PROCESSING OF SMOKING AND MONETARY REWARDS AMONG CHRONIC SMOKERS: CHARACTERIZATION OF NEURAL RESPONSE, MODERATION BY ABSTINENCE, AND ASSOCIATION WITH SMOKING OUTCOMES

by

Maggie M. Sweitzer

Bachelor of Arts, University of Akron, 2005

Master of Science, University of Pittsburgh, 2008

Submitted to the Graduate Faculty of

the Deitrich School of Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2013

UNIVERSITY OF PITTSBURGH

DEITRICH SCHOOL OF ARTS AND SCIENCES

This dissertation was presented

by

Maggie M. Sweitzer

It was defended on

April 15, 2013

and approved by

Stephen Manuck, Distinguished Professor, Psychology

Erika Forbes, Assistant Professor, Psychiatry and Psychology

Peter Gianaros, Assistant Professor, Psychiatry

Kathryn Roecklein, Assistant Professor, Psychology

Dissertation Advisor: Eric Donny, Associate Professor, Psychiatry and Psychology

PROCESSING OF SMOKING AND MONETARY REWARDS AMONG CHRONIC SMOKERS: CHARACTERIZATION OF NEURAL RESPONSE, MODERATION BY ABSTINENCE, AND ASSOCIATION WITH SMOKING OUTCOMES

Maggie M. Sweitzer, Ph.D.

University of Pittsburgh, 2013

Theoretical models suggest that chronic smoking may be associated with both hypersensitivity to smoking and related cues and hyposensitivity to alternative reinforcers, and that these effects may be more pronounced during deprivation from smoking. However, neural responses to smoking and non-smoking rewards are rarely evaluated within the same paradigm, and current neuroimaging evidence on the effects of deprivation on reward processing is limited. Bias toward smoking reward in lieu of alternative rewards during abstinence could represent a fundamental mechanism contributing to relapse during a quit attempt. In this dissertation, I present a series of analyses to address three primary aims: 1) to characterize the neural response to smoking and non-smoking rewards among chronic smokers within the same paradigm, 2) to determine the impact of deprivation upon the neural response to both reward types, and 3) to evaluate the association between neural responses to both reward types and the choice to smoke in lieu of alternative reinforcement. Smokers each participated in two separate fMRI scans, one after smoking ad libitum and one following 24 hours of abstinence. A rewarded guessing task was conducted during each scan to evaluate BOLD response during anticipation and delivery of both smoking and monetary rewards. Following completion of both scans, smokers engaged in a quit attempt supported by contingency management, during which abstinence from smoking was reinforced with monetary

reward. Results indicated that smoking and monetary rewards both activated the same reward-related circuitry, including ventral and dorsal striatum, anterior cingulate cortex, medial prefrontal cortex, and bilateral insula. Abstinence from smoking was associated with an increase in anticipatory activation to smoking reward and a parallel decrease in anticipatory activation to monetary reward in the same reward-related regions. Furthermore, preliminary analyses suggested that larger decreases in anticipatory activation to monetary reward in the right caudate were associated with higher likelihood of lapse during contingency management. Collectively, these results suggest that reward processing may be biased toward smoking reward at the expense of alternative rewards during abstinence—a bias which may directly impact smoking behavior during a quit attempt.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

I owe tremendous gratitude to numerous people who have helped me throughout my graduate training. First and foremost, I would like to thank my advisor, Eric Donny, who has consistently supported my development as a junior colleague and challenged my thinking as an independent scientist. His curiosity and enthusiasm, commitment to scientific integrity, and dedication to teaching and training have truly been an inspiration and have made him an exceptional mentor. I would also like to thank members of my dissertation committee, Peter Gianaros, Erika Forbes, Kathryn Roecklein, and Stephen Manuck, for their guidance and advice throughout this project. Stephen Manuck, in particular, has served on each of my milestone and fellowship training committees, and I am extremely grateful for his wisdom and insight. Special thanks go also to Kathryn Roecklein and Ahmad Hariri for their generous mentorship during my IGERT and Behavioral Brain research training. Finally, none of this work could have been accomplished without the hard work and dedication of the entire Nicotine and Tobacco Research Lab, past and present, including graduate students and post-docs, research assistants, and undergraduate students.

In my personal life, I owe an insurmountable debt of gratitude to my dear husband, Chris Sweitzer, whose continual support and sacrifices have made this journey possible. I would not be where I am today without his love, friendship, and encouragement. He is a wonderful man and a fantastic father. Finally, I would like to dedicate this work to our beautiful daughters, Celeste and Zoe, who have taught me to cherish each moment and remember what is most important in life. Always remember to be true to yourself and follow your passion—you can achieve anything in life that you put your heart and mind to.

1. INTRODUCTION

Tobacco smoking remains a leading cause of preventable death. Despite grave health consequences, many people who attempt to quit smoking are unable to do so. Improving our understanding of the mechanisms that lead to difficulty quitting smoking is critical to improving treatment efforts. One potential mechanism contributing to relapse among chronic smokers making a quit attempt is dysregulated reward processing. Several theories posit that drug dependence reflects neuroadaptations involving midbrain dopaminergic function resulting from chronic drug exposure, which lead to 1) an increase in the incentive properties of drug and drug-associated stimuli and 2) a decrease in the incentive value of other rewarding stimuli concurrently available in the environment. This bias in reward processing is thereby likely to contribute to a narrowing of the behavioral repertoire, such that individuals increasingly choose the drug over other non-drug reward alternatives. Such dysregulated reward processing has been demonstrated for drugs such as cocaine and alcohol, and the severity of this reward imbalance is thought to contribute to difficulty abstaining. However, despite the intuitive appeal of this model, parallel processes have only recently begun to be investigated for smoking, and responses to both drug and non-drug rewards are rarely investigated within the same model. *Therefore, it is a primary objective of this dissertation to characterize the neural response to both monetary and smoking rewards among chronic smokers*.

Importantly, alterations in reward processing among chronic smokers may be moderated by the presence or absence of nicotine in the brain. In particular, abstinence from smoking may

exacerbate biases toward an overvaluation of smoking reward and an undervaluing of monetary reward. Converging behavioral evidence suggests that this is the case, but neuroimaging evidence directly evaluating neural response to rewards as a function of deprivation state is limited to date. *Therefore, a second primary objective of this dissertation is to compare neural response to monetary and smoking rewards during an abstinent and non-abstinent state.* Given existing behavioral evidence among animal and human models, it is expected that a dissociation in the neural response to reward will be observed, such that abstinence augments the response to smoking reward but attenuates the response to non-smoking (monetary) reward. Further explanation and support for these hypotheses are presented in the following sections.

Beyond evaluation of overall group level effects, a further consideration is that individual differences in reward function may interact with the neurophysiological consequences of repeated nicotine use, contributing to variability in the resultant reward processing imbalance. Thus, some smokers may be at relatively greater risk for developing a pattern of reward processing in which smoking is "overvalued" and non-smoking reinforcers are "undervalued" during abstinence, rendering these individuals more likely to smoke in lieu of alternative rewards for abstinence. Indeed, even in the absence of overall main effects of abstinence on reward function, individual variability in the relative neural activation to smoking versus non-smoking rewards as a function of abstinence may predict real-life decision making when smoking rewards are pitted against non-smoking rewards. Contingency management, which provides monetary incentives for biochemically verified abstinence, provides an ideal framework in which to test the choice to smoke over an alternative monetary reinforcement. *Thus, the third objective of this dissertation is to begin to explore the association between neural response to smoking and non-smoking rewards and the ability to refrain from smoking when given an incentive to do so.*

I begin with an overview of reward processing and its theoretical role in maintaining smoking behavior (Chapter 2). This chapter first provides a basic overview of reward circuitry, since a discussion of how perturbations in this system are involved in nicotine dependence hinges upon an understanding of this basic circuitry. I then present theoretical and empirical evidence for reward dysfunction as a central factor in drug addiction, including a discussion of what is currently known about reward dysfunction in nicotine dependence. Building upon this basic framework, I then outline the rationale and discuss evidence in support of the hypotheses that 1) deprivation state will moderate the neural response to smoking and non-smoking rewards and 2) individual differences in neural response to smoking and non-smoking rewards will predict the ability to abstain from smoking when given an incentive to do so. Building toward a direct test of the latter hypothesis, contingency management is then discussed as an established approach to smoking cessation that is ideal for testing the behavioral choice between smoking and non-smoking reward alternatives.

Following presentation of this background information, Chapter 3 provides details of the study design and methods used to address the primary objectives. Chapters 4-6 describe the analytic strategy and present the results and a brief discussion for each set of analyses. Finally, implications and future directions are discussed in Chapter 7.

2. THE ROLE OF REWARD PROCESSING IN SMOKING

Reward processing is fundamental to animal and human behavior. Pursuit of primary rewards, such as food, water, and sex, enable reproduction of the species and ensure survival. From a behavioral perspective, rewards can be considered as any stimulus that acts as a reinforcer—that is, anything that serves to increase the probability of the behavior that lead to the reward occurring again in the future (McClure, York, & Montague, 2004). This reinforcement may or may not co-occur with a subjective hedonic sensation of pleasure or a conscious motivation to obtain the reward (Berridge, Robinson, & Aldridge, 2009). Research has begun to parse out different aspects of reward processing and their neural substrates, suggesting that different neurophysiological mechanisms and cortical and subcortical regions may give rise to different aspects of reward processing. In addition, different types of rewards may not activate this circuitry in a uniform manner. Primary rewards can be differentiated from secondary rewards in that secondary rewards (e.g. money) gain their reinforcing value through learned associations with primary rewards. Although diverse rewards have been shown to activate common neural pathways, evidence also suggests some reward-type specific areas of activation (Sescousse, Caldu, Segura, & Dreher, 2013). Furthermore, drug rewards may have a particularly unique impact on reward circuitry, given that drugs of abuse act directly upon reward-related pathways and thereby have the potential to artificially induce neurochemical changes. Indeed, numerous theories have been developed to explain how perturbations in reward circuitry caused by repeated drug administration give rise to the compulsive behavioral manifestations of addiction.

The following chapter provides a brief overview of basic reward processing and its relevance for addiction. While I focus primarily on the striatum, given its central role in reward processing and addiction, I also discuss interconnected regions including medial prefrontal cortex, insula, and amygdala. After introducing the role of these regions in healthy reward processing, I then turn to theoretical perspectives on the role of reward processing in addiction. Because nicotine has actions that overlap with other drugs of abuse, I draw on the larger addiction literature for relevant theories, but also discuss studies pertaining specifically to smoking. I discuss findings from the literature that directly inform the hypotheses of this dissertation, as well as identifying gaps in the literature that will be addressed by the current project. Finally, I introduce contingency management as an ideal model of smoking cessation for testing the impact of individual variability in reward processing on the ability to quit smoking.

2.1 HEALTHY REWARD PROCESSING

Extensive research has delineated the basic circuitry involved in processing rewards, as well as the underlying neurophysiological processes associated with specific components of reward processing. Indeed, reward processing is complex, incorporating multiple distinct signals encoding a variety of anticipatory and consummatory properties of rewarding stimuli (O'Doherty, 2004; Schultz, 2000). Several regions have consistently emerged as key nodes in the functional networks supporting multiple aspects of reward processing, including the ventral and dorsal striatum (VS and DS, respectively), medial prefrontal cortex (medial PFC), and orbitofrontal cortex (OFC) (Apicella, Ljungberg, Scarnati, & Schultz, 1991; Breiter, Aharon,

Kahneman, Dale, & Shizgal, 2001; Delgado, Locke, Stenger, & Fiez, 2003; Elliott, Newman, Longe, & Deakin, 2003; Haber & Knutson, 2010; Hikosaka & Watanabe, 2000; Roesch & Olson, 2003, 2004; Thut et al., 1997).

Midbrain dopaminergic projections from the ventral tegmental area (VTA) to the VS have been consistently shown to play a central role in reward processing. Indeed, converging evidence from both human neuroimaging and animal electrophysiological studies have found the VS to be active in response to both anticipation and receipt of a wide range of both primary and secondary reinforcers (Bassareo & Di Chiara, 1999; Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; O'Doherty, 2004; Schultz, 2000). Prominent theories suggest that midbrain dopamine neurons are particularly responsible for reward-related learning and reward prediction, such that they fire in response to both conditioned stimuli signaling impending reward, and in response to unanticipated unconditioned rewards, thereby facilitating, in conjunction with the amygdala, the formation of Pavlovian associations for future predictions (Cardinal et al., 2002; McClure et al., 2004; Schultz & Dickinson, 2000). Consistent with the theory of reward prediction, and partially fueled by findings of a dissociation between aspects of reward processing within the addiction literature, other theorists have proposed that dopamine signaling within the VS is involved more with incentive salience or "wanting" of reward, rather than the actual hedonic experience of reward (Berridge et al., 2009; Robinson & Berridge, 1993). By contrast, the hedonic experience of "liking" a reward is thought to be mediated primarily by endogenous opioid signaling and localized to hedonic "hotspots" such as regions of the ventral pallidum (Berridge et al., 2009; Robinson & Berridge, 1993).

The ventral striatum, encompassing the nucleus accumbens, has long been considered central to reward and motivational processing, given its rich dopamine input and

interconnections with limbic structures, while more dorsal portions of the striatum, including caudate and putamen, were traditionally thought to involve primarily sensorimotor processing (Robbins & Everitt, 1992). However, VS and DS are not anatomically distinct (Groenewegen & Trimble, 2007), and more recent evidence suggests that DS is also involved in reward processing and motivated, goal-directed behavior, much like VS (Koepp et al., 1998; O'Doherty et al., 2004; O'Doherty, Deichmann, Critchley, & Dolan, 2002; Zald et al., 2004). Indeed, VS and DS appear to operate along a ventromedial to dorsolateral gradient of corticostriatal loops, with affective and sensorimotor information processed along this gradient but integrated across adjacent circuits and within prefrontal cortex to guide behavior (Haber & McFarland, 2001).

The OFC and medial PFC, which comprises the medial portion of the OFC, also receive midbrain dopaminergic innervations and, as noted above, are reciprocally interconnected with the VS and DS, as well as other associated limbic regions including the amygdala and anterior cingulate cortex (Haber, Kunishio, Mizobuchi, & Lynd-Balta, 1995; Ray & Price, 1993; Volkow, Fowler, & Wang, 2003). Like the striatum, the OFC/medial PFC have been shown to be responsive to a variety of primary and secondary rewards. In particular, this region is thought to be involved in representation of the value and magnitude of reward (Phillips, Drevets, Rauch, & Lane, 2003), and has been shown to be activated in proportion to the subjective hedonic value of a stimulus (Kringelbach, 2005). Consistent with this, some studies suggests that the VS is primarily activated during reward expectation and the OFC is primarily activated by reward delivery (Knutson, Fong, Adams, Varner, & Hommer, 2001; Knutson & Wimmer, 2007), but other evidence suggests that both regions may similarly encode outcome expectancies, so that such a clear distinction cannot be made (Roesch, Calu, Esber, & Schoenbaum, 2010). In addition, the medial and lateral portions of the OFC has been shown to respond preferentially to

reward and punishment, respectively, and these regions appears to be important for learning stimulus-reinforcement associations and guiding behavior according to reward and punishment related contingencies (Elliott, Dolan, & Frith, 2000; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; Rolls, 2000; Schoenbaum, Setlow, & Ramus, 2003). Thus, the VS, DS, and medial PFC are critically involved in reward processing and share similar, although potentially distinct roles in reward prediction and valuation.

Of course, activation of these reward-related regions takes place within a much larger context of interconnected circuitry incorporating diverse processes such as attention, arousal, and executive control. For example, the amygdala is strongly interconnected with the VS and OFC and has been shown to be activated by a variety of rewarding stimuli (Hamann & Mao, 2002; Hommer et al., 2003), as well as negative emotional stimuli (Calder, Lawrence, & Young, 2001; LeDoux, 2000), leading to speculation that the amygdala may respond to emotional salience or intensity of stimuli (Anderson & Sobel, 2003). Furthermore, other regions not typically thought of as "reward-related" have also been shown to be involved in processing a variety of rewards, including anterior insula, mediodorsal thalamus, and lateral OFC, possibly mediating such functions as subjective affective feeling of reward or arousal and attention toward anticipated rewards (Sescousse et al., 2013). Thus, while the striatum is at the heart of reward processing circuitry, many other interconnected regions play a significant role in responding to rewards and motivating behavior. Evidence suggesting a reward dysfunction involving the striatum and associated circuitry in compulsive drug use, including nicotine addiction, is discussed in the next section.

2.2. REWARD DYSFUNCTION IN COMPULSIVE DRUG USE

All drugs of abuse, including nicotine, act on regions of the brain thought to mediate processing of reward, including the VS, amygdala, and prefrontal cortex (Brody, 2006; Johnson & Gerstein, 1998; Robinson & Berridge, 1993; Robinson & Kolb, 2004). Acute nicotine exposure stimulates phasic midbrain dopamine release (Brody et al., 2004; Takahashi et al., 2008), which is thought to mediate nicotine's reinforcing effects (Corrigall & Coen, 1991; Corrigall, Franklin, Coen, & Clarke, 1992). Over repeated exposure, chronic stimulation of the reward pathways leads to a variety of neuroadaptations which serve to confer heightened motivational incentive properties to the drug and associated stimuli (Robinson & Berridge, 1993), while at the same time blunting the incentive value of other non-drug reinforcers (Koob & Le Moal, 2005). Each of these effects is described in greater detail below.

2.2.1. Evidence for Heightened Sensitivity to Drug Reward

According to incentive sensitization theory, repeated exposure to drugs of abuse, including nicotine, results in a sensitization of the dopamine response to the drug and related cues (Kalivas & Stewart, 1991; Robinson & Berridge, 1993; Vanderschuren & Kalivas, 2000; Vezina, 2004)—an effect which has been shown to predict future drug self-administration (Vezina, 2004; Vezina, McGehee, & Green, 2007). Over time, stimuli which have been repeatedly paired with a drug of abuse begin to elicit a striatal dopamine response and acquire a heightened incentive value of their own, thereby motivating drug seeking behavior (Di Ciano & Everitt, 2004; Duvauchelle et al., 2000; Kiyatkin & Stein, 1996; Phillips, Stuber, Heien, Wightman, & Carelli, 2003; Vanderschuren, Di Ciano, & Everitt, 2005; Weiss et al., 2000). Accordingly, human

neuroimaging studies have consistently demonstrated the ability of drug related stimuli to activate basic reward circuitry. For example, drug related cues have been shown to elicit heightened striatal dopamine release relative to neutral cues as measured by [(11)C]raclopride displacement among cocaine dependent individuals—the magnitude of which was associated with greater craving and addiction severity (Volkow et al., 2006; Wong et al., 2006). Furthermore, compared with control subjects, cocaine and alcohol dependent individuals demonstrated increased BOLD response to drug related cues relative to neutral cues in reward related regions including the medial PFC, OFC, anterior cingulate cortex, and striatum (Goldstein et al., 2009; Grusser et al., 2004; Heinz et al., 2004; Wrase et al., 2002; Wrase et al., 2007). Importantly, heightened activation in these regions has been shown in some studies to predict subsequent drinking outcomes (Braus et al., 2001; Grusser et al., 2004), suggesting that the recruitment of the brain's natural reward mechanisms by drug reward predictive stimuli may contribute to motivation for continued drug use.

Similar patterns of findings have been observed for nicotine. Presentation of smoking cues compared with neutral cues among chronic smokers increases self-reported craving for cigarettes (Bailey, Goedeker, & Tiffany, 2009), and elicits BOLD activation in reward-related areas including the striatum, amygdala, OFC, ACC, insula and hippocampus (David et al., 2005; Franklin et al., 2007; McClernon, Hiott, Huettel, & Rose, 2005). Although the importance of cue-induced craving in predicting smoking outcomes has been questioned (Perkins, 2009), evidence suggests that increased craving in response to smoking related stimuli may be an important determinant of vulnerability to relapse (Ferguson & Shiffman, 2009). Furthermore, although few studies have examined the association between neural response to smoking cues and subsequent treatment outcomes, one recent study found that decreased functional

connectivity among reward-related regions including the anterior cingulate cortex was associated with increased likelihood of a slip during a cessation attempt (Janes et al., 2010). Together, these studies suggest that smokers experience a hypersensitivity to smoking and associated stimuli relative to non-drug related stimuli, which likely contributes to continued smoking behaviour.

