPFC in modulating VS activity during reward learning, future work should involve modifications of the experiment presented in **Chapter 3**. Substantial neuroimaging work on reinforcement learning implicate the VS and vmPFC and anterior cingulate cortex in signaling prediction errors (Garrison et al., 2013), which guide reward-based learning by indicating the presence and absence of an expected or anticipated reward (Schultz, 1998). Infralimbic inactivation in rodents results in aberrant nucleus accumbens signaling, which corresponds to disinhibited responses to unreinforced stimuli following successful discrimination learning (Ghazizadeh et al., 2012). A simple probabilistic reward-learning or reversal-learning task that relies on this vmPFC-VS circuit and tests a subject's ability to learn based on changing stimulus-outcome contingencies may be more sensitive to

group differences that could not be detected with the MID task. Including a younger age group as an additional comparison group in future studies involving older lesion patients may also help tease apart the effects of age on learning from rewards and punishments. Understanding the behavioral consequences of altered vmPFC/OFC and VS interactions during reward learning will be necessary to show that humans depend on the normative function of this circuit to make adaptive choices.

This basic research has strong implications for individuals exhibiting antisocial personality and criminal recidivism, who may be failing to incorporate information about rewards and punishments to make socially acceptable decisions. Indeed, psychopathy is associated with a disproportionately high incidence of violent crime and substance abuse and recidivism (Smith and Newman, 1990; Hare, 2003). Psychopathic personality traits share striking similarities to personality changes that follow vmPFC/OFC damage, including lack of empathy, impulsivity, and poor decision-making. “Pseudopsychopathy” (Blumer and Benson, 1975) or “acquired sociopathy” (Eslinger and Damasio, 1985) following vmPFC/OFC damage has led researchers to test theories of vmPFC/OFC dysfunction in psychopathy (Kiehl, 2006; Blair, 2008; Koenigs, 2012). A critical distinction between the ‘acquired’ form of sociopathy seen in lesion patients and the developmental form of sociopathy seen in criminal inmates is that the vmPFC/OFC lesions patients do not demonstrate destructive or harmful behaviors towards others (Bechara et al., 2000). Patients with nonprogressive, early onset (before 16 months of age) vmPFC damage, however, develop severe antisocial behavior in early adulthood (Anderson et al., 1999), suggesting early developmental prefrontal cortex dysfunction as a mechanism for the development of psychopathic traits. The lesion patients in our sample experienced vmPFC/OFC damage following late-onset, slow-growing tumors that may have resulted in gradual brain

reorganization in tandem with meningioma growth (Abel et al., 2015). Future work examining causal models derived from vmPFC lesion patient data and observed neural deficits in psychopathy should consider age at lesion onset and how the lesion was acquired.

To effectively address the question of dysfunction of a frontostriatal circuit in psychopathy, future work would benefit from including the full range of psychopathy scores and relating neural outcome measures to individual factors of the disorder. Since the study in **Chapter 4** was conducted, relationships between larger striatal volumes as a function of psychopathy score and more specifically to the lifestyle/antisocial features (e.g., impulsivity, irresponsibility, criminal versatility) that are shared with other externalizing disorders have since been established in a larger inmate sample (Korponay et al., unpublished). Recent work shows that the integrity of frontostriatal white matter fibers predicts improvements in the ability to delay gratification from childhood to early adulthood (Achterberg et al., 2016). Therefore, future work may also wish to address the relationship between structural integrity of frontostriatal white matter tracts and psychopathy scores and, more specifically, Factor 2 lifestyle/antisocial traits relating to impulsivity in this larger inmate sample. This sample also exhibits a high rate of substance abuse and dependence, which provides opportunities for future work to investigate vmPFC/OFC-VS functional and structural connectivity following abuse of different types of substances, including alcohol, cannabis, cocaine, and opiates. Any observed similarities between psychopathy severity and substance use disorder in vmPFC/OFC-VS circuit function or structure may indicate neuropathophysiological substrates that are common across two categorically distinct disorders.

5.3 Conclusion

The ultimate goal of research on this vmPFC/OFC-VS circuit in humans is to identify the basic dimensions of brain function and structure underlying the full range of decision-making and responses to rewards, from adaptive to maladaptive. The present findings further efforts to meet this goal by identifying (1) a causal role for vmPFC/OFC in attenuating susceptibility to bias during decision-making, (2) causal interactions between vmPFC/OFC and VS during normative anticipation for rewards, and (3) increased VS activity to rewarded outcomes among individuals who demonstrate poor decision-making and diminished behavioral restraint to obtain rewards. As the translation from basic neuroscience to psychiatric patient care continues to progress, the brain's reward circuit has shown to play a prominent role in the treatment of psychiatric disorder symptoms related to reward processing and decision-making, such as major depressive disorder and substance use disorder. Progress in this area of research will therefore be critical for the advancement and development of neuropathophysiologically-based strategies for diagnosis and treatment.

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