2.2.2. Evidence for Reduced Sensitivity to Non-Drug Reward

The hyperdopaminergic striatal response to drug reward and associated stimuli described above may take place against a backdrop of overall hypodopaminergic function, possibly mediated by a down-regulation of D2 receptors (Fehr et al., 2008) or reduced baseline striatal extracellular dopamine during withdrawal (Domino & Tsukada, 2009). This perspective is consistent with opponent process theory, which posits that chronic drug exposure results in a compensatory alteration in reward processing in an attempt to correct the imbalance that is produced by constant stimulation of the reward pathways (Koob & Le Moal, 2005). Thus, over time *non-drug rewards* lose their incentive value and fail to motivate behavior. Human neuroimaging studies have demonstrated decrements in reward processing among individuals dependent on a variety of drugs of abuse. For example, cocaine addicts exhibit decreased prefrontal sensitivity to monetary reward and sexually evocative cues assessed with fMRI (Garavan et al., 2000; Goldstein et al., 2007), as well as attenuated baseline prefrontal metabolism assessed with PET (Volkow et al., 1993) relative to healthy controls. Similar patterns of diminished striatal response to reward have been observed among detoxified opiate addicts and alcoholics. For example, opiate addicts exhibit reduced striatal BOLD response to non-monetary reinforcement feedback relative to healthy controls (Martin-Soelch et al., 2001), and detoxified alcoholics

demonstrate reduced striatal BOLD response to monetary reward relative to control subjects (Beck et al., 2009; Wrase et al., 2007).

Although research is limited, studies among smokers are generally consistent with the hypothesis of reduced sensitivity to non-drug rewards relative to nonsmoking controls. Indeed, evidence suggests that chronic smokers in an abstinent state experience diminished capacity for reward relative to both satiated smokers and non-smokers, including less enjoyment from ordinarily pleasurable events and reduced response to financial reward during a card sorting task (Dawkins, Powell, West, Powell, & Pickering, 2006; Powell, Dawkins, & Davis, 2002; Powell, Pickering, Dawkins, West, & Powell, 2004). In addition, a handful of neuroimaging studies using PET and fMRI to assess neural response to non-drug rewards among smokers have addressed this issue. In one PET study, smokers failed to show striatal activation observed in non-smokers in response to monetary reward (Martin-Solch et al., 2001). A second PET study found that, in contrast to non-smokers who demonstrate a reliable correlation between the magnitude of monetary rewards and rCBF in the striatum, no relationship is observed in smokers, suggesting an attenuated striatal response to even the largest rewards (Martin-Soelch, Missimer, Leenders, & Schultz, 2003). In a recent fMRI study, chronic smokers undergoing a reinforcement learning procedure demonstrated attenuated reward-related activity in the striatum and medial prefrontal cortex relative to non-smokers—effects that were correlated with duration of smoking history and cigarettes smoked per day (Rose et al., 2012). Interestingly, another recent study found attenuated VS activation during reward anticipation among adolescent smokers relative to non-smokers, even among individuals who had smoked fewer than 10 times (Peters et al., 2011). Together, these studies provide increasing evidence for reduced

responsiveness to non-drug rewards among chronic smokers and suggest a role for individual differences both in response to accumulating drug exposure and as a possible predisposing vulnerability.

2.2.3. Predicting a Dissociation between Drug and Non-drug Reward Processing

One implication of the research described above is that sensitivity to smoking and alternative rewards may be dissociated (or inversely correlated) in smokers. Although the drug and non-drug literatures implicate similar circuitry in the processing of rewards, drug reinforcers may have unique properties that result in a distinct pattern of effects. As described above, Volkow and colleagues hypothesize that addictive drugs produce supraphysiological effects on DA systems that result in compensatory neuroadaptations, rendering users less sensitive to other non-drug rewards (Kalivas & Volkow, 2005; Volkow, Fowler, & Wang, 2004). This disruption of the DA system may further increase the salience of drug and drug-associated stimuli, as these stimuli have the potential to overcome the deficits in reward processing, whereas natural rewards do not. Indeed, one recent study suggested that sensitization of the dopamine response to nicotine occurs among non-human primates, but this was only evident when accounting for an overall decrease in striatal dopamine function (Domino & Tsukada, 2009). These studies suggest that parallel increases in sensitivity to drug reward and decreases in sensitivity to non-drug rewards may co-occur and may even be inversely related. Such a dissociation may be regulated in part by neuroadaptations in glutamatergic afferent pathways arising from the prefrontal cortex (Kalivas & Volkow, 2005; McFarland, Lapish, & Kalivas, 2003; Vanderschuren & Kalivas, 2000; Volkow et al., 2007; Vorel, Liu, Hayes, Spector, & Gardner, 2001). Indeed, overall reductions in prefrontal metabolism during protracted withdrawal as measured by PET, combined with

enhanced prefrontal metabolism associated with craving, have been observed among cocaine addicts, and are speculated to contribute to perseverative drug seeking behavior (Volkow & Fowler, 2000). Furthermore, increases in medial prefrontal BOLD activation associated with craving and response to drug-related cues have been linked with low levels of striatal D2 receptors (Heinz et al., 2004; Volkow et al., 2006), suggesting the potential role of this circuit in mediating a reward dysfunction characterized by both heightened response to drug reward and attenuated response to non-drug reward.

Despite this rich theoretical background, direct empirical evidence for a neural dissociation between responses to drug versus non-drug rewards has been limited by a scarcity of studies examining both reward types simultaneously and a lack of comparable measures of drug and non-drug rewards. However, some direct evidence of a dissociation between responses to drug and non-drug rewards has been previously observed for cocaine and alcohol. For example, compared to non-users, cocaine users demonstrate increased activation in prefrontal and limbic areas to cocaine cues but reduced activation to sexually evocative cues (Garavan et al., 2000). Similar findings were also recently observed among detoxified heroin addicts, who showed increased reward related activation to drug cues but decreased activation to positive affective stimuli, relative to control subjects (Zijlstra, Veltman, Booij, van den Brink, & Franken, 2009). In another study, recently detoxified alcoholics exhibited decreased VS activation in response to monetary reward and increased VS activation in response to alcohol cues, relative to non-alcoholics (Wrase et al., 2007). Furthermore, craving for alcohol was negatively correlated with neural response to monetary reward and positively correlated with neural response to alcohol cues. Finally, consistent with our predictions, VS activation in response to positive affective non-drug stimuli was inversely related to the number of drinking days in 11 alcoholics engaged

in an abstinence attempt (r=-.60) (Heinz et al., 2007). These findings suggest that the VS may be a critical region mediating differential response to drug versus non-drug reward and that individual differences in activation of this region to non-drug rewards are predictive of abstinence.

Among smokers, only one recent study tested neural response to both monetary and cigarette rewards using the same task in the same subjects (Buhler et al., 2010). While occasional non-daily smokers exhibited greater reward-related neural activation in anticipation of monetary reward compared with smoking reward, no differences in response to the two reward types was observed among dependent daily smokers. This pattern of findings was also mirrored behaviorally in the rate of instrumental responding for each type of reward. These data suggest that it is the relative balance of the incentive salience for smoking versus non-smoking rewards which is critical for motivating continued smoking behavior, rather than simply heightened salience of smoking reward per se. Other evidence also hints at the possible inverse relationship between incentive salience of smoking and non-smoking rewards. In one study, both craving for cigarettes and the impending opportunity to smoke are inversely related to neural response to monetary rewards (Wilson, Sayette, Delgado, & Fiez, 2008). In another recent study of chronic smokers, severity of depression—a disorder characterized in part by diminished motivation and enjoyment of natural rewards—was positively correlated with BOLD response to smoking cues in brain areas associated with processing reward and attentional bias, particularly when subjects were in an abstinent state (Kushnir et al., 2010). These data emphasize that increased incentive processing of cigarettes is likely to be related to attenuated processing of monetary rewards.

2.3. IMPACT OF DEPRIVATION ON REWARD DYSFUNCTION

The pattern of reward dysfunction described above may be particularly pronounced in the absence of nicotine, when underlying processing deficits may be "unmasked" by the removal of the acute effects of nicotine and/or the emergence of a withdrawal state. For example, smoking self-administration is heightened when chronic smokers are in a deprived relative to satiated state (Barrett, 2010; Kollins et al., 2012; McKee, Weinberger, Shi, Tetrault, & Coppola, 2012), and smokers routinely report lower craving after smoking (Schuh & Stitzer, 1995). Thus, smokers may be hypersensitive to smoking-related rewards when abstinent. Evidence also suggests possible hyposensitivity to non-drug rewards during abstinence. For example, evidence from animal studies suggests that acute nicotine enhances—while withdrawal from nicotine attenuates—the incentive value of other reinforcers (Besheer & Bevins, 2003; Chaudhri et al., 2006; Donny et al., 2003; Powell et al., 2002; Thiel, Sanabria, & Neisewander, 2009; Weaver et al., 2012). Nicotine administration lowers intracranial self-stimulation (ICSS) thresholds (Kenny & Markou, 2006), suggesting that nicotine acutely renders reward systems hypersensitive to non-drug rewards, while nicotine withdrawal increases ICSS thresholds (Epping-Jordan, Watkins, Koob, & Markou, 1998; Skjei & Markou, 2003). Recent human studies are consistent with these findings; non-smokers administered transdermal nicotine demonstrated greater response bias to monetary reward compared to placebo patch (Barr, Pizzagalli, Culhane, Goff, & Evins, 2008). In other studies, abstinent smokers demonstrate less interference from pleasure-related words during a modified Stroop task than satiated smokers (Dawkins, Acaster, & Powell, 2007) and rated unfamiliar faces as less attractive (Attwood, Penton-Voak, & Munafo, 2009).

Furthermore, as noted above, reward processing deficits revealed by behavioral indices of reward functioning are observed among smokers compared with non-smokers only when smokers are in an abstinent state; no differences between smokers and non-smokers are seen when smokers are in a satiated state (Dawkins et al., 2006; Powell et al., 2002; Powell et al., 2004). Thus, acute reinforcement enhancing effects of nicotine may serve to mask underlying reward processing deficits among chronic smokers, thereby contributing to a powerful negative reinforcement of continued smoking behavior.

Despite the rich theoretical background and behavioral evidence, few studies have examined neural response to smoking rewards among smokers tested in both an abstinent and non-abstinent state, and results have been mixed. Some studies have demonstrated heightened BOLD response to smoking cues (McBride, Barrett, Kelly, Aw, & Dagher, 2006; McClernon, Kozink, Lutz, & Rose, 2009) or in cued anticipation of intravenous nicotine (Gloria et al., 2009) in reward-related areas among smokers in deprived relative to satiated states. However, other studies have shown minimal effect of abstinence on response to smoking reward (Buhler et al., 2010) or opposite effects, such as greater VS response to smoking cues during non-abstinence compared with abstinence (David et al., 2007). A recent meta-analysis of neuroimaging studies of smoking cues found some evidence of increased reward-related activation during abstinence relative to non-abstinence, but effects were relatively small and sample sizes were limited (Engelmann et al., 2012). In addition, few studies have examined abstinence effects on neural response to non-drug rewards, with similarly mixed findings. One study found blunted reward-related activation during abstinence only among highly dependent smokers (Sweitzer, Donny, & Hariri, 2012), while other studies found no effect of abstinence (Buhler et al., 2010; Rose et al., 2012), or a combination of heightened and attenuated activation across different reward-related

regions (Addicott et al., 2012). Thus, despite clear theoretical predictions, effects of abstinence from smoking on neural response to reward remain equivocal. Furthermore, even if abstinence from smoking does enhance neural processing of smoking rewards, it is unclear whether this heightened response generalizes to other non-drug rewards or dissociates based on reward type. Finally, although both smoking and non-smoking rewards recruit the same neural pathways, it is unclear whether this potential dissociated response is instantiated in the same circuitry, or whether different regions are recruited depending on type of reward.

One possible reason for the current lack of conclusive findings is that many of these studies employed relatively small sample sizes (average $n = 14$), with three studies including 10 or fewer participants. Furthermore, methodological differences described above prevent direct comparisons across studies. Most notably, studies of smoking reward typically rely on passive presentation of smoking related stimuli (e.g. a cigarette or lighter), while non-smoking rewards commonly utilize performance-contingent reward delivery (e.g. earning monetary reward). Thus, studies of exposure to smoking reward may primarily tap into anticipatory processing, while studies of non-smoking rewards are more geared to evaluate reward outcome or delivery (although many monetary reward studies do include an anticipation phase). Furthermore, the smoking stimuli utilized in these studies are usually divorced from any true predictive relationship with smoking. Thus, the presentation of a cigarette is not directly linked with expectancy of actually smoking the cigarette—a distinction which may profoundly alter neural processing (Wilson, Sayette, Delgado, & Fiez, 2005; Wilson et al., 2008; Wilson, Sayette, & Fiez, 2004). Thus, comparisons across studies employing different methodological frameworks are insufficient to determine how abstinence from nicotine may differentially affect processing of smoking versus non-smoking rewards.

One recently published neuroimaging study has thus far directly assessed changes in neural processing of nondrug-related rewards as a function of deprivation state among chronic smokers. As described above, Buhler and colleagues investigated BOLD response to both smoking and monetary rewards within the same task (Buhler et al., 2010). In addition to examining effects of daily versus non-daily smoking status, they also manipulated deprivation state among daily smokers in order to determine the effects of withdrawal on neural processing of each reward type. They found that although regular, daily smokers exhibited reduced activation in reward-related brain regions in anticipation of monetary reward compared with occasional smokers, within-subjects comparisons based on deprivation state revealed only a small main effect increase in medial PFC response to both types of reward as a function of withdrawal.

This lack of a significant reward type by deprivation state interaction is surprising given the existing behavioral data and theoretical background described above, and it suggests that reward deficits seen among chronic smokers are not a state dependent phenomenon. However, this conclusion should be qualified by several considerations. First, only 21 daily smokers were tested. Although this is a typical sample size for a within-subjects design, it is possible that the study was underpowered to detect a complex interaction involving reward type, reward magnitude, and deprivation state. The sample size of 38 subjects included in the present study provides a much more powerful test of an abstinence by reward type interaction. Second, although the authors largely dismissed their findings, the observed withdrawal-induced increase in medial PFC activation is intriguing, given that this is a key reward-related region. Although this result is not in the predicted direction for monetary reward, a replication of this unexpected effect could have important implications for understanding reward processing in nicotine

dependence. Third, even small differences in task design may have a profound influence on observed BOLD activation. For example, subjects in the Buhler et al. study earned cigarettes which were to be smoked over the following 24 hours, rather than puffs earned for the next hour as proposed here. One possible consequence of the longer duration is that this may have created an overall expectancy of abstinence after the scan, particularly during early trials when subjects were not yet sure that they would earn enough cigarettes to satiate cravings for that length of time. Although other interpretations are certainly possible, this example highlights the importance of replication across a variety of studies and tasks. Given the suggestive behavioral evidence and the dearth of neuroimaging studies addressing this topic, further research is needed to definitively conclude a lack of abstinence effects on processing of non-drug rewards.

A final consideration is that individuals could vary in the extent to which they are susceptible to effects of withdrawal on reward function. Indeed, preliminary data from our own lab suggest that even among daily smokers, abstinence-induced changes in BOLD response to reward may be moderated by severity of nicotine dependence, thereby washing out any overall main effect (Sweitzer et al., 2012). Our data revealed decreases in VS response to monetary gain during abstinence compared with satiation only among a subset of highly dependent smokers, while low dependent smokers showed an opposite—possibly protective—pattern. Although preliminary, these findings underscore the need for a larger sample given substantial inter-individual variability, and suggest an important role that such variability may play in understanding smoking behavior. Overall, although the limited neuroimaging data to date is mixed, the above data suggest that dysregulation in reward processing characterized by hypersensitivity to smoking reward and hyposensitivity to non-smoking reward may be exacerbated during nicotine withdrawal. This may be particularly true among severely

dependent smokers, thereby interfering with the ability to maintain abstinence by further shifting the balance of incentive attribution toward smoking rewards and away from non-smoking rewards.

2.4 THE ROLE OF INDIVIDUAL DIFFERENCES IN REWARD PROCESSING AND SMOKING BEHAVIOR

As described above, individuals may vary greatly in the extent to which reward dysfunction underlies their smoking behavior. This is not surprising, given that substantial variability in nicotine dependence has been observed even among relatively long-term daily smokers (Donny & Dierker, 2007; Donny, Griffin, Shiffman, & Sayette, 2008). Indeed, understanding the factors that lead some individuals to have greater difficulty quitting smoking than others is of paramount importance for improving treatment efforts. To the extent that reward dysfunction described above is not uniform across all smokers, then variability in hypersensitivity to smoking reward and hyposensitivity to non-smoking reward at the neural level may directly mediate behavioral choices between smoking and non-smoking reward alternatives.

As noted above, some evidence within the existing literature suggests that this may be the case. For example, heightened PET metabolism and BOLD activation in reward related regions in response to smoking cues has been associated with elevated reports of craving (Brody et al., 2002; McClernon et al., 2005), greater severity of nicotine dependence (McClernon, Kozink, & Rose, 2008) and has been shown to predict smoking relapse during a quit attempt (Janes et al., 2010), suggesting that individual variability in hypersensitivity to smoking-related stimuli may be an important determinant of smoking behavior. Furthermore, individual variability in reward

deficits appears to be important for ability to maintain abstinence. Greater attenuation of striatal response to reward among detoxified alcoholics was linked with an increase in later drinking (Heinz et al., 2007), and reports of diminished capacity to experience pleasure among chronic smokers predicts craving during abstinence (Cook, Spring, McChargue, & Hedeker, 2004) and later relapse (Cook, Spring, McChargue, & Doran, 2010). Together, these studies provide preliminary support for the hypothesis that the imbalance in reward processing resulting from the combination of a hypersensitivity to smoking reward and a reduced sensitivity to alternative rewards is likely to contribute to a preference for smoking reinforcement over other benefits which may result from abstaining from smoking. In the next section, I discuss contingency management as a smoking cessation model that provides a direct test of the trade-offs between smoking reinforcement and alternative rewards.

2.5 CONTINGENCY MANAGEMENT AS A MODEL FOR SMOKING CESSATION

Contingency management (CM) is a well-established treatment for smoking cessation (Alessi, Badger, & Higgins, 2004; Dallery, Glenn, & Raiff, 2007; Dunn, Sigmon, Thomas, Heil, & Higgins, 2008; Higgins et al., 2004; Roll & Higgins, 2000; Roll, Higgins, & Badger, 1996; Tidey, O'Neill, & Higgins, 2002), which provides an ideal framework for examining how sensitivity to smoking and non-smoking rewards may predict smoking behavior during a quit attempt. In general, CM involves promoting a desired behavior (e.g. drug abstinence or treatment compliance) by providing reinforcement contingent upon successful performance of that behavior. Typically, smokers are paid in cash or vouchers for merchandise for each interval of biochemically verified abstinence according to an ascending payment schedule, such that

larger incentives are earned for maintaining continuous periods of abstinence. While smoking behavior often involves some sort of trade-off between drug and non-drug rewards, such as weighing the immediate benefits of smoking against long-term benefits of quitting, CM manipulations make this trade-off immediate and explicit, thereby directly pitting smoking and non-smoking rewards against each other in the decision to smoke or abstain. Because of this, the ability to successfully quit smoking using CM is likely to be particularly sensitive to the relative balance between the incentive values of drug versus non-drug rewards.

Using CM to examine variability in smoking behavior provides other benefits as well. As described above, dysregulation in reward processing may be particularly pronounced during abstinence from smoking, so a reward processing imbalance may exert the greatest influence on smoking behavior when subjects are attempting to quit smoking. As a specific cessation strategy, CM offers the advantage of providing effective treatment while incentives are maintained without relying on nicotine replacement or other pharmacotherapy which could alter underlying neurochemistry. Furthermore, as with all smoking cessation treatments, substantial variability is observed between subjects, such that some individuals respond better to the financial incentives than others (Dallery et al., 2007; Glenn & Dallery, 2007). This point is critical since this dissertation is concerned with how variability in neural processing of rewards may predict variability in smoking cessation outcomes. Finally, while other laboratory based models of abstinence, such as that described above, can offer similar benefits of pitting money against smoking, CM offers the advantage of assessing a real-world quit attempt, thereby providing greater validity and generalizability.

One potential problem with CM for smoking cessation has been its implementation, given that biochemical measures are necessary to verify abstinence and expired CO has a

relatively short half-life, thereby necessitating frequent sampling which can become overly burdensome to participants (Meredith, Grabinski, & Dallery). To address this problem, researchers have developed an internet-based CM procedure, in which smokers provide twice daily biochemical verification of abstinence via CO samples video recorded and submitted over the internet (Dallery et al., 2007; Glenn & Dallery, 2007). This procedure eliminates the need for participants to make repeated visits to the laboratory, thereby dramatically increasing the practicality and availability of this strategy. Studies implementing this approach have demonstrated excellent compliance with the submission procedure and significant reductions in smoking behavior as a result of the reinforcement contingencies (Dallery et al., 2007; Glenn & Dallery, 2007; Reynolds, Dallery, Shroff, Patak, & Leraas, 2008; Stoops et al., 2009). Given these advantages, I employed a variant of this internet-based CM procedure to investigate how individual variability in reward dysfunction predicts the ability to abstain from smoking when given an incentive to do so.

2.6 SUMMARY AND SIGNIFICANCE

Increasing evidence suggests that chronic smoking may be associated with a reward processing imbalance in which smoking reward and associated stimuli are "overvalued" and non-smoking rewards are "undervalued", potentially contributing to a powerful motivation to continue smoking. Furthermore, evidence suggests that dysregulated reward processing may be particularly pronounced during abstinence from smoking, potentially contributing to an increased vulnerability to relapse during a quit attempt. However, limitations in the literature leave several questions unanswered. First, investigation of neural response to smoking cues and reward

processing of non-drug rewards, such as monetary reward, have largely evolved from two separate literatures, with few studies combining both reward types within the same paradigm. Thus, little is known about how these disparate reward types are instantiated within reward-related circuitry. Furthermore, few studies have investigated the effects of abstinence on reward processing, and those studies that have typically employed small samples and restricted investigation to a single reward type. Finally, little is known about how potential changes in reward processing during abstinence might contribute to smoking behavior during a quit attempt.

The study presented in this dissertation was designed to address these limitations in the following ways: In the initial phases of the study, daily smokers underwent two separate fMRI sessions, during which they could earn both smoking and monetary rewards. I adapted an event-related rewarded guessing task previously used to assess processing of monetary wins and losses (Delgado et al., 2000; Forbes et al., 2009). Our modified task incorporates stimuli signaling both monetary and smoking reward trial types (as well as a neutral condition), thereby allowing us to directly compare the circuitry engaged by each reward type within the same paradigm. Of the two fMRI sessions, one was completed following smoking *ad libitum* and the other after 24 hours of abstinence from smoking, allowing for direct comparison of the neural processing of each reward type as a function of abstinence. This novel design provides a unique opportunity to test for potentially dissociated effects of abstinence on each reward type, which is theoretically expected but thus far remains unconfirmed in the literature. Furthermore, the present study employed a much larger sample size than other recent studies attempting to address a similar questions (e.g., Buhler et al., 2010), with better power to detect complex interaction effects within the targeted region of the striatum. In the final phase of the study, smokers then engaged in a quit attempt using a 21-day contingency management protocol, during which abstinence

from smoking was reinforced with money. The use of contingency management provides an ideal framework for investigating how neural response to monetary and smoking rewards—particularly as this changes during abstinence—may be associated with smoking behavior during a quit attempt.

I hypothesized that both smoking and monetary rewards would elicit significant BOLD activation in the striatum and throughout associated reward circuitry using our modified fMRI reward paradigm. I further hypothesized that BOLD response to smoking reward would be increased during abstinence, while BOLD response to monetary reward would be attenuated during abstinence relative to satiation. Finally, I hypothesized that BOLD response to both types of reward—specifically heightened response to smoking reward and blunted response to monetary reward during abstinence—would be associated with greater difficulty abstaining from smoking during the internet-based CM procedure.

3. RESEARCH DESIGN AND METHODS

The previous chapter discussed background information relevant to the present study and provided a brief overview of the hypotheses to be tested. I now turn to a more detailed account of the study design, procedures, and analytic strategy. Chronic smokers underwent three study phases, including initial screening (1 session), functional neuroimaging (2 sessions), and an internet-based contingency management procedure (21 days with 2 in-person sessions). The following sections outline the details of the overall study design, procedures, and basic analytic strategy. I begin with a description of the participants, including inclusion and exclusion criteria, followed by a detailed discussion of the procedures for each phase of the study. Subsequent sections provide a description of the fMRI task, methods for fMRI data acquisition and processing, and the statistical model for single-subject and group level analyses. The statistical model described here provides the framework for all subsequent analyses described in greater detail in chapters 4-6. A final section is devoted to preliminary analyses conducted on a subset of participants aimed at determining the optimal number of runs needed to maximize power within the neuroimaging task and minimize habituation effects to reward.

3.1. PARTICIPANTS

Fifty-six daily smokers were recruited from the community as part of a larger study investigating genetic predictors of abstinence during a quit attempt. Smokers were eligible to

participate if they were between the ages of 18 and 65, self-reported smoking 5 or more cigarettes per day during the past year, provided a minimum expired breath carbon monoxide (CO) level of 8 ppm, and were willing to make a quit attempt. Individuals who were interested in using smoking cessation medications were referred elsewhere. Exclusion criteria included self-reported psychiatric illness or significant medical illness in the past year, current heavy drug use (use on 10 or more of the past 30 days) or heavy alcohol use (4 or more drinks per day on 10 or more of the past 30 days), current use of any psychotropic medication or other tobacco products, pregnancy/lactation, head trauma with loss of consciousness in the past year, claustrophobia, and any known risk from exposure to high-field strength magnetic fields. Because the parent study involved a genetic component, participation was restricted to Caucasians to minimize population stratification. All participants provided informed consent in accordance with the University of Pittsburgh Institutional Review Board.

Out of 56 individuals initially recruited, 12 were excluded from all analyses because of failure to complete the imaging sessions or initiate the quit attempt (Figure 1). Of these 12 participants, 5 failed to attend one or both imaging sessions, 3 failed to meet abstinence criteria prior to the abstinent scan, 1 was intoxicated prior to a scanning session, 1 withdrew due to claustrophobia, 1 could not be scanned due to size constraints, and 1 participant had a brain abnormality detected during the first scan. The remaining 44 participants ranged from 18 to 58 years of age (M = 34.7 years, SD = 12.6), and 54.5% were female. Participants smoked between 5 and 30 cigarettes per day (M = 14.0, SD = 6.6) for an average of 15.7 years (SD = 11.9) and were mildly to moderately dependent according to the Fagerström Test for Nicotine Dependence (FTND) (M = 3.5, SD = 2.3). Of the 44 participants who completed both imaging sessions, data from 6 participants were excluded from fMRI analyses due to technical issues and

procedural errors, and data from 4 participants were excluded from CM analyses due to drop-out and procedural errors. Consequently, sample sizes varied for each specific analysis.

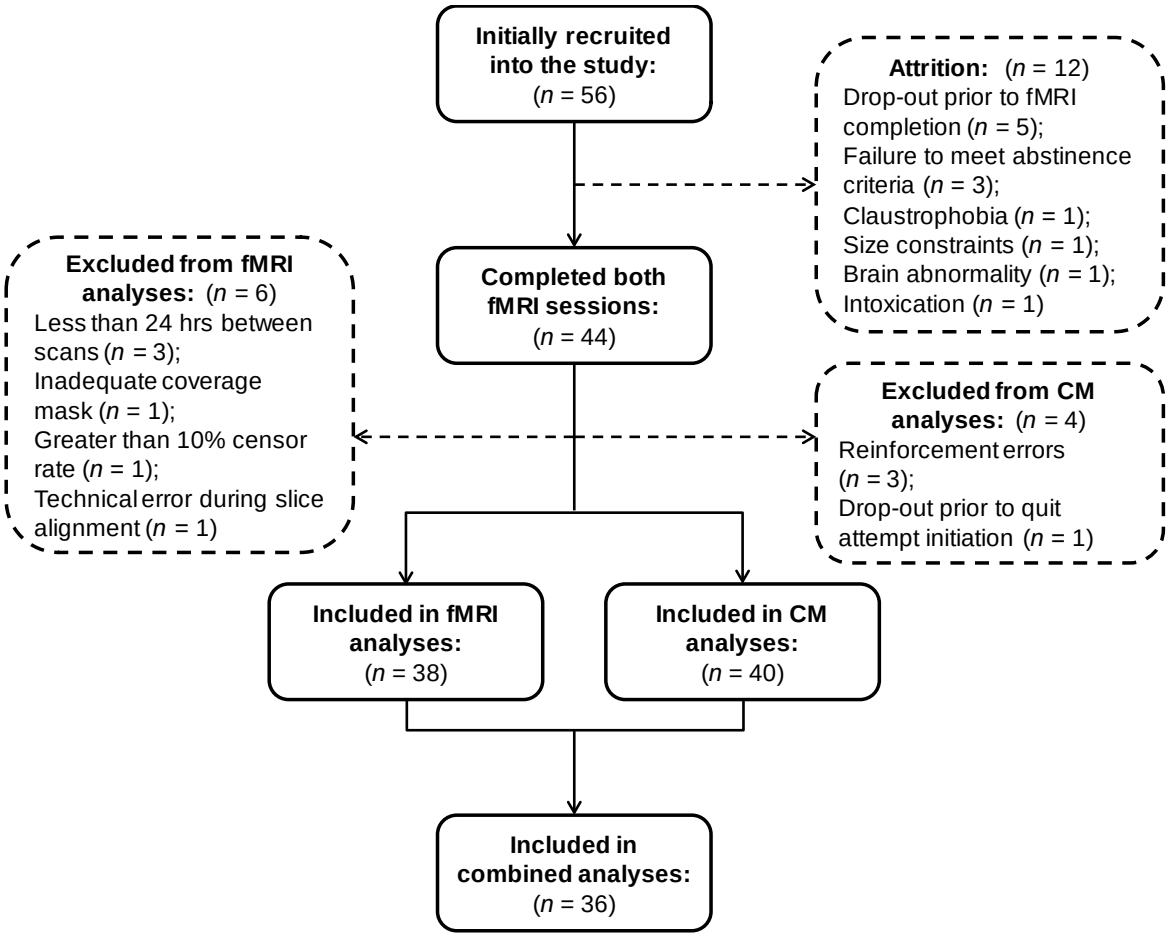


Figure 1. Flow diagram of participant attrition and exclusions among those determined to be eligible during initial in-person screening.

3.2. PROCEDURES

Participants were recruited through flyers and advertisements placed on buses, newspapers, and online. Daily smokers over age 18 who were willing to make a quit attempt were invited to contact the laboratory to learn more about the study and complete an initial telephone eligibility screen. Participants deemed eligible during the initial phone screen subsequently attended an in-person assessment during which informed consent was obtained, final eligibility was determined, and additional assessment measures were completed. Participants then completed two separate fMRI sessions, a minimum of 24 hours apart. Finally, participants underwent a quit attempt using an internet-based contingency management procedure. Details of each session are described in the sections below.

3.2.1. Screening session

During the initial session, participants completed a variety of self-report measures assessing smoking, medical and psychiatric history, and physiological measures were obtained. Breath and urine samples were collected to assess blood alcohol level and illicit drug use, respectively. Expired CO was assessed both upon arrival and after smoking a cigarette in the laboratory. To prevent exclusion of participants who had not smoked recently prior to the visit, the minimum CO inclusion criterion was satisfied if either CO sample was greater than 8 ppm. In all but 5 cases, this criterion was met with the first CO sample, prior to the participant smoking a cigarette. Participants then completed a battery of computer-administered questionnaires assessing demographics, medical and psychiatric history, nicotine use history, and nicotine dependence, including the Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton,

Kozlowski, Frecker, & Fagerstrom, 1991), the Nicotine Dependence Syndrome Scale (NDSS) (Shiffman, Waters, & Hickcox, 2004), and the Wisconsin Inventory of Smoking Dependence Motives (WISDM) (Piper et al., 2004).

3.2.2. fMRI sessions

At the conclusion of the initial session, eligible participants who wished to continue with the study were then scheduled for two identical fMRI sessions conducted at the NeuroImaging Center (NIC) on two different days. Details of these sessions are described below. Subjects were asked to abstain from smoking for 24 hours prior to one of the scans (abstinent); prior to the other scan subjects were permitted to smoke *ad libitum* (non-abstinent). Order of abstinent and non-abstinent sessions was randomly assigned. Of the final 38 participants included in imaging analyses, 17 completed the abstinent session first. Given scheduling constraints and an effort to avoid attrition, time between sessions ranged from 1 to 99 days (M = 15.0, SD = 18.6). A minimum of 24 hours was required between fMRI sessions to ensure that abstinence could be met. Abstinence was verified via self-report and an expired CO level of less than 8 ppm or a 50% reduction from baseline. Prior to each scan participants underwent task training and completed subjective measures, including a 4-item version of the Questionnaire on Smoking Urges (QSU-4) (Toll, Katulak, & McKee, 2006), the Positive and Negative Affect Scale (PANAS) (Watson, Clark, & Tellegen, 1988), and the Minnesota Withdrawal Scale (MNWS) (Hughes & Hatsukami, 1986). The QSU-4 was repeated immediately after the scans. During the non-abstinent session, participants smoked a cigarette immediately prior to the scan to prevent unintended withdrawal. CO was then measured after smoking to provide a comparison with the abstinent session.

Participants were then positioned in the scanner, where they remained for approximately one hour. Following acquisition of T2 localizers (about 5 minutes), subjects completed four runs of a rewarded guessing task, during which they could earn both monetary and smoking rewards. In order to increase the salience of the smoking rewards, subjects were told that they would not be permitted to smoke for one hour after the scan except for the puffs that they earned during the task. They were reminded that any puffs they earned would be available to them immediately after the scan. After completion of the task, subjects were permitted to relax while structural and resting state images were acquired.

Following the scan, participants were paid for their monetary winnings ($6.00) and offered the opportunity to smoke (12 puffs). Puffs were administered by allowing the subject to smoke freely in the outdoor smoking area of the NIC, while number of puffs taken was observed. Participants were not required to smoke all earned puffs. During the hour following the first scan, participants were trained on use of the computer equipment and website which would be used for the contingency management procedure. During the hour following the second scan, participants practiced with the computer and website, and American Cancer Institute guidelines for quitting smoking were reviewed. During the training following the second scan, participants were asked to set a quit date and schedule two remaining in-person visits. Participants then returned home and began the contingency management procedure over the internet on their designated day. The contingency management procedure is described in detail below.

3.2.3. fMRI task

During each fMRI scan, participants completed a rewarded card guessing task modified for an event-related design, enabling dissociation of anticipation and outcome phases of reward

processing. This task has previously been shown to robustly engage the ventral and dorsal striatum and other reward-related areas (Delgado et al., 2000; Forbes et al., 2009; Forbes, Olino, et al., 2010; Forbes, Ryan, et al., 2010). During the task, participants could earn rewards by "guessing" whether a computer-generated number was higher or lower than 5. A schematic illustrating the events of each trial is presented in Figure 2. Trials began with a four second presentation of a question mark, during which participants indicated their guess via a button press of their index or middle finger. Next, an image was presented for six seconds depicting the type of reward that could be won on that trial if the guess was correct (50 cents, a puff of a cigarette, or nothing). The "actual" number was then presented on the screen for 500-msec, followed by 500-msec feedback indicating whether the guess was correct and the reward was won. The feedback phase was followed by a 9-second inter-trial interval (ITI), marked by a white fixation cross. The task was divided into 4 runs of 18 trials each, with each run lasting for 6 minutes, 10 seconds. Reward type and outcome were predetermined and presented in a fixed, pseudorandom order such that each run contained 6 trials of each reward type, with 50% of each reward type resulting in a win. Participants were informed during training of the amount of reward available for each trial (e.g., 50 cents or 1 puff) but were led to believe that outcomes were dictated by the accuracy of their guesses. Across the four runs of the task, subjects won money 12 times ($6 total) and cigarette puffs 12 times (12 puffs total).

Although previous studies have shown that fewer runs may be necessary to adequately detect neural response to monetary reward (Forbes, Olino, et al., 2010), differences in the relative neural response to smoking versus monetary reward and the change as a function of abstinence may be more subtle and require greater power. Thus, we increased the number of runs to ensure an adequate sampling of each trial type. However, due to possible habituation

effects, it was necessary to empirically determine the impact of including all four runs prior to testing the research hypotheses. Details of preliminary analyses examining task length effects are described in the section on habituation effects below.

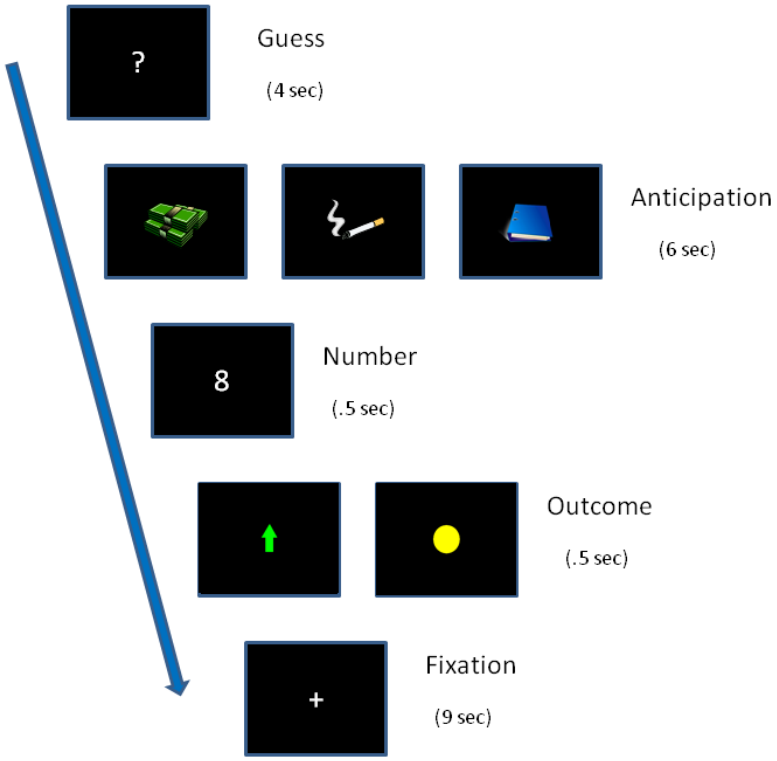


Figure 2. Schematic of events within each trial of the fMRI reward task.

Subjects first make their guess, and are then presented with the type of reward they may earn on that trial (monetary, smoking, or neutral). After 6 seconds, the actual number is presented, followed by win or no win feedback (up arrow or yellow circle, respectively). A fixation cross is present for the 9 second intertrial interval.

3.2.4. Contingency management

Following assessment of reward processing in the fMRI sessions, participants made a smoking quit attempt using an adapted internet-based contingency management procedure (Dallery & Glenn, 2005). This procedure was divided into three phases: initial training, baseline, and abstinence incentive. As noted above, initial training took place during the hour following each scanning session. During the initial training, subjects were given computer equipment to be used for abstinence verification, including a netbook with webcam and a Bedfont Pico CO monitor, and were instructed on how to use this equipment. Participants were also given the "Clearing the Air: Quit Smoking Today" manual as recommended by the U.S. Department of Health and Human Services, the National Institute of Health, and the National Cancer Institute as a guide for smoking cessation. This manual was briefly reviewed with participants, and any problems or concerns they anticipated which may interfere with abstinence were discussed. Subjects then set a target quit date, and baseline cotinine levels were obtained.

Participants were instructed to begin submitting CO samples for the baseline period three days prior to their target quit date. This baseline period allowed participants to become acclimated to the submission procedure prior to initiating smoking abstinence and allowed for trouble-shooting any difficulties they may encounter. During the baseline period, participants were required to submit CO samples twice per day, at least 8 hour apart, between the hours of 5 am and 4 am. They were permitted to continue smoking *ad libitum* and were paid $3.00 for each submitted sample, regardless of the CO level. Participants submitted samples by logging into their user account on the study website, recording a video of their exhalation into the Pico CO monitor and outcome reading over the webcam, and uploading the video to the site. They were also asked to self-report whether or not they smoked since their last submission. Immediate

financial reinforcement was then provided based on their reported CO value in the form of credits to an online account, as well as a graphical representation of their progress. Videos were later verified to ensure accuracy of reported data. Participants could request payment to be transferred from their account onto their assigned bank card at any time throughout the procedure.

Participants then initiated abstinence on their target quit date, immediately following the 3 day baseline period. During the 18 day abstinence incentive phase, participants continued to submit CO samples twice daily, but were reinforced only if they met criteria for abstinence (CO of 7 ppm or less, or a 30% drop from the previous sample). Target CO value of 7 ppm was based on initial pilot data used to determine optimal cutoff for maximizing both sensitivity and specificity (data not shown). The reinforcement schedule for abstinent samples is shown in Figure 3. This schedule was modeled after Dallery and Glenn (2005), which previously demonstrated substantial variability in cessation success using a similar schedule. Participants received $3.00 for the first abstinent sample. For each subsequent consecutive abstinent sample, this amount increased by 25 cents (e.g. $3.25 for the next sample, then $3.50). Participants received an additional $5.00 bonus every time they submitted 3 consecutive abstinent samples. Submitted samples not meeting abstinence criteria were not reinforced. In addition, when a non-abstinent sample was submitted (or if the participant failed to submit a sample), the schedule of reinforcement for the next abstinent sample was reset to the starting amount. Thus, a participant who relapsed and then reinstated abstinence was reinforced with $3.00 for the first abstinent sample following the relapse, $3.25 for the second, etc. Once three consecutive abstinent samples were submitted, the payment schedule was once again reset to the highest amount previously reached and continued to increase from there.

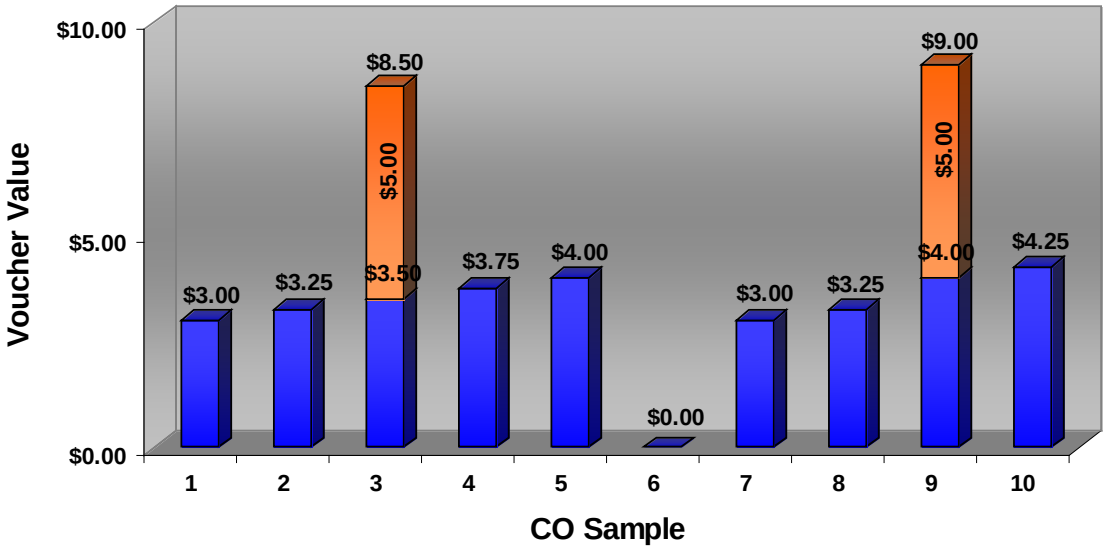


Figure 3. Examples of incentives earned during contingency management procedure.

Example of incentives earned for submission of 5 consecutive abstinent samples, followed by a single lapse, and then 4 more consecutive abstinent samples. Incentives increase by 25 cents for each consecutive abstinent sample, and $5.00 bonuses are earned for 3 consecutive abstinent samples. Positive samples result in no incentive earned and a return to the $3.00 baseline for the next abstinent sample. After 3 more consecutive abstinent samples, the incentive value returns to the highest previous value ($4.00 in this case).

Participants were asked to attend an in-person session between days 2 and 4 of the abstinence incentive phase to collect a second cotinine sample. This was used as a secondary biochemical measure to confirm the CO readings being submitted online. However, only the CO readings were used to determine the incentives earned. This in-person session also allowed for trouble-shooting any problems participants may be experiencing with the computer equipment or online submission system, or any problems they may be having with maintaining abstinence. Participants returned for a final in-person visit on the next day following completion of the abstinence incentive procedure. During this visit, participants provided a 3rd cotinine sample, returned computer equipment, and received payment for study participation. Participants were

also debriefed about the reasons for the study. Relapse prevention strategies from the "Clearing the Air" manual were reviewed, and those participants seeking additional smoking cessation treatment were given referral information.

3.3. IMAGING METHODS

3.3.1. Image acquisition

BOLD functional images were acquired using a 3.0 Tesla Siemens Allegra scanner with gradient EPI sequence covering 34 interleaved axial slices of 3 mm thickness with the following parameters: TR = 2 sec; TE = 29 ms; flip angle = 90 degrees; 64 X 64 matrix with FOV = 20 X 20 cm. A T1 weighted structural image was also acquired using a 3-dimensional volume MPRAGE pulse sequence covering 176 axial slices of 1 mm thickness. Prior to acquisition, a reference EPI scan was collected and examined to ensure good signal across the volume and no artifacts (e.g. ghosting).

3.3.2. Preprocessing

Functional images were preprocessed using SPM8 (www.fil.ion.ucl.ac.uk/spm). Images were corrected for interleaved acquisition timing, realigned to the mean functional image, and unwarped to correct for rotational and translational head movement and to minimize distortion from task related movement. Structural images were segmented into native space grey matter and coregistered to the mean of the functional images. All functional images were then spatially normalized into Montreal Neurologic Institute stereotactic space using parameters determined through normalization of the coregistered structural image and resampled to a voxel size of 2 x 2

x 2 mm. Images were smoothed with a Gaussian filter set at 6 mm Full-width at Half Maximum (FWHM), and a high pass filter (128 seconds) was applied to remove low frequency scanner drift. Individual scans were visually inspected at each stage of preprocessing to ensure that all steps were operating correctly. Images failing automated normalization were manually reoriented to the AC/PC line and then resubmitted through the remainder of the preprocessing pipeline.

Following preprocessing, effects of head motion and other artifacts were further examined using the ART artifact-detection program (www.nitrc.org/projects/artifact_detect). Artifactual volumes with signal deviating from the global mean by > 4.5 standard deviations were identified, and regressors were generated to censor problematic scans from first level models. Participants exhibiting a censor rate of > 10% in ART (n = 1) were excluded from analyses.

3.3.3. Single-subject statistical analyses

Preprocessed data were analyzed using the general linear model (Friston et al., 1995; Worsley & Friston, 1995; Zarahn, Aguirre, & D'Esposito, 1997). BOLD responses to task events were modeled by convolving stimulus onset times with a canonical hemodynamic response function. Regressors of interest were included to model three levels of reward anticipation (money, smoking, or neutral), six possible outcomes (win or no win for each of the three reward types), and a baseline period encompassing the last 3 seconds of fixation for each trial. Motion parameters derived from realignment and regressors generated through ART were entered as regressors of no interest to control for head movement. After model specification, individual participant effects were estimated for each scan using a fixed effects model, and contrast images

were created comparing money > neutral and puff > neutral for the anticipation phase and win > no win for each trial type for the outcome phase. Separate contrast images were also created comparing each event type with baseline to allow for further exploratory analyses.

3.3.4. Second-level (Group) Model

First-level contrasts were then submitted to second-level random effects ANOVA for group analyses. The full factorial model was used to allow for modeling of abstinence condition and reward type as within-subjects factors and scan order or other covariates as between-subjects factors, as needed. Details of each model and analyses are described in the statistical analyses sections of chapters 4-6. Thresholds for significance varied for each analysis and were determined depending on the nature of the question (exploratory or confirmatory), expected effect size, and brain areas under investigation. Significance testing for analyses involving general task-related activation, expected to have large effect sizes, was performed across the whole-brain using family wise error (FWE) correction of $P < 0.05$, with 20 voxel extent threshold. Comparisons involving main effects of abstinence condition or abstinence state X reward type interaction effects, expected to involve targeted regions and to have smaller effect sizes, were tested within the *a priori* anatomically-defined striatal region of interest (ROI; described below), with monte carlo simulations used to control for multiple comparisons. Exploration of possible activations beyond the predetermined ROI was conducted across the whole brain using uncorrected $p < 0.001$, with 20 voxel extent threshold (Buhler et al., 2010). Exploratory analyses examining differential activation associated with specific task conditions were subjected to even more liberal significance thresholds (e.g., $p < .01$, uncorrected),

particularly when identification of subthreshold effects was deemed useful for interpretation of other significant findings. Throughout the results, details of significance thresholds are presented with each analysis.

3.3.5. Region of Interest Definition

A region of interest centered on the striatum was selected as this region is consistently implicated in reward processing and has been previously shown to be activated by the original monetary versions of the task (Delgado et al., 2000; Forbes et al., 2009; Forbes, Ryan, et al., 2010). The defined ROI included bilateral ventral striatum, defined using the procedure previously described by Gianaros and colleagues (Gianaros et al., 2011) and encompassing the anterior portions of the ventral caudate and putamen, as well as anterior globus pallidus, and bilateral dorsal striatum, defined using the WFU_PickAtlas toolbox (www.ansir.wfubmc.edu) to include the head, body, and tail of the caudate (Maldjian, Laurienti, Kraft, & Burdette, 2003). This mask encompassed a combined volume of 16,504 mm^3 or 2,063 voxels. Correction for multiple comparisons was achieved by determining combined voxel-level and cluster extent thresholds using Monte Carlo simulations implemented in 3DclusterSim, taking into account smoothness across voxels for each subject and total search volume, for an overall corrected false positive detection rate of $P < 0.05$. Smoothness kernel estimates used for simulations were FWHMx = 8.34, FWHMy = 8.13, and FWHMz = 7.40. Significance level for individual voxels was set to $p < 0.005$, resulting in a cluster extent threshold of 29 voxels across the specified search volume.

3.4. PRELIMINARY ANALYSES OF HABITUATION EFFECTS

As described above, participants each completed four runs of 18 trials each during the fMRI guessing task. The inclusion of four runs was intended to increase power to detect significant effects by increasing the total number of trials. However, given the possible habituation of the neural response to repeated presentation of reward (Forbes, Olino, et al., 2010; Koob & Le Moal, 2008), it is possible that additional runs may reduce power by diminishing the response to reward during later trials relative to earlier trials. In addition, smoking reward is likely to decrease in subjective value with increasing puffs earned due to anticipated satiety effects, further underscoring the likely heterogeneity of reward effects over time. Thus, prior to testing research hypotheses at the group level, additional first level models were created to test the impact of task length.

Because head movement tended to increase over time, a subset of 12 scans that maintained < 2 mm head motion across all four runs was selected for task length analyses. For those 12 scans, first-level contrasts were created comparing money > neutral anticipation and puff > neutral anticipation using varying task lengths, including combining across all four runs, three runs, two runs, or just one run. Contrasts were also created comparing runs 1 and 2 > runs 3 and 4 and run 1 > run 2 for each reward type to allow for a direct comparison of task-related BOLD activation from the first and second halves of the task and from the first and second runs. One sample *t*-tests were then conducted at the group level to determine significance for each comparison. Given the small sample size, a significance threshold of $p < 0.01$ with 10 voxel extent was used. Comparisons were restricted the ventral and dorsal striatum given that this is a

primary region engaged by the task and where habituation to repeated reward presentation is likely to occur (Forbes, Olino et al., 2010; Koob & Le Moal, 2008).

Significant areas of activation for each reward type analyzed with inclusion of varying number of functional runs are presented in Figure 4 and Table 1. For monetary reward, significant clusters emerged when only the first run or the first two runs were included. No significant activation was detected when the later runs of the task were included, suggesting substantial habituation across the third and fourth runs of the task. Larger and more significant bilateral clusters emerged when two runs were used compared with only one run, suggesting that two runs provided the optimal balance between increasing power without loss of signal due to habituation. Direct comparisons across runs confirmed this qualitative impression. A region of 83 voxels encompassing right ventral striatum and portions of right dorsal striatum was significantly more active during the first half of the task compared with the second half of the task (Figure 5). A similar comparison between the first and second runs of the task suggested some slightly reduced activation in the left ventral striatum during the second run compared with the first; however, this encompassed only 19 voxels suggesting only minimal habituation within the first half of the task. For smoking reward, bilateral striatal activation was relatively robust regardless of number of runs included. Indeed, the strongest signal was detected when all four runs were included (Figure 4), suggesting that habituation was not weakening the ability to detect an effect as the task progressed. Consistent with these observations, direct comparisons across runs of the task indicated no significant differences between the first and second halves of the task or between the first and second runs.

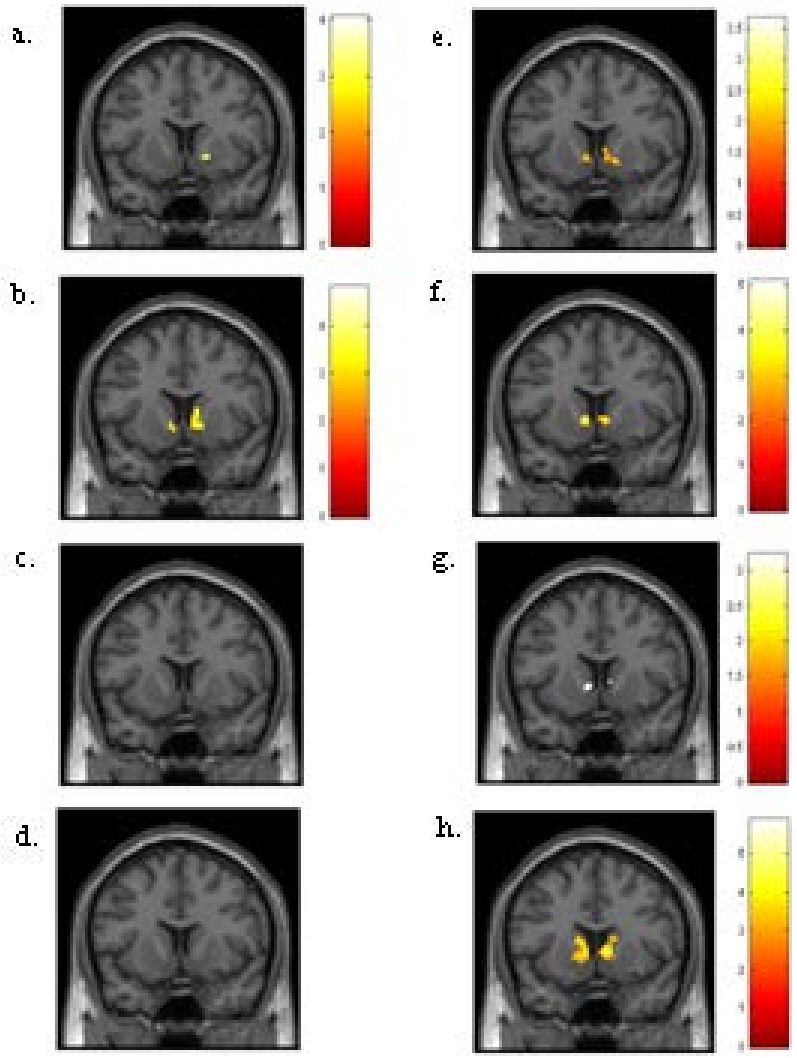


Figure 4. Habituation to reward in the striatum: Anticipatory activation to monetary reward diminishes with inclusion of additional runs of the task.

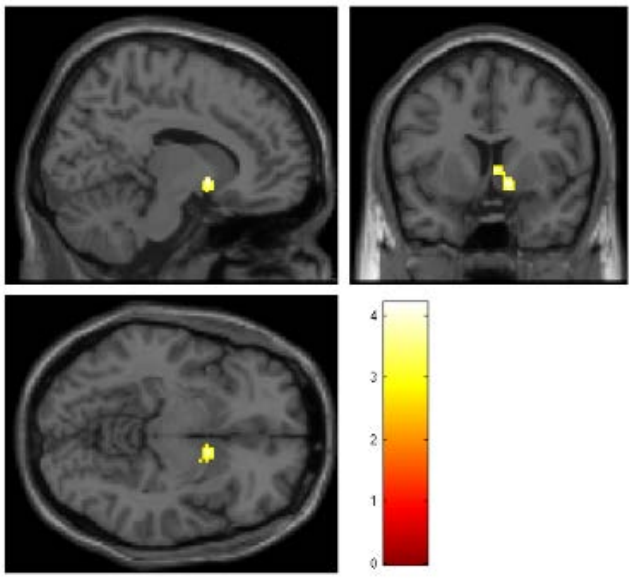
Areas of significant activation during anticipation of money or puff reward > neutral trials within ventral/dorsal striatum mask at $p < .01$, uncorrected, 10 voxel extent threshold for varying task lengths. Anticipation of money reward trials > neutral trial when including 1 run only (a), 2 runs (b), 3 runs (c), or all 4 runs (d). Anticipation of puff reward trials > neutral trials when including 1 run only (e), 2 runs (f), 3 runs (g), or all 4 runs (h). All figures are shown at y = 10.

Table 1. Striatal activation for monetary or smoking reward > neutral trial anticipation as a function of number of runs included in analyses.

Number of Runs	Hemisphere	Voxels	Location			*T* Value	
			x	*y*	*z*		
Money Anticipation > Neutral Anticipation							
1	Right	37	12	2	-12	4.06	*
	Left	0					
2	Right	102	12	4	-2	4.35	*
	Left	38	-20	4	-10	4.82	**
		34	-6	16	-6	3.69	*
Puff Anticipation > Neutral Anticipation							
1	Right	135	12	2	-6	3.66	*
	Left	40	-6	14	-4	2.70	*
2	Right	70	6	12	0	3.98	*
	Left	85	-8	12	0	5.09	**
3	Right	16	6	12	4	3.02	*
	Left	26	-10	12	0	3.23	*
4	Right	202	8	14	6	4.59	**
	Left	202	-14	6	14	5.88	**

Note: Location refers to Montreal Neurological Institute (MNI) coordinates for peak voxel of each cluster.
*$p < 0.01$, uncorrected
**$p < 0.001$, uncorrected

a.



b.

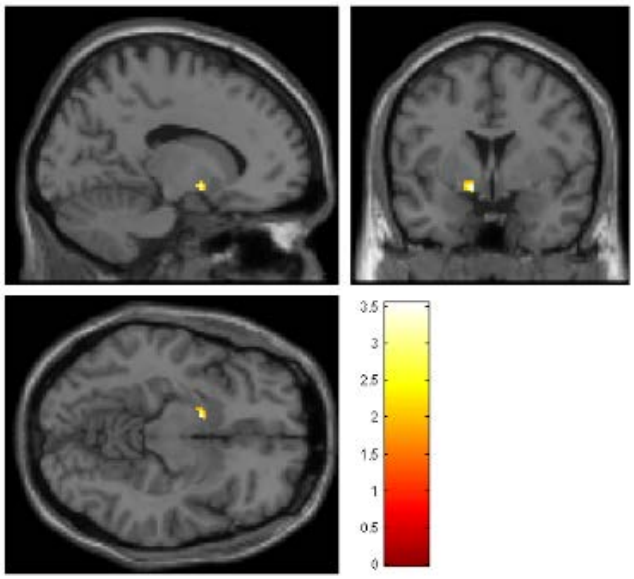


Figure 5. Habituation to reward in the striatum: Anticipatory activation to monetary reward is greater during the first half of the task than for the second half.

Areas of greater activation during anticipation of money reward > neutral trials during earlier versus later runs of the task within ventral/dorsal striatum mask at $p < .01$, uncorrected, 10 voxel extent threshold. *a.* Greater activation during runs 1 and 2 compared with runs 3 and 4. Slices shown at x = 12, y = 8, z = -8. Right ventral and dorsal striatum: 6, 8, 2; $T = 4.20$, 83 voxels. *b.* Greater activation during run 1 compared with run 2. Slices shown at x = -14, y = 2, z = -10. Left ventral striatum: -12, 2, -8; $T = 3.55$, 19 voxels.

Thus, preliminary analyses suggested an attenuation of striatal response in anticipation of monetary reward but not smoking reward during the second half of the task. The lack of habituation for smoking reward is particularly surprising given expected satiety effects. It is possible that subjective value of the smoking reward was maintained or even increased over the duration of the task as the impending delivery of the actual reward became more proximal or as cigarette craving increased (discussed in chapter 5). Regardless, when considering data from both monetary and smoking rewards, two runs appeared to be the optimal task length to maximize the ability to detect a signal for both reward types, thereby maximizing power and minimizing habituation. Thus, all subsequent analyses were restricted to the first two runs.

4. QUESTION #1: ARE SMOKING AND MONETARY REWARDS INSTANTIATED IN THE SAME CIRCUITRY?

4.1. INTRODUCTION

A primary objective of this dissertation was to characterize the BOLD response to smoking and monetary rewards within the same paradigm. In this first set of analyses, I examined whole-brain activation in anticipation and delivery of monetary and smoking rewards. By equating other aspects of task design, I sought to eliminate procedural differences between rewards, allowing me to focus on similarities and differences between the rewards themselves. I hypothesized that daily smokers would exhibit significant BOLD activation during anticipation and delivery of both reward types relative to neutral trials throughout reward-related circuitry, including the ventral and dorsal striatum and the medial prefrontal cortex.

Addressing this first question served two goals: Perhaps most importantly, because the monetary reward guessing task used in this study was substantially altered in order to include smoking rewards, demonstrating significant reward-related activation was critical for establishing that the task was working. Secondly, the study design allowed me to examine the extent to which neural response to each reward type was instantiated in the same, overlapping circuitry among chronic smokers. I sought to examine patterns of activation across the whole-brain for each reward type, in order to determine areas that might be preferentially activated by one reward type or the other. This question is necessarily exploratory, and no specific

predictions were made about regions that may exhibit activation specific to a particular reward. Furthermore, no specific predictions were made differentiating regions or reward types with respect to timing of reward (i.e., anticipation versus outcome). However, reward anticipation and delivery phases were dissociated within the fMRI task and analyzed separately for each region, as reward type differences within these regions may help to inform the nature of reward dysfunction.

4.2. STATISTICAL ANALYSES

Separate models were created for anticipation and outcome phases of the task. For both models, abstinence condition was included as a factor to account for task design but was not directly analyzed here. Effects of reward type and abstinence condition on anticipatory activation were modeled with a 2 X 3 random-effects ANOVA, with condition (abstinent, non-abstinent) and reward type (money > baseline, puff > baseline, or neutral > baseline) entered as within-subjects factors. Effects of reward outcome were modeled with a 2 X 2 X 2 random-effects ANOVA, with condition (abstinent, non-abstinent), reward type (money or puff), and outcome (win > baseline or no win > baseline) entered as within-subjects factors. Neutral trials were excluded from outcome analyses given that the primary comparisons involved win versus no win outcomes.

For each phase of the task, planned *t* contrasts were used to examine reward anticipation and outcome in a series of four basic steps. First, general task-related activation was assessed by combining both reward types and comparing them with neutral trials (anticipation phase) or no win trials (outcome phase). This provided an initial verification that the task, as a whole, was

engaging expected reward-related circuitry. Contrasts were specified as money and smoking reward > neutral for the anticipation model and money and smoking win > no win for the outcome model.

Second, monetary reward trials and smoking reward trials were each evaluated separately to provide a descriptive picture of the patterns of activation associated with each reward type. Contrasts were specified as follows: money > neutral and smoking > neutral for anticipation phase; money win > no win and smoking win > no win for outcome phase. Masks were created from these contrasts for use in conjunction analyses (discussed below). Significance for each of these comparisons was tested across the whole brain, with family wise error (FWE) correction of $P < 0.05$, with a 20 voxel extent threshold.

Third, to determine the amount of overlap in the patterns of activation identified above for each reward type, conjunction analyses were performed. This enabled reward-related circuitry to be parsed into voxels responding to both rewards, to monetary reward only, or to smoking reward only. To identify regions of significant activation to both rewards, analyses of smoking reward described above (smoking > neutral for anticipation phase or smoking win > no win for outcome phase) were repeated, but results were masked to include only those voxels also showing significant effects of monetary reward (money > neutral or money win > no win). To identify areas of unique activation for each reward type, the same contrasts were performed using *exclusive* masks for areas of significant activation for the alternate reward type.

Finally, monetary reward and smoking reward trials were contrasted against each other directly, to provide a more rigorous statistical test of any regional differences. For the anticipation phase, contrasts of money > smoking and smoking > money were used to identify regions demonstrating significant differences in activation as a function of reward type. To

directly test differences between money and puff rewards for the outcome phase, the reward type X outcome interaction was examined within the 2 X 2 X 2 model. Areas demonstrating significant interaction *F* tests were followed up with directionally specific *t* contrasts to explore the nature of the interaction. Because these effects were expected to be smaller than overall task effects, whole-brain analyses were conducted with a more liberal significance threshold of $p < 0.001$, uncorrected, with 20 voxel extent threshold.

A fifth set of exploratory analyses was also conducted comparing each trial type to baseline activation in order to further probe activation patterns and to identify the direction of effects contributing to significant differences between task conditions. These analyses and results are described in Appendix A.

4.3. ANTICIPATION PHASE

4.3.1. Combined effects of monetary and smoking reward relative to neutral trials

Anticipation of smoking or monetary reward compared with neutral trials, collapsed across abstinence condition, produced robust activation across expected reward-related circuitry (Figure 6, Table 2). Significant activation was observed in the bilateral striatum, including caudate and anterior putamen; anterior cingulate extending to medial prefrontal cortex; bilateral insula extending to inferior frontal gyrus, bilateral hippocampus, midbrain, and occipital lobe.

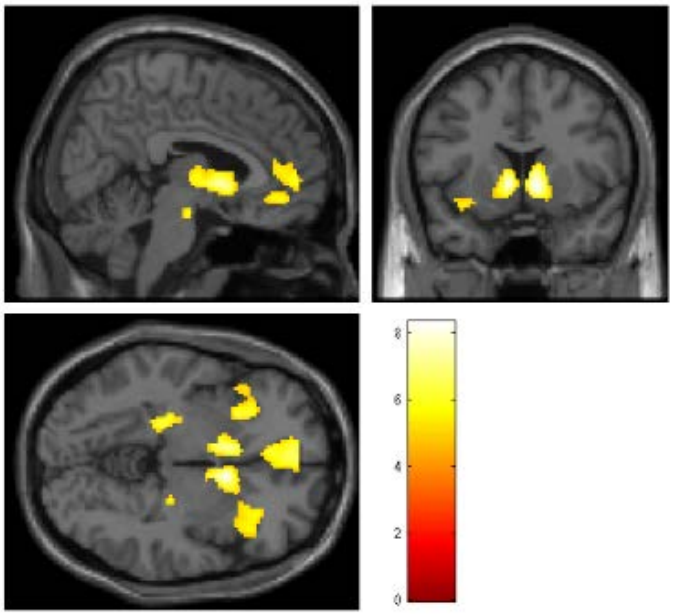


Figure 6. Combined effects of monetary and smoking reward anticipation > neutral trials reveal robust task-related activation throughout reward-related circuitry.

Overall task-related activation associated with money or puff reward anticipation compared with neutral trial anticipation, collapsed across abstinence condition, with whole-brain family-wise error (FWE) correction of $P < 0.05$, 20 voxel extent threshold. Slices shown at x = 6, y = 10, z = -4.

Table 2. Suprathreshold clusters associated with combined effects of monetary and smoking reward anticipation > neutral, collapsed across abstinence condition.

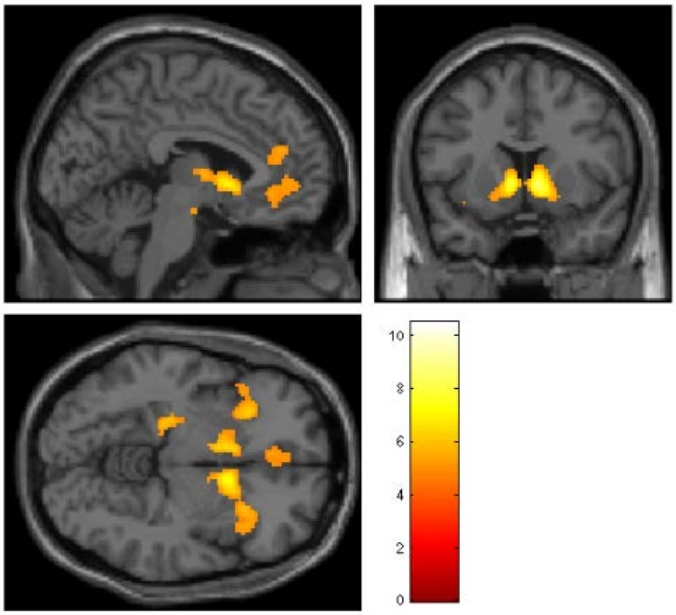
	Voxels	Location			T	Brain areas
		x	y	Z	(df = 222)	
1	1360	-4	54	-2	6.81	Anterior cingulate cortex, medial frontal gyrus
2	1202	8	10	-2	8.33	Right and left caudate head
3	476	30	30	-2	6.26	Right inferior frontal gyrus, right insula
4	378	-30	18	-8	6.56	Left insula, left inferior frontal gyrus
5	132	-24	-28	-2	6.29	Left hippocampus
6	68	4	-12	-18	6.11	Right and left brainstem
7	49	-30	-86	8	7.21	Left middle occipital gyrus
8	36	34	-88	12	7.61	Right middle occipital gyrus
9	25	-8	-88	30	-5.39	Left cuneus
10	21	26	-24	-6	5.73	Right hippocampus

Note: Location refers to Montreal Neurological Institute (MNI) coordinates for peak voxel of each cluster.

4.3.2. Effects of monetary and smoking reward analyzed separately

When examined separately, monetary reward anticipation relative to neutral trials was associated with patterns of activation similar to those observed when both reward types were examined together, with only minor exceptions (Figure 7a, Table 3). In particular, monetary reward trials appeared to activate a much smaller region of medial prefrontal cortex compared with the combined contrast, while occipital lobe activation clusters were relatively larger for monetary reward than when both rewards were combined. When smoking reward anticipation relative to neutral trials was examined separately, clusters of activation appeared to be smaller and were restricted to key reward-related regions, including bilateral caudate, anterior cingulate cortex/medial prefrontal cortex, and bilateral insula (Figure 7b, Table 4). Interestingly, activation in the anterior cingulate appeared to be much greater for smoking reward relative to what was seen for monetary reward (962 voxels compared with 304 voxels, respectively), while striatal activation appeared to be much smaller (359 voxels compared with 1430 voxels, respectively).

a.



b.

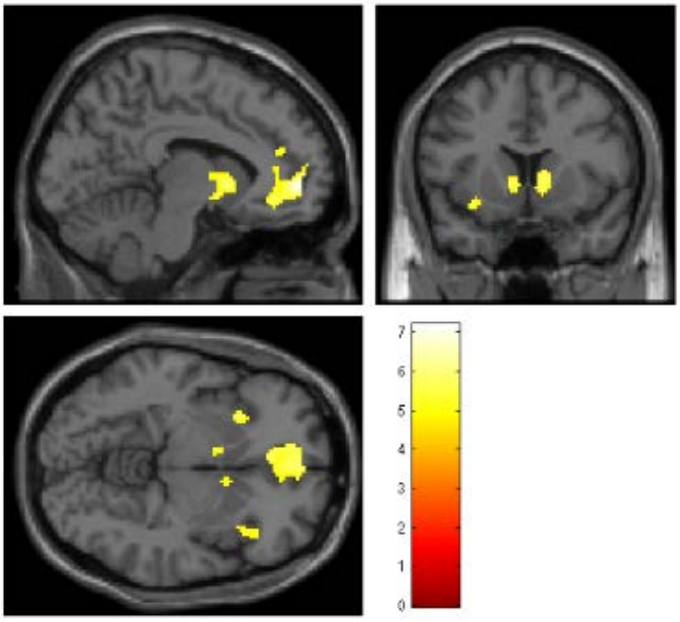


Figure 7. Anticipation of monetary and smoking rewards > neutral trials, analyzed separately by reward trial type suggests both rewards activate common circuitry.

Activation associated with reward trials compared with neutral trial anticipation, collapsed across abstinence condition, with whole-brain family-wise error (FWE) correction of $P < 0.05$, 20 voxel extent threshold. *a.* Activation associated with money > neutral anticipation. Slices shown at x = -4, y = 10, z = -6. *b.* Activation associated with smoking > neutral anticipation. Slices shown at x = -8, y = 12, z = -6.

Table 3. Suprathreshold clusters associated with monetary reward anticipation > neutral anticipation, collapsed across abstinence condition.

	Voxels	Location			T	Brain areas
		x	y	Z	(df = 222)	
1	1430	8	10	-2	8.56	Right and left caudate head, right inferior frontal gyrus, right insula
2	304	-8	40	14	5.47	Anterior cingulate cortex, medial frontal gyrus
3	221	-30	24	-6	6.24	Left insula, left inferior frontal gyrus
4	125	34	-88	12	10.54	Right middle occipital gyrus
5	123	-26	-88	12	9.90	Left middle occipital gyrus
6	123	-22	-30	-2	6.50	Left hippocampus
7	28	4	-12	-18	5.55	Right brainstem

Table 4. Suprathreshold clusters associated with smoking reward anticipation > neutral anticipation, collapsed across abstinence condition.

	Voxels	Location			T	Brain areas
		x	y	Z	(df = 222)	
1	962	-10	54	0	7.20	Anterior cingulate cortex, medial frontal gyrus
2	228	10	10	-2	5.85	Right caudate head
3	131	-8	10	2	5.95	Left caudate head
4	65	-32	14	-12	5.86	Left insula, left inferior frontal gyrus
5	43	40	20	-8	5.29	Right inferior frontal gyrus, right insula

Note: Location refers to Montreal Neurological Institute (MNI) coordinates for peak voxel of each cluster.

4.3.3. Conjunction analyses examining degree of overlap between monetary and smoking reward clusters

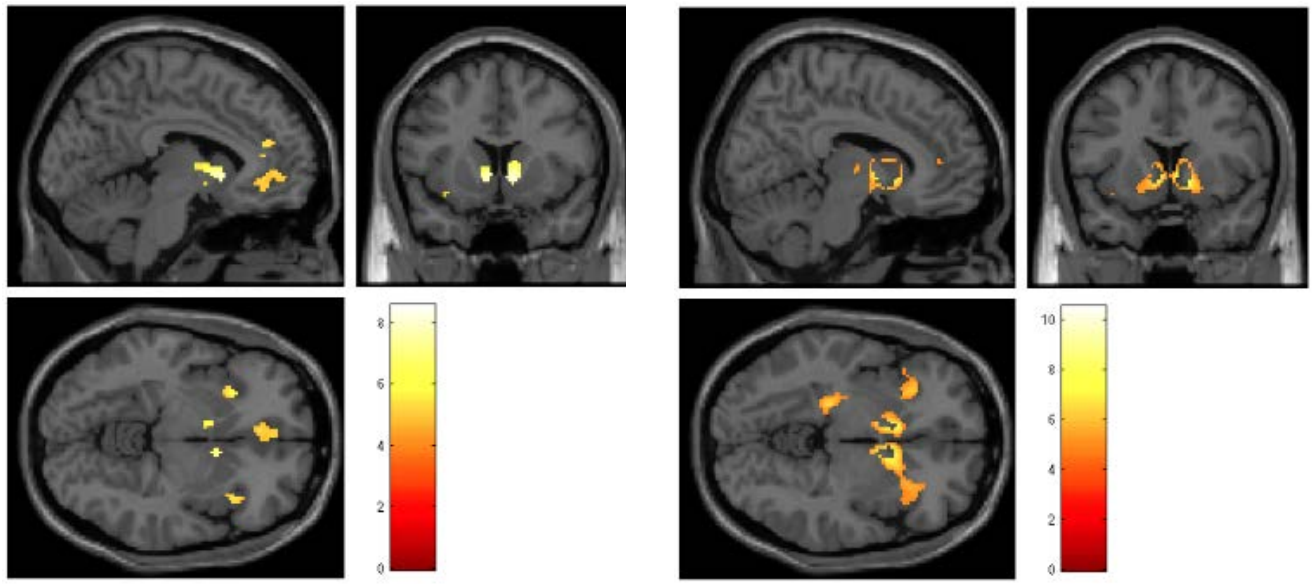
Conjunction analyses generally confirmed the observations described above. Anticipation of monetary and smoking rewards tended to activate many of the same overlapping regions (Figure 8a, Table 5). Monetary reward preferentially activated occipital cortex, hippocampus, brainstem, and larger regions of bilateral caudate and insula than smoking reward (Figure 8b, Table 6). There were no areas exclusively activated by smoking reward anticipation, but smoking anticipation did recruit a larger region of anterior cingulate/medial prefrontal cortex than monetary reward anticipation (Figure 8c).

4.3.4. Direct comparisons between monetary and smoking reward

Direct comparisons between monetary versus smoking reward anticipation revealed no statistically significant differences in any reward-related regions. Activation in bilateral middle occipital gyrus was significantly greater in response to monetary reward anticipation than to smoking reward anticipation (Right: 34, -88, 14, T = 8.113, 168 voxels; Left: -26, -88, 12, T = 8.572, 95 voxels). No areas were significantly greater for smoking reward than for monetary reward when corrected across the whole brain using FWE of $P < 0.05$. Additional areas of activation emerged when examining a more liberal threshold of $p < 0.001$, uncorrected (Figure 9a and b, Tables 7 and 8); however, these were constrained to posterior parietal and occipital regions and did not encompass reward-related areas.

a.

b.



c.

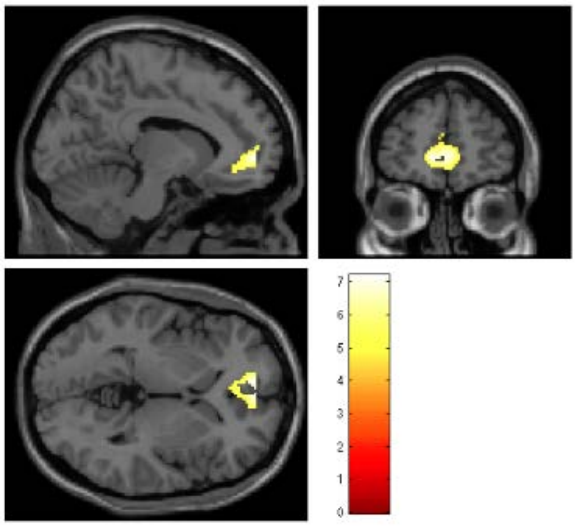


Figure 8. Conjunction analyses: Areas activated by anticipation of both monetary and smoking rewards, monetary reward only, or smoking reward only.

Conjunction analyses for activation associated with monetary and/or smoking reward trials compared with neutral trial anticipation, collapsed across abstinence condition, with whole-brain family-wise error (FWE) correction of $P < 0.05$, 20 voxel extent threshold. *a.* Activation associated with both money > neutral *and* smoking > neutral anticipation. Slices shown at x = -6, y = 12, z = -6. *b.* Activation associated with money > neutral anticipation *only*. Slices shown at x = 10, y = 10, z = -4. *c.* Activation associated with smoking > neutral anticipation *only*. Slices shown at x = -10, y = 54, z = 0. Medial prefrontal cortex: -10, 54, 0; $T = 7.20$, 732 voxels.

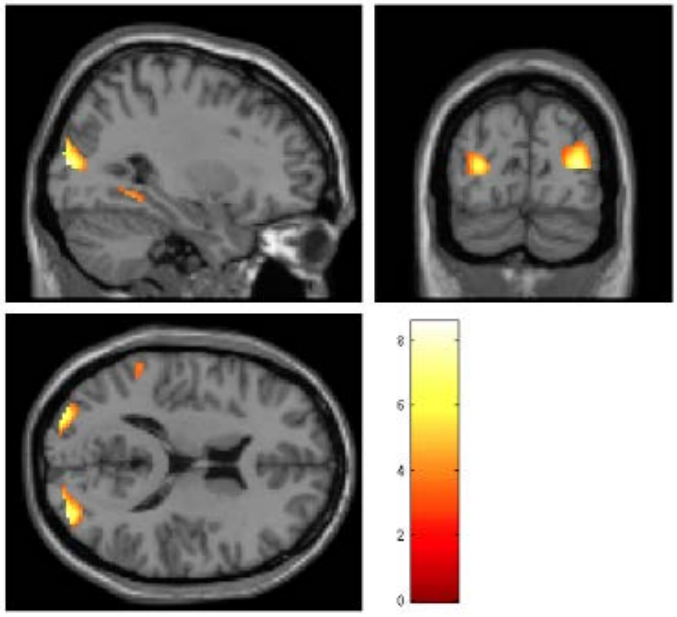
Table 5. Suprathreshold clusters associated with monetary reward > neutral anticipation, masked to include only voxels shown to also be activated by smoking reward > neutral anticipation.

	Voxels	Location			T	Brain areas
		x	y	z	(df = 222)	
1	229	-4	42	20	5.39	Anterior cingulate cortex, medial frontal gyrus
2	221	8	10	-2	8.56	Right caudate head
3	127	-8	12	2	7.93	Left caudate head
4	65	-28	22	-6	6.03	Left insula, left inferior frontal gyrus
5	43	40	20	-8	5.49	Right inferior frontal gyrus, right insula

Table 6. Suprathreshold clusters associated with monetary reward > neutral anticipation, masked to exclude voxels shown to be activated by smoking reward anticipation > neutral anticipation.

	Voxels	Location			T	Brain areas
		x	y	z	(df = 222)	
1	1052	6	10	0	7.45	Right and left caudate head, right inferior frontal gyrus, right insula
2	42	-8	40	14	5.47	Anterior cingulate cortex, medial frontal gyrus
3	30	12	42	10	5.07	Anterior cingulate cortex
4	149	-30	24	-6	6.24	Left insula, left inferior frontal gyrus
5	125	34	-88	12	10.54	Right middle occipital gyrus
6	123	-26	-88	12	9.90	Left middle occipital gyrus
7	123	-22	-30	-2	6.50	Left hippocampus
8	28	4	-12	-18	5.55	Right brainstem

a.



b.

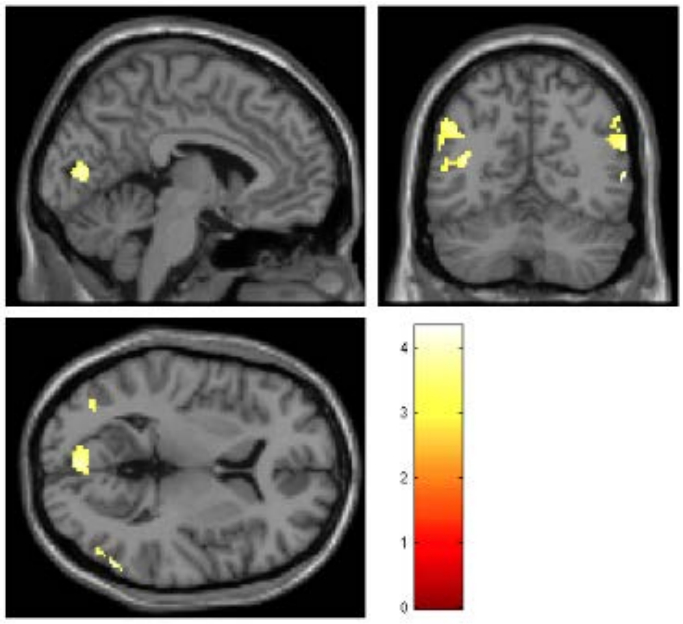


Figure 9. Direct comparisons between monetary and smoking reward anticipation indicate significant differences only in visual and visual association cortices.

Direct comparisons between monetary and smoking reward anticipation, collapsed across abstinence condition, with $p < 0.001$, uncorrected, 20 voxel extent threshold. *a.* Activation associated with money > smoking anticipation. Slices shown at x = 30, y = -84, z = 16. *b.* Activation associated with smoking > money anticipation. Slices shown at x = -4, y = -62, z = 6.

Table 7. Suprathreshold clusters associated with direct comparison of monetary reward > smoking reward anticipation, collapsed across abstinence condition.

	Voxels	Location			T	Brain areas
		x	y	z	(df = 222)	
1	345	34	-88	14	8.11	Right middle occipital gyrus
2	205	-26	-88	12	8.57	Left middle occipital gyrus
3	55	-58	-44	14	3.94	Left superior temporal gyrus
4	41	30	-48	-8	4.33	Right fusiform gyrus

Table 8. Suprathreshold clusters associated with direct comparison of smoking reward > monetary reward anticipation, collapsed across abstinence condition.

	Voxels	Location			T	Brain areas
		x	y	z	(df = 222)	
1	264	-38	-64	18	4.26	Left angular gyrus, middle temporal gyrus
2	153	-2	-80	10	4.26	Cuneus
3	57	58	-62	24	3.89	Right angular gyrus, superior temporal gyrus
4	38	-38	-72	4	3.99	Left middle occipital gyrus
5	28	58	-62	6	4.33	Right middle temporal gyrus
6	20	60	-52	40	3.37	Right inferior parietal lobule

Note: Location refers to Montreal Neurological Institute (MNI) coordinates for peak voxel of each cluster. Significance threshold set at $p < 0.001$, uncorrected across the whole-brain, 20 voxel extent threshold.

4.4. OUTCOME PHASE

4.4.1. Combined effects of monetary and smoking reward win relative to no win outcomes

Examination of combined effects of smoking or monetary reward win trials compared with no win trials revealed robust activation in the bilateral caudate and ventral striatum, as well as small clusters in posterior cingulate cortex, posterior parietal cortex, and left middle frontal gyrus (Figure 10, Table 9).

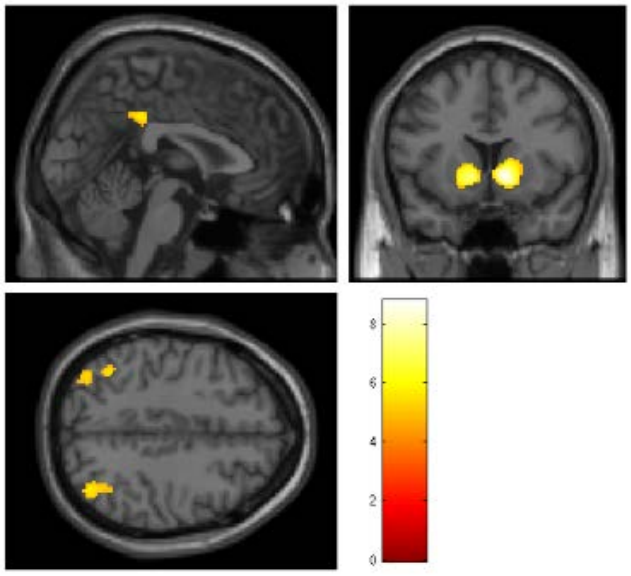


Figure 10. Combined effects of monetary and smoking win > no win outcomes reveal robust task-related activation in the bilateral striatum.

Overall task-related activation associated with money or puff reward win compared with no win trial outcomes, collapsed across abstinence condition, with whole-brain family-wise error (FWE) correction of $P < 0.05$, 20 voxel extent threshold. Slices shown at x = 2, y = 12, z = 44.

Table 9. Suprathreshold clusters associated with combined effects of monetary and smoking reward win > no win outcomes, collapsed across abstinence condition.

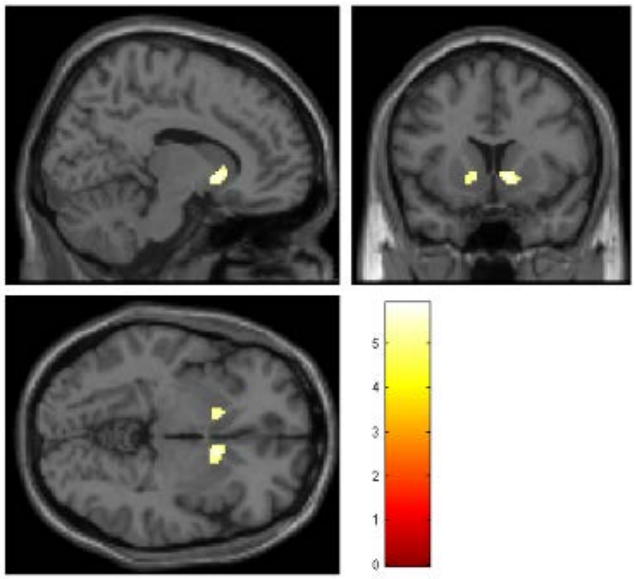
	Voxels	Location			T	Brain areas
		x	Y	z	(df = 296)	
1	454	10	12	-2	8.77	Right caudate, ventral striatum
2	354	-10	12	-4	7.42	Left caudate, ventral striatum
3	176	36	-68	44	5.60	Right inferior parietal lobule/angular cortex
4	86	2	-38	36	5.70	Posterior cingulate cortex
5	50	-36	-72	44	5.29	Left superior parietal lobule/precuneus
6	46	-38	-58	44	5.57	Left inferior parietal lobule
7	24	-44	50	6	5.07	Left middle frontal gyrus, inferior frontal gyrus

Note: Location refers to Montreal Neurological Institute (MNI) coordinates for peak voxel of each cluster.

4.4.2. Effects of monetary and smoking outcomes analyzed separately

When win > no win contrasts for monetary and smoking rewards were examined separately, only caudate head/ventral striatum survived FWE correction for each reward type, suggesting a loss of power may have limited detection of smaller, relatively weak clusters when the reward types were separated. Significant bilateral striatum activation was observed for monetary win > no win outcomes, while the contrast for smoking win > no win was significant only in the right striatum (Figure 11).

a.



b.

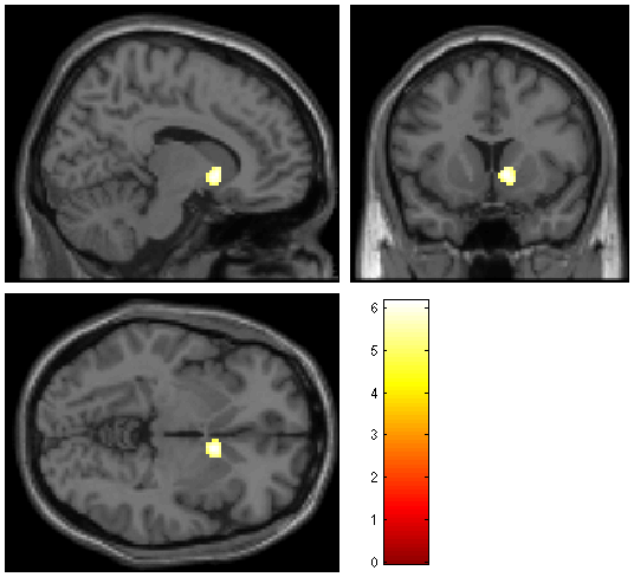


Figure 11. Activation associated with monetary or smoking win > no win outcome, analyzed separately by reward trial type.

Activation associated with reward win trials compared with no win outcomes, collapsed across abstinence condition, with whole-brain family-wise error (FWE) correction of $P < 0.05$, 20 voxel extent threshold. Slices shown at x = 12, y = 12, z = -4. *a.* Activation associated with money win > no win outcome. Right caudate head: 10, 14, -2; $T = 5.90$, 100 voxels. Left caudate head: -12, 12, -4; $T = 5.19$, 36 voxels. *b.* Activation associated with smoking win > no win outcome. Right caudate head: 10, 10, -4; $T = 6.16$, 103 voxels.

4.4.3. Conjunction analyses examining degree of overlap between monetary and smoking rewards

Conjunction analyses indicated 46% overlap for monetary win > no win and smoking win > no win outcomes in the right ventral striatum, indicating that the two rewards were generally activating the same region.

4.4.4. Direct comparisons between monetary and smoking reward

Direct comparisons of monetary versus smoking reward outcomes were evaluated by testing the reward type X outcome interaction within the 2 x 2 X 2 ANOVA model. Only one small cluster within the right insula indicated a significant interaction at the significance threshold of $p < 0.001$, uncorrected (42, 0, 6; $F = 12.82$, 33 voxels). Post-hoc contrasts specifying stronger activation for win compared with no win outcomes for monetary reward than for smoking reward revealed an even larger cluster of activation within the right insula (42, 0, 6; $T = 3.58$, 83 voxels). No statistically significant areas of activation were observed for contrasts specifying stronger activation for win compared with no win outcomes for smoking reward than for monetary reward.

4.5 SUMMARY AND CONCLUSIONS

In this first set of analyses, I examined whole-brain activation during anticipation and delivery of monetary and smoking rewards in order to characterize the BOLD response to both reward types within the same paradigm. When reward types were combined, robust activation throughout

expected regions was observed, including the striatum, medial prefrontal cortex, bilateral anterior insula, hippocampus, and midbrain. These areas were consistent with those previously reported in studies of reward processing (Apicella et al., 1991; Breiter et al., 2001; Delgado et al., 2003; Elliott et al., 2003; Roesch & Olson, 2004; Sescousse et al., 2013; Thut et al., 1997), indicating that the task as a whole was working to engage reward-related circuitry.

Similar patterns of activation were observed for anticipation and outcome phases of the task. As predicted, bilateral caudate was engaged during both anticipation and outcome phases. By contrast, mPFC activation and anterior insula activation were observed for anticipation phase only, while posterior cingulate cortex activation was observed only during the outcome phase. While bilateral caudate activation during both phases of the task was consistent with previous studies (Diekhof, Kaps, Falkai, & Gruber, 2012), preferential activation of the mPFC during anticipation was somewhat surprising given that several previous studies have demonstrated the opposite effect, with mPFC activation observed primarily during reward outcome (Knutson et al., 2001; Knutson & Wimmer, 2007). Indeed, a recent meta-analysis of studies incorporating both anticipation and outcome phases of reward processing tasks found that mPFC activation occurred only in outcome phase, while no activation was observed during the anticipation phase (Diekhof et al., 2012). However, previous monetary reward versions of the task used here have demonstrated mPFC activation during anticipation (Forbes, Olino, et al., 2010; Forbes, Ryan, et al., 2010), and activation within this region is consistent with the putative role of mPFC in coding for expected reward value (Rushworth & Behrens, 2008). Furthermore, as noted in the appendix, significant activation in this region during anticipation may have been partially driven by deactivation during neutral trials. Since neutral trials were not part of the comparison for outcomes, this may explain a lack of activation in this region during the outcome phase. In any

case, robust engagement of the striatum during the outcome phase indicates that lack of mPFC activation was not simply a failure of the modified task to engage reward circuitry.

Both monetary and smoking rewards served to activate key reward pathways. Indeed, remarkable similarities were observed when examining activation patterns for each reward type separately. Conjunction analyses revealed a large degree of spatial overlap in regions of activation for both anticipation and delivery of monetary and smoking rewards, particularly in the areas most central to reward processing, including the caudate, insula, and medial prefrontal cortex. This suggests that, when presented within a consistent paradigm, monetary and smoking rewards are largely activating common reward pathways. Monetary rewards did tend to produce some relatively larger clusters of activation (e.g., within the caudate and insula) than did smoking rewards, and some areas, such as the hippocampus and insula, responded only to monetary rewards. However, none of these regions exhibited significant differences when directly contrasting monetary and smoking rewards, suggesting that differences in cluster sizes likely reflected reduced power leading to subthreshold significance for some voxels when reward types were separated rather than actual regional specificity.[1] The only areas showing significant differences between reward types when compared directly were those restricted to visual and parietal cortex.

Interestingly, despite the trend for clusters of activation to be slightly smaller for smoking rewards, anticipatory activation in the mPFC/ACC showed the opposite pattern, with substantially larger activation for smoking than for monetary rewards. Given a recent meta-analysis of smoking cue reactivity studies that indicated strong effects of smoking cues relative to neutral cues in the medial prefrontal cortex/ACC (Engelmann et al., 2012), it is tempting to

[1] Although not tested here, the observation that it was primarily smoking reward that tended to exhibit this loss of power may also reflect heightened variability between abstinence conditions contributing to increased error (see Chapter 5).

speculate that the mPFC may be responding preferentially to anticipation of smoking reward. However, as noted above, direct comparisons between reward types were not significant, and monetary rewards did show some, albeit smaller, activation within this region. This highlights the commonality of reward pathway activation for the two reward types within the present study.

The overlap in reward pathways observed here is generally consistent with another recent study that aimed to incorporate both smoking and affective stimuli into a common paradigm. Versace and colleagues similarly found similar overlap in circuitry engaged by smoking, erotic, romantic, sad, and mutilating stimuli (Versace et al., 2011). While several regions (e.g. visual association cortex, dorsal striatum, cingulate gyrus) exhibited greater magnitude of activation to erotic pictures than to other stimuli, only the insula exhibited selective activation to cigarette cues. The insula is thought to be relevant for interoceptive awareness and has been shown to be important for maintaining smoking behavior (Janes et al., 2010; Naqvi, Rudrauf, Damasio, & Bechara, 2007), possibly through heightened awareness of internal craving states (Brody et al., 2002). However, other previous studies have demonstrated insula activation in anticipation of non-drug rewards (Diekhof et al., 2012), and the present findings are consistent with a nonspecific role of the insula in anticipatory reward processing. One possible reason for the discrepancy across studies is that the passive presentation of smoking stimuli, as used by Versace et al. (2011), may evoke an anticipatory craving state (i.e., imagining smoking once the experiment is over) that is not evoked by passive presentation of other stimuli. The present experiment (and many others demonstrating insula activation to non-drug rewards) used actual rewards with an expressly manipulated anticipation phase, which may have served to better equate the processing of different reward types.

The importance of procedural differences is also relevant for findings in the striatum. The present study demonstrated robust activation in the striatum during both anticipation and outcome phases of the task, for both smoking and monetary rewards. By contrast, previous significant findings in the striatum in response to smoking cues have been inconsistent, with studies generally showing only weak activation in this area (Engelmann et al., 2012). This discrepancy may be explained by the theoretical role of the dorsal striatum—particularly the head of the caudate nucleus—in responding to reinforcement for action and supporting instrumental conditioning, rather than simply responding to reward per se (Delgado, 2007; O'Doherty et al., 2004). Furthermore, given the theoretical role of the ventral striatum in encoding prediction error, uncertainty of reward presentation may be a critical feature for eliciting striatal activation (Delgado, 2007; Sescousse et al., 2013). These factors represent key differences from the way that smoking reward is typically studied, in which smoking cues are passively (and often predictably) presented, highlighting that important effects within the striatum may be missed by divorcing smoking stimuli from any action or behavior. This does not dismiss the importance of traditional cue reactivity work, as classical conditioning processes are certainly relevant for addiction, but does underscore the importance of methodology and the difficulty in making inferences about reward processing across studies. Given that activation in the head of the caudate has previously been shown to correlate with motivation to obtain reward (Buhler et al., 2010), this region is an important area of investigation for understanding reward processing and smoking. Thus, it is a major strength of the present task design that both smoking and monetary rewards robustly engaged this circuitry, thereby providing a framework for further examination of the effects of abstinence and the association with smoking behavior.

In sum, findings from the first set of analyses comparing response to smoking and monetary rewards within the same paradigm demonstrated that the novel task used here was effective at eliciting reward-related activation, and that both monetary and smoking rewards activated common reward pathways, including the striatum, medial prefrontal cortex, and anterior insula. It is important to note that lack of significant differences when directly comparing monetary versus smoking rewards (e.g., in the mPFC) could be due to underlying differences in response to each reward type as a function of abstinence. In the next chapter, we turn to address this question directly, examining the effects of abstinence on processing of monetary and smoking rewards.

5. QUESTION #2: EFFECTS OF ABSTINENCE ON PROCESSING OF MONETARY AND SMOKING REWARDS

5.1 INTRODUCTION

The second primary aim of this study was to evaluate the effects of smoking abstinence on BOLD response to both smoking and monetary rewards. Having demonstrated significant reward-related activation elicited by both monetary and smoking rewards within the modified guessing task, I next analyzed both main effects of abstinence and interactions between reward type and abstinence state, controlling for scan order (i.e., abstinent or non-abstinent session first). Based on theoretical and behavioral evidence suggesting that abstinence from smoking may exacerbate underlying reward dyregulation, I hypothesized that abstinence from smoking would exert differential effects on BOLD response to smoking versus monetary reward, resulting in a significant reward type by abstinence state interaction in the key reward-related region of the striatum. Specifically, I predicted that smokers would exhibit heightened BOLD response during anticipation and delivery of smoking reward but attenuated response during anticipation and delivery of monetary reward in the striatum following 24 hours of abstinence compared with smoking as usual.

Given the central role of the striatum in reward processing and drug addiction, this region was targeted as the primary region of interest (ROI) for analyses examining effects of abstinence. Restricting primary interaction analyses to the striatal ROI allows for adequate control of

multiple comparisons across a smaller region, thereby maximizing the ability to detect an effect. However, it is acknowledged that variation in BOLD signal within the striatum may reflect modulatory input from other interconnected brain regions. Thus, whole-brain analyses were also conducted to explore additional circuitry which may be involved in processing of monetary and smoking rewards.

In addition to overall group-level effects of abstinence, I also explored whether individual differences in subjective measures taken before each scan were associated with abstinence-induced changes in reward functioning. Based on previous findings of associations between higher levels of cigarette craving or nicotine dependence and heightened response to smoking cues (Brody et al., 2002; McClernon et al., 2005; McClernon et al., 2008) or attenuated response to non-drug rewards (Cook et al., 2004; Sweitzer et al., 2012), I hypothesized that those individuals scoring highest on measures of nicotine dependence or those experiencing the greatest abstinence-induced changes in craving, mood, and withdrawal would also experience the largest disruptions to reward functioning during abstinence. Specifically, I predicted that higher levels of nicotine dependence would be associated with greater abstinence-induced increases in striatal response to smoking reward and decreases in response to monetary reward. I further predicted that smokers reporting the greatest increases in craving, withdrawal and negative affect, along with decreases in positive affect, would exhibit the same pattern, with larger increases in striatal response to smoking reward and larger decreases in striatal response to monetary reward as a function of abstinence.

5.2 STATISTICAL ANALYSES

Effects of abstinence on subjective and behavioral measures were first examined using paired *t*-tests. Next, to examine effects of abstinence on BOLD response to rewards, separate models were again created for anticipation and outcome phases of the fMRI task. For the anticipation phase, effects of reward type and abstinence condition were modeled with a 2 x 2 x 2 ANOVA. Condition (abstinent, non-abstinent) and reward type (money > neutral, puff > neutral) were entered as within-subjects factors and scan order (abstinence session first, non-abstinent session first) was entered as a between-subjects factor. Contrasts with neutral trials were used to allow for meaningful interpretation of main effect and interaction *F* tests. For the outcome phase of the task, a 2 (condition) x 2 (money or smoking reward type) x 2 (scan order) random-effects ANOVA was specified using win > no win contrast images for each trial type. Win > no win contrasts were used to simplify the overall model, limiting it to three factors with the inclusion of scan order.

For both anticipation and outcome models, main effects of abstinence condition were first examined within the striatal ROI, with control for multiple comparisons as described in Chapter 3 to achieve a corrected $P < 0.05$. Given the expected dissociation between smoking and monetary rewards as a function of abstinence (discussed below), I did not predict any overall main effects of abstinence within this region. Order effects were also evaluated by examining the scan order X abstinence condition interaction, to identify any possible confounding effects of scan order.

The primary hypothesis of a reward type X condition interaction was then tested within the striatal ROI. The 3-way interaction with scan order was also tested to determine if order

effects may be moderating any observed effects. Several steps were taken to explore significant interactions: The first eigenvariate was extracted from significant clusters, allowing for data to be plotted graphically and exported to SPSS for further analyses. Within SPSS, directionality of significant effects was explored using paired *t*-tests. As an alternate approach, significant findings were also followed with directionally specific *t* contrasts within SPM, in order to explore the simple effects contributing to the interaction. In areas where different reward types exhibited opposing patterns of activation as a function of abstinence, conjunction analysis was conducted to determine the extent of regional overlap.

To explore possible activations beyond this predetermined ROI, main effect and interaction tests were repeated across the whole brain using uncorrected $p < 0.001$, with 20 voxel extent threshold. Effects of abstinence for each reward type were examined separately across the whole brain to explore any patterns which may not have been sufficient to contribute to a significant interaction. In addition, these analyses were also extended to evaluate the alternative contrasts: comparing smoking versus monetary rewards within each abstinence condition. This provided a follow-up from reward type comparisons conducted in Chapter 4, allowing for further exploration of differences between reward types when separated by abstinence condition. These results are presented in Appendix B.

Finally, using first eigenvariate data extracted from striatal clusters showing a significant reward type by condition interaction, correlations between change scores for each reward type and selected behavioral measures were evaluated.

5.3. BEHAVIORAL AND SUBJECTIVE RESULTS

Scores on subjective measures during abstinence compared with non-abstinence are presented in Table 10. As expected, self-reported craving was significantly higher during abstinence than non-abstinence, when measured both pre-scan [$t(36) = 7.71$, $p < 0.001$] and post-scan [$t(37) = 3.65$, $p < 0.001$]. Craving during non-abstinence increased from pre- to post-scan [$t(37) = 5.49$, $p < 0.001$], while craving during abstinent sessions remained unchanged [$t(36) = 0.55$, *ns*]. Self-reported withdrawal and negative affect both significantly increased during abstinence compared with non-abstinence, while positive affect significantly decreased.

Data on latency to first puff smoked after the scan and total number of puffs smoked during the one hour waiting period were available for a subset of participants. There were no significant differences between abstinent and non-abstinent sessions for either of these variables. However, small sample size ($n = 20$) for latency data may have prevented detecting a significant effect, as results were in the predicted direction, with shorter latencies during abstinence. The vast majority of participants smoked all 12 out of 12 available puffs following each session, limiting any differences between conditions. Reaction time for making guesses during the imaging task did not differ as a function of abstinence; however, participants were significantly faster during the second scan than during the first ($t = 2.124$, $p < 0.05$).

Table 10. Differences in smoking and affective measures during abstinence compared with non-abstinence.

Variable	Mean (SD) Non- Abstinent	Mean (SD) Abstinent	t-value (df=37)[1]
Carbon Monoxide	20.18 (14.69)	3.82 (2.62)	-7.603**
Pre-scan QSU-4	16.28 (20.70)	56.62 (29.57)	7.717**
Post-scan QSU-4	41.22 (25.28)	58.75 (28.73)	3.654**
Average QSU-4	28.54 (18.12)	57.99 (27.81)	6.969**
MNWS	119.61 (102.80)	214.76 (159.18)	3.599**
PANAS-Positive	33.84 (7.73)	29.47 (7.80)	-3.437*
PANAS-Negative	13.95 (4.29)	17.00 (6.19)	2.632*
Guess Reaction Time	937.87 (183.44)	939.44 (202.38)	0.049
Latency to First Puff	14.25 (16.01)	8.55 (8.44)	-1.408
Number of Puffs Smoked	10.04 (3.53)	10.60 (3.11)	.844

Abbreviations: QSU-4-Questionnaire of smoking urges, 4 item version (Toll et al., 2006); MNWS-Minnesota Withdrawal Scale (Hughes & Hatsukami, 1986); PANAS-Positive and Negative Affect Scale (Watson et al., 1988).
[1]Abstinent pre-scan QSU-4 data was missing for one subject; latency to first puff data was only available for 20 subjects; number of puffs smoked was available for 25 subjects.

*$p < .01$

**$p < .001$

5.4. ANTICIPATION PHASE

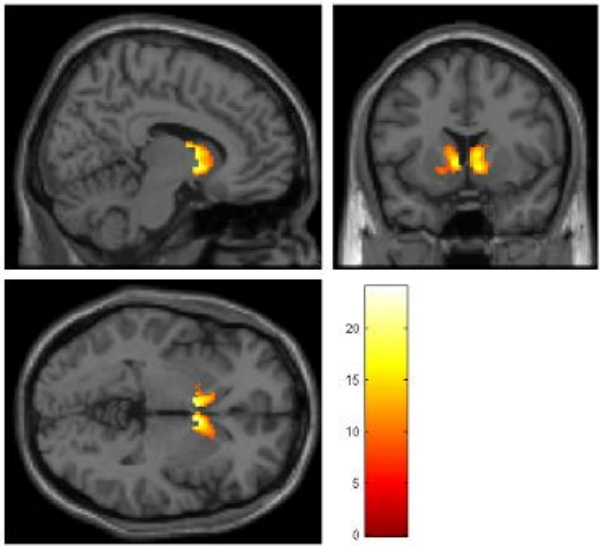
5.4.1. Main effects of abstinence condition within striatal ROI

As expected, there were no significant main effects of abstinence condition within the ventral and dorsal striatum. In addition, no significant interactions with scan order were observed, suggesting minimal learning or habituation effects between scans in these regions.

5.4.2. Reward by condition interaction within striatal ROI

My primary hypothesis of a reward X condition interaction was first tested within the *a priori* ROI of the ventral and dorsal striatum. As predicted, a significant reward X condition interaction was observed bilaterally in the caudate head (Figure 12a). The three-way interaction with scan order was not significant, suggesting that this effect was not moderated by session order effects. Consistent with my hypotheses, analyses conducted using extracted data within SPSS suggested that abstinence from smoking was associated with a significant bilateral decrease in anticipatory activation to monetary rewards [$t(37) = 3.250$ and 2.916, both p's < 0.01] and a parallel bilateral increase in anticipatory activation to smoking rewards [$t(37) = 4.951$ and 4.622, both p's < 0.001] relative to non-abstinence (Figure 12b). These findings confirmed my primary hypotheses of a dissociated effect of abstinence on smoking versus monetary rewards in the striatum, with the predicted pattern emerging of both abstinence-induced increase in anticipation of smoking rewards and decrease in anticipation of monetary rewards.

a.



b.

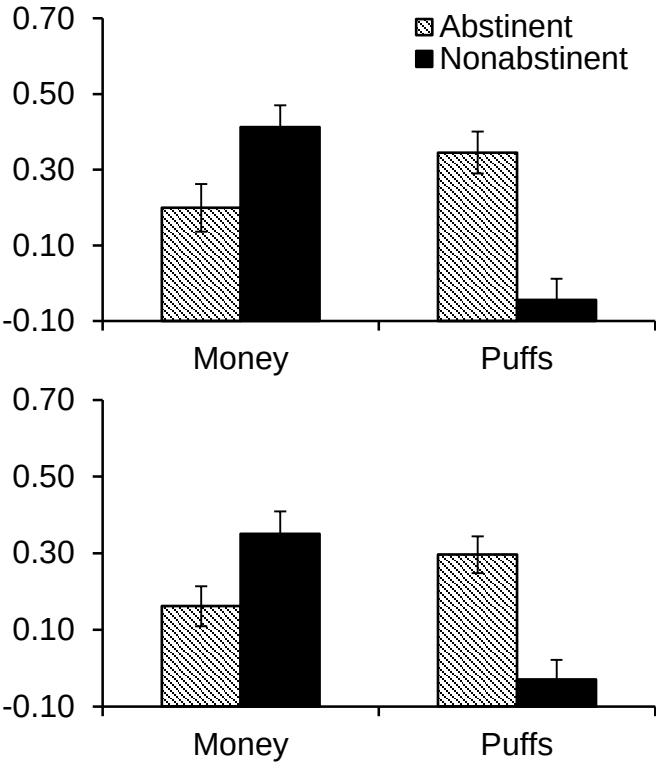
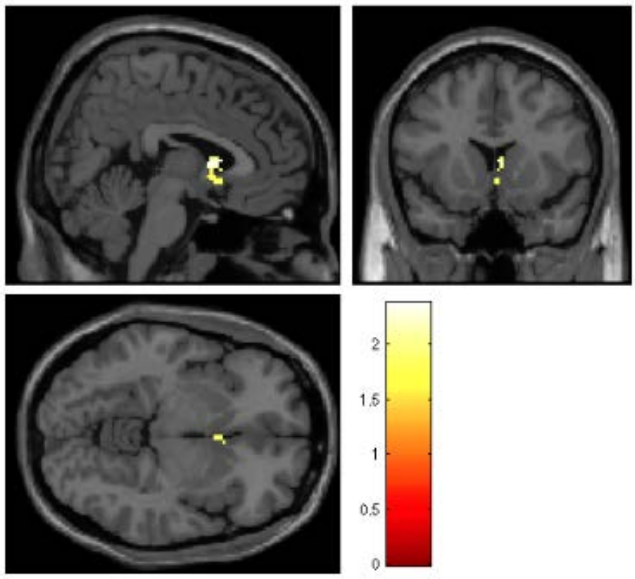


Figure 12. Anticipatory activation in the striatum associated with reward type X abstinence condition interaction.

a. Striatal activation associated with reward anticipation trial type (money > neutral or smoking > neutral) X condition (abstinent or non-abstinent) interaction. Slices shown at x = 10, y = 10, z = -2. Right caudate head: 6, 4, 2; F = 24.01, 292 voxels. Left caudate head: -4, 6, -2; F = 20.26, 264 voxels. ***b.*** Extracted eigenvariate from right striatum (top) and left striatum (bottom).

a.



b.

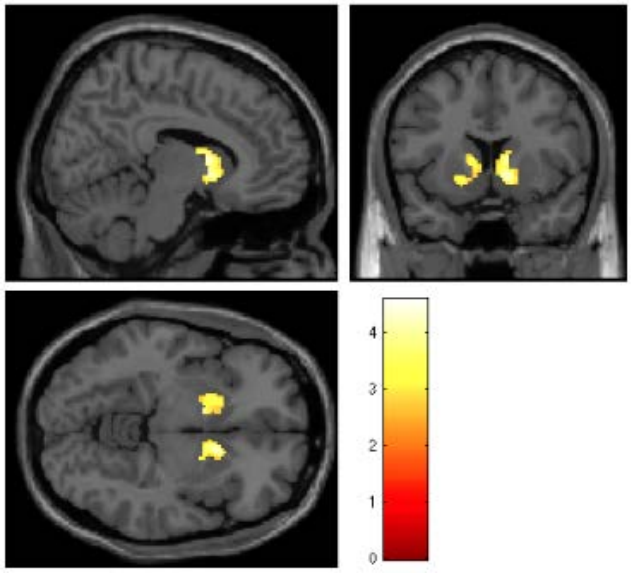


Figure 13. Simple effects of abstinence on anticipatory activation to reward in the striatum, analyzed separately by reward trial type.

Activation as a function of abstinence for monetary and smoking reward anticipation within striatal ROI. *a.* Activation associated with non-abstinence > abstinence for monetary reward trials, $p < 0.05$, uncorrected, 20 voxel extent threshold. Slices shown at x = 4, y = 14, z = -6. Right caudate head: 4, 8, 6; $T = 2.38$, 63 voxels. *b.* Activation associated with abstinence > non-abstinence for smoking reward trials, $p < 0.005$, 29 voxel extent threshold. Slices shown at x = 10, y = 10, z = -6. Right caudate head: 14, 12, -4; $T = 4.57$, 342 voxels. Left caudate head: -12, 0, 12; $T = 4.26$, 331 voxels.

Within SPM, contrasts specifying stronger activation during abstinence for puff rewards and the opposite pattern for monetary rewards revealed an even larger cluster of activation within the bilateral caudate (right: 6, 4, 2; T = 4.90, 346 voxels; left: -4, 6, -2, 354 voxels). No statistically significant areas of activation were observed for contrasts specifying stronger activation during abstinence for monetary rewards and weaker activation for puff rewards during abstinence. Contrasts examining effects of abstinence on anticipatory activation for each reward type separately revealed robust abstinent > non-abstinent activation for puff reward in the bilateral striatum (Figure 13a) but, surprisingly, no effect of abstinence on anticipation of monetary reward. This lack of monetary reward effect may have been due to greater variability when conducting voxel-based tests within SPM, thereby reducing ability to detect a small effect. When loosening significance criteria to a more liberal threshold of $p < 0.05$, uncorrected, a small cluster of non-abstinent > abstinent activation was evident for monetary reward in the right dorsal striatum (Figure 13b). Despite the large size of the smoking reward cluster, conjunction analyses revealed only 11 voxels of overlap between the dissociated abstinence effects for the two reward types, with the sub-threshold monetary reward effects appearing more medially than the robust puff reward clusters.

5.4.3. Whole-brain analyses

Exploratory analyses conducted across the whole brain at a threshold of $p < 0.001$ revealed only small areas of activation associated with overall main effects of abstinence state (Figure 14). However, several additional activation clusters emerged related to the condition X reward interaction throughout reward-related circuitry, including the anterior cingulate (ACC) extending to the mPFC, the right insula, and right brainstem (Figure 15). Within the brainstem, pairwise

comparisons of extracted data conducted in SPSS revealed a similar pattern as that observed in the caudate, with abstinence leading to a decrease in anticipatory activation to monetary reward [$t(37) = 2.194$, $p < 0.05$] and increased anticipatory activation to smoking reward [$t(37) = 4.777$, $p < 0.001$] relative to non-abstinence. Within the mPFC and insula, only the increase in anticipatory activation to smoking reward was significant [$t(37) = 4.008$ and 5.246, respectively, both p's < 0.001].

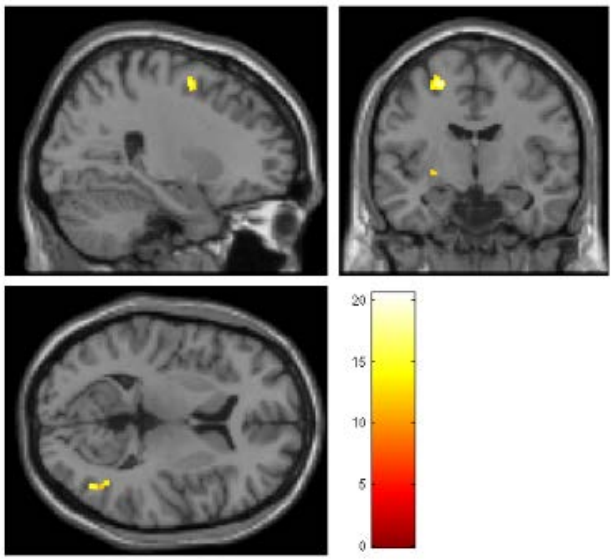
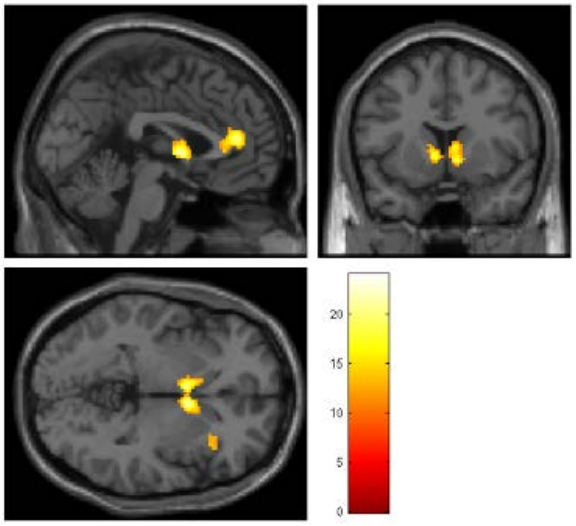


Figure 14. Minimal main effects of abstinence on monetary and smoking reward anticipation combined, examined across whole-brain.

Whole-brain activation during reward anticipation associated with main effects of abstinence condition, collapsed across reward type. Slices shown at x = 26, y = -8, z = 8. Left middle frontal gyrus: -24, -10, 56; $F = 20.52$, 63 voxels; Right middle frontal gyrus: 28, 0, 58; $F = 17.39$, 28 voxels; Left putamen: -28, -12, -6; $F = 17.00$, 45 voxels. Right middle temporal gyrus: 44, -66, 10; $F = 15.14$, 46 voxels.

a.



b.

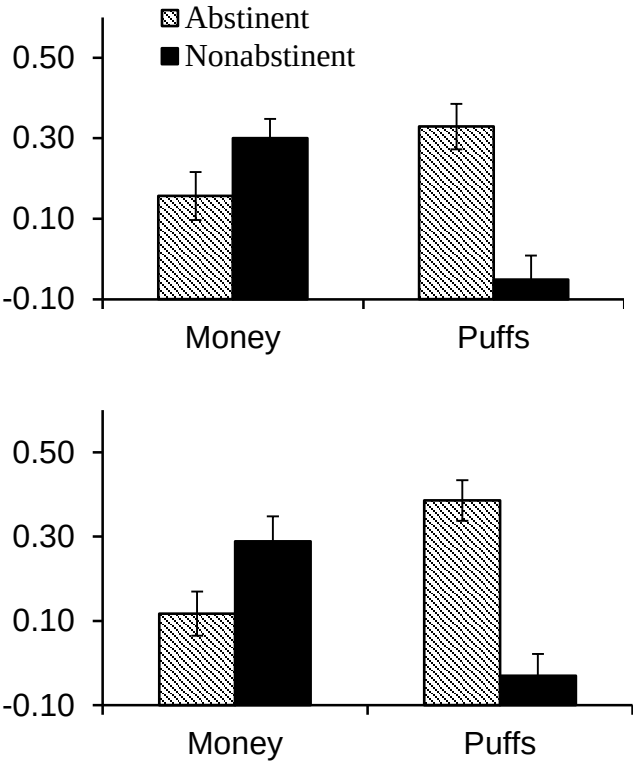
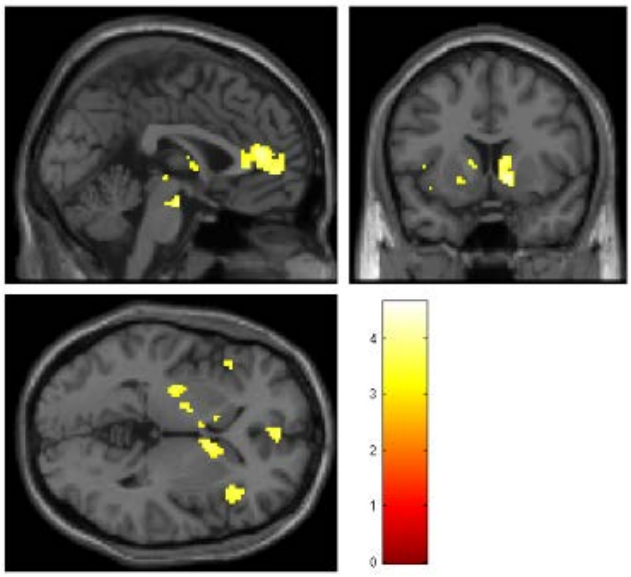


Figure 15. Whole-brain anticipatory activation associated with reward type X abstinence condition interaction reveals robust effects throughout reward-related circuitry.

a. Whole-brain activation associated with reward anticipation trial type (money > neutral or smoking > neutral) X condition (abstinent or non-abstinent) interaction. Slices shown at x = 0, y = 10, z = -2. Right insula: 30, 28, 4; *F* = 14.48, 79 voxels. Medial prefrontal cortex: 2, 40, 12; *F* = 20.67, 190 voxels. Right brainstem: 12, -20, -18; *F* = 18.68, 50 voxels. ***b.*** Extracted eigenvariate from right insula (top) and medial prefrontal cortex (bottom).

a.



b.

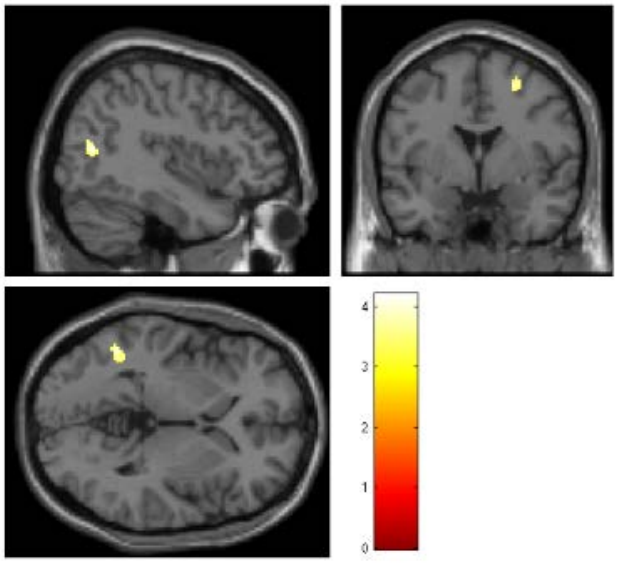


Figure 16. Robust abstinence-induced increases in anticipatory activation to smoking reward but minimal effects of abstinence on monetary reward anticipation when examined separately across the whole-brain.

Activation as a function of abstinence for monetary and smoking reward anticipation, $p < 0.001$, 20 voxel extent threshold. *a.* Activation associated with abstinence > non-abstinence for smoking reward trials. Slices shown at x = 0, y = 10, z = 0. *b.* Activation associated with non-abstinence > abstinence for monetary reward trials. Slices shown at x = 42, y = 0, z = 0. Right middle temporal gyrus: 42, -68, 14; $T = 4.20$, 65 voxels. Left middle temporal gyrus: -48, -52, 0; $T = 4.16$, 53 voxels. Right middle frontal gyrus: 26, 0, 56; $T = 3.89$, 33 voxels.

Table 11. Suprathreshold clusters associated with anticipation of smoking reward during abstinence > non-abstinence.

	Voxels	Location			T	Brain areas
		X	y	z	(df = 144)	
1	624	12	-6	8	4.64	Right caudate head
2	343	42	18	-10	4.59	Right insula, inferior frontal gyrus
3	330	2	42	10	4.25	Anterior cingulate cortex, medial frontal gyrus
4	262	-42	18	-10	4.12	Left inferior frontal gyrus, left insula
5	127	-28	-12	-4	4.57	Left putamen
6	88	-12	4	-6	4.03	Left globus pallidus, left putamen
7	25	6	-20	-4	3.93	Right brainstem
8	23	-10	12	4	3.76	Left caudate head
9	21	-16	-8	0	3.81	Left thalamus

Note: Location refers to Montreal Neurological Institute (MNI) coordinates for peak voxel of each cluster. Significance threshold set at $p < 0.001$, uncorrected across the whole-brain, 20 voxel extent threshold.

When examined separately within SPM, anticipation of smoking reward was associated with robust abstinence > non-abstinence activation throughout reward-related circuitry, including bilateral caudate, left putamen, bilateral insula, ACC, and brainstem (Figure 16a, Table 11). Monetary reward anticipation during non-abstinence > abstinence was associated with activation in three small clusters including bilateral middle temporal gyrus and right middle frontal gyrus (Figure 16b). Reverse contrasts (smoking reward non-abstinence > abstinence or monetary reward abstinence > non-abstinence) were not associated with any significant clusters.

5.5. OUTCOME PHASE

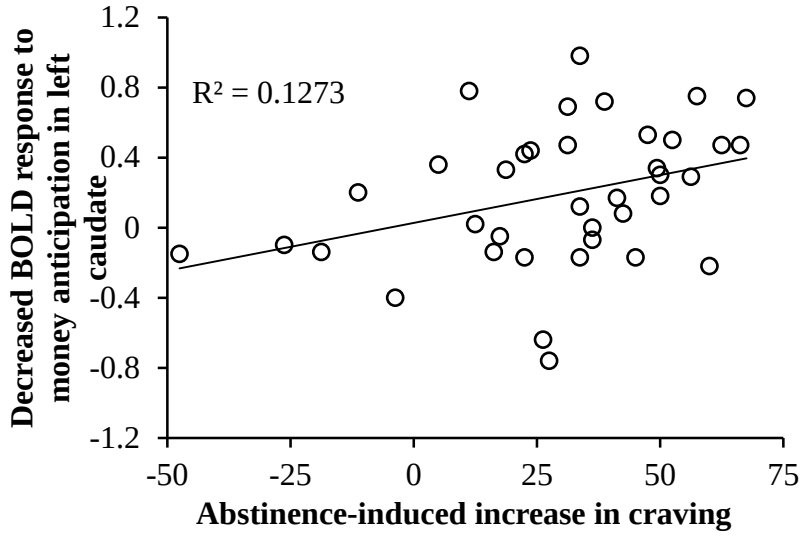
No main effects of abstinence condition were observed either within the striatal ROI or across the whole brain, and there were no significant interactions between abstinence condition and scan order save for a small cluster in the left inferior frontal gyrus (-44, 26, 12; F = 16.81, 38 voxels). Contrary to the anticipation phase, there was no significant abstinence condition x reward type interaction within the striatal ROI. A small, difficult to interpret, cluster of activation emerged in the left parietal cortex for whole brain analyses at a threshold of $p < 0.001$ (-18, -18, 60; F = 15.81, 20 voxels). Two small right parietal cortex clusters were associated with the abstinence condition X reward type X scan order interaction (26, -52, 32; F = 19.12, 51 voxels and 26, -38, 38; F = 26, -38, 38, 28 voxels). As these were small clusters outside of the reward areas implicated in the task, these interactions were not examined further.

Activation associated with abstinence for each reward type was then examined. Within the striatal ROI, response to puff win outcomes was greater during abstinence than non-abstinence in the right caudate head (6, 2, 4; t = 3.12, 70 voxels). An additional small cluster in the thalamus could be seen at $p < 0.001$ across the whole brain (-4, -4, 10; T = 3.59, 37 voxels). There was no effect of abstinence on response to monetary win > no win outcome.

5.6. ASSOCIATIONS WITH CRAVING, WITHDRAWAL, AND NICOTINE DEPENDENCE

Given the significant reward x condition interaction within the bilateral caudate head observed during the anticipation phase of the task, I asked whether abstinence-induced changes in anticipatory activation to each reward type were correlated with severity of nicotine dependence or abstinence-induced changes in craving, mood, or withdrawal. Difference scores were computed characterizing the decrease in anticipatory activation to monetary reward during abstinence and increase in anticipatory activation to smoking reward using values extracted from significant interaction clusters in the right and left caudate head (Figure 12a). I further computed difference scores for subjective measures taken before each scan (except for craving in which we used the average of pre and post-scan QSU-4 scores). In the left caudate, a larger decrease in anticipatory activation to monetary reward during abstinence compared with non-abstinence was associated with greater abstinence-induced increases in craving ($r = .356$, $p < 0.05$; Figure 17a) and withdrawal ($r = .334$, $p < 0.05$; Figure 17b). No association was found with change in positive or negative affect. The association between decreased activation in anticipation of monetary reward and increased withdrawal during abstinence was replicated in the right caudate ($r = .370$, $p < 0.05$); associations with craving, positive affect, and negative affect were non-significant. Surprisingly, the increase in anticipatory activation to smoking reward was unrelated to all measures. Finally, there were no significant associations with nicotine dependence, measured with the FTND, NDSS, or the WISDM.

a.



b.

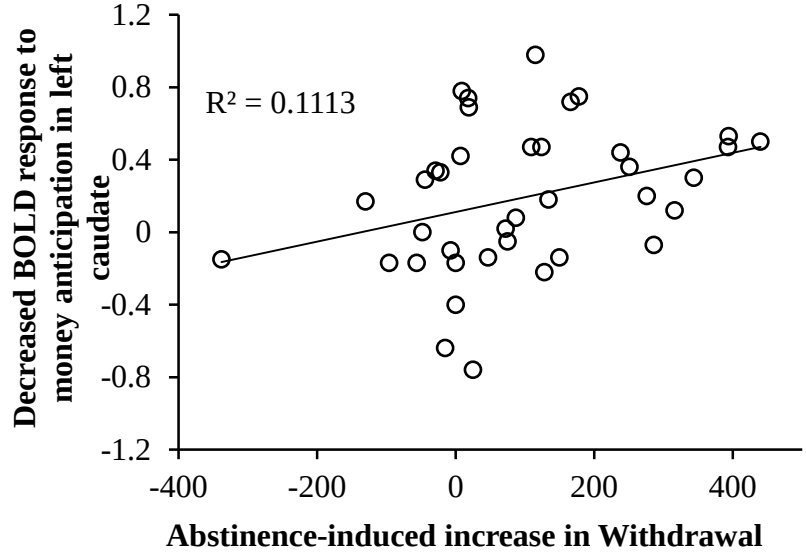


Figure 17. Increased craving and withdrawal during abstinence compared with non-abstinence is associated with decreased anticipatory activation to monetary reward in the left caudate.

a. Association between increase in craving during abstinence and decrease in BOLD response to monetary > neutral anticipation during abstinence, relative to non-abstinence. Decrease in BOLD response is expressed as eigenvariate extracted from non-abstinent scans minus abstinent scans. ***b.*** Association between increase in withdrawal during abstinence and decrease in BOLD response to monetary > neutral anticipation during abstinence relative to non-abstinence.

5.7. SUMMARY AND CONCLUSIONS

Given that smoking and monetary rewards were shown to activate common neural pathways within the reward task used in this study, I next turned to examine the effects of abstinence on processing of each reward type. As expected, I found that abstinence contributed to both heightened activation in anticipation of smoking rewards and attenuated activation in anticipation of monetary rewards. This interaction was particularly robust within the striatal ROI, but also extended to additional reward-related regions, including the brainstem, right insula, and ACC extending to the mPFC. Together, bias throughout this circuitry toward smoking reward during abstinence may contribute to a powerful motivation to smoke at the expense of other rewards.

Although a few previous studies have observed abstinence-induced changes within reward-relevant circuitry for monetary reward or smoking cues separately (Addicott et al., 2012; Gloria et al., 2009; McBride et al., 2006; McClernon et al., 2009), this study is the first to demonstrate parallel, dissociated effects of abstinence on processing of both types of rewards within the same paradigm. These results differ from a previous study that examined effects of smoking withdrawal on motivation to obtain both monetary and smoking rewards but failed to find significant changes beyond a small cluster in the mPFC showing heightened activation in anticipation of both reward types during abstinence (Buhler et al., 2010). Although lack of a comparable interaction effect to that seen here is somewhat surprising, the increased power from the larger sample size in the present study may have enabled detection of effects missed in other studies.

Data extracted from interaction clusters in the bilateral striatum and brainstem indicated a significant decrease in monetary reward anticipation during abstinence; however, contrasts evaluated within SPM indicated that this effect was only evident at sub-threshold levels in a very small, medial portion of the right striatum. Because analyses of extracted data relied on the eigenvariate, which characterizes activation across the region of selected voxels as a single, most representative value, this approach may have minimized voxel to voxel variability, thereby increasing the ability to detect a significant effect through reduction of error. The lack of strong monetary reward effects observed within SPM makes it difficult to draw firm conclusions from conjunction analyses indicating only a few voxels of overlap between dissociated effects for each reward type. Thus, it remains unclear the extent to which increased anticipation of smoking reward and decreased anticipation of monetary reward during abstinence are occurring in overlapping regions.

Nonetheless, it is clear that the increased responsiveness to smoking reward during abstinence is a much more robust, widespread effect. Indeed, the effects of abstinence on response to smoking reward were evident throughout reward-related circuitry, including bilateral caudate, bilateral anterior insula, ACC/mPFC, and left putamen and globus pallidus. The robust effects observed here present a strong contrast with the existing cue reactivity literature indicating weak or inconsistent effects of abstinence (Buhler et al., 2010; David et al., 2007; McBride et al., 2006; McClernon et al., 2009). Larger sample size may have contributed to the ability to detect significant findings in the present study, but it is also likely that task design, incorporating response-contingent reward presentation, provided distinct advantages in engaging

reward circuitry, particular in the striatum where primary effects were observed. Thus, as noted in Chapter 4, it is likely that studies relying solely on passive presentation of smoking stimuli may miss important effects.

The findings of increased anticipatory activation to smoking reward during abstinence compared with non-abstinence also has the potential to shed light on the reward type differences (or lack thereof) in Chapter 4. Specifically, it is likely that the larger area of activation in the mPFC during smoking reward anticipation was driven by increased activation during abstinence, whereas direct comparisons were likely weakened by lower activation during non-abstinence. Similarly, a lack of significant differences between monetary reward and smoking reward anticipation in the striatum may have been detected if tested separately within the non-abstinent condition. Follow-up analyses presented in Appendix B indicate that this is indeed the case.

The dissociation between effects of abstinence on monetary versus smoking rewards observed here raises important questions about potential underlying mechanisms. One possibility is that the pattern of results during abstinence may be the result of altered top-down prefrontal modulation of striatal reward processing. Neurons of the prefrontal cortex are known to project to the head of the caudate (Rolls, Thorpe, & Maddison, 1983), and recent studies have demonstrated altered activation in several prefrontal regions during affective processing or cognitive control tasks among chronic smokers (Froeliger et al., 2013; Nestor, McCabe, Jones, Clancy, & Garavan, 2011). Further evidence suggests that activation in these regions—particularly the anterior cingulate—may be heightened during abstinence (Azizian, Monterosso, O'Neill, & London, 2009; Froeliger, Modlin, Wang, Kozink, & McClernon, 2012), possibly reflecting state-based inefficiency in inhibitory control networks. Thus, diminished prefrontal cognitive control during abstinence may exacerbate bottom-up reward dysregulation favoring

smoking at the expense of other rewards. Janes and colleague (2012) recently found greater medial prefrontal cortex – left frontoparietal connectivity among smokers compared with non-smokers, and enhanced connectivity between these regions and the insula and dorsal striatum—many of the same regions implicated in the present study—was associated with greater striatal response to smoking cues (Janes, Nickerson, Frederick Bde, & Kaufman, 2012). Although it is unknown how connectivity within this circuitry may change as a function of abstinence, it is tempting to speculate that a tighter coupling of these regions during abstinence may give rise to an automatic, habitual response toward smoking reward at the expense of alternative rewards. Further research should explore this possibility.

The fMRI paradigm used in the present study allowed for dissociation of reward anticipation versus outcome. Both phases elicited robust activation within the bilateral striatum. However, the interaction between abstinence condition and reward type was evident only during anticipation. This suggests that reward dysregulation modulated by smoking abstinence preferentially involves incentive motivational processes driving expectation of reward rather than hedonic impact of reward delivery. This is consistent with the central role of incentive motivational processes in drug dependence and suggests that studies failing to separate anticipatory versus outcome phases of reward processing may miss important effects.

Results indicated significant correlations between increased withdrawal symptoms and cigarette craving during abstinence and decreased anticipatory activation to monetary reward. The association with withdrawal was particularly robust, indicating that observed effects were likely due to deprivation rather than acute effects of nicotine delivered prior to the non-abstinent scan. Consistent with previous findings (Wrase et al., 2007), these results highlight the importance of individual differences and suggests that some individuals may be more susceptible

to abstinence-induced changes in reward processing than others. While it is surprising that cigarette craving and anticipation of puff reward were not correlated, the inverse association between reported craving to smoke and anticipatory activation to monetary reward suggests that these alternate rewards may be in competition within common reward-related neural circuitry. Although causation cannot be inferred, the intriguing possibility exists that increasing the salience of alternative rewards could actually diminish motivation to smoke. Indeed, one recent study found that manipulating increased social reward in the context of romantic love led to diminished smoking cue reactivity among abstinent smokers (Xu et al., 2012).

The lack of association between increased craving or withdrawal and increased anticipatory activation to smoking reward during abstinence may be due to ceiling effects limiting variability. As noted above, increased anticipatory activation to smoking reward was quite robust at the group level; thus it seems likely that all participants experienced a relatively strong increase in activation, regardless of subjective craving state or withdrawal symptoms. However, it is also possible that meaningful variability in activation did still occur, but that abstinence-induced craving and withdrawal symptoms are simply unrelated to increased anticipatory activation to smoking reward. Cue reactivity studies have previously demonstrated that abstinence-induced craving and smoking cue-induced craving operate in an additive, rather than interactive manner (Bailey et al., 2009). Although the task employed here was meant to move beyond simple assessment of cue reactivity, it is possible that anticipation of smoking reward and craving during abstinence are simply distinct, unrelated processes.

The present findings may have important implications for smoking cessation. Deprivation from smoking during early stages of a quit attempt may lead to increasing bias toward smoking reward, contributing to greater likelihood of relapse for individuals most

susceptible to these changes. In the next chapter, I turn to a direct test of this hypothesis, analyzing the association between the reward type by abstinence interaction effects observed here and abstinence outcomes during a contingency management-based quit attempt.

6. QUESTION #3: PREDICTING SMOKING CESSATION OUTCOMES

6.1. INTRODUCTION

The third specific aim of this dissertation was to determine whether individual differences in the BOLD response to monetary and smoking rewards, both during abstinence and in the change from non-abstinence to abstinence, predicts the ability to refrain from smoking when given an incentive to do so. Having observed a significant reward type x abstinence condition interaction in the striatum, suggesting an increase in reward dysregulation during abstinence, I next asked whether the magnitude of this abstinence–induced dysregulation predicted abstinence outcomes during the three-week contingency management trial. I hypothesized that individuals exhibiting greater abstinence-induced disruption to reward processing, characterized by a larger increase in striatal BOLD response to smoking reward and a larger decrease in striatal BOLD response to monetary reward, would achieve fewer days of abstinence and be more likely to lapse during contingency management.

By characterizing reward processing as a change from non-abstinent to abstinent state, I am proposing that individuals who are most vulnerable to relapse are those whose reward processing is most disrupted by abstinence, regardless of their baseline starting point. This approach allows for direct targeting of the interaction observed in Chapter 5 and provides the added advantage of controlling for relative scaling of monetary versus smoking reward subjective values, which were not standardized and thus may vary from one individual to the

next. However, it is also possible that the change in reward functioning between abstinence and non-abstinence is not as important as the absolute level of reward functioning during abstinence. It may be that once an individual enters into an abstinent state through initiation of a quit attempt, it is the relative balance of smoking versus alternative rewards at that moment that contributes to behavior, regardless of baseline level of functioning. Thus, I also analyzed the association between BOLD response to monetary and smoking rewards during abstinence and success during contingency management. I predicted that results of these analyses would mirror those using change scores, in that higher BOLD response to smoking reward and lower BOLD response to monetary reward during abstinence would be predictive of fewer abstinent samples and greater likelihood of lapse during contingency management.

Analyses of neuroimaging predictors of abstinence outcomes were restricted to the striatal ROI in general, and to the cluster of voxels demonstrating a significant reward type by abstinence condition interaction specifically. Using data extracted from this region allowed for a focus directly on an area of theoretical importance demonstrating the most robust effects of abstinence, while at the same time minimizing multiple comparisons. Analyses were also restricted to the anticipation phase of the task. This decision had both a theoretical and empirical basis. Addiction has been posited to be a disorder of pathological motivation (Kalivas & Volkow, 2005), such that drug use is overvalued, often in spite of diminished experience of pleasure (Robinson & Berridge, 1993). In practice, the decision to smoke during a quit attempt, particularly when using contingency management, involves weighing expected reward values, which is most akin to anticipation of reward rather than actual reward delivery. Furthermore, abstinence analyses discussed in Chapter 5 revealed interaction effects only during the

anticipation phase of the task, suggesting that this is the most sensitive timing of the task to target further analyses. Thus, I focus on the anticipation phase of the reward task in the analyses described below.

6.2. STATISTICAL ANALYSES

6.2.1. Coding procedures for CM samples

Outcome data for the CM procedure was coded according to self-report and CO readings submitted online during the abstinence phase. In the event that an equipment failure prevented sample submission or led to inaccurate CO readings (discussed in detail below), self-reported smoking data was used. Samples in which participants reported smoking *or* submitted a CO reading falling above the target value were coded as positive; samples in which the participant reported not smoking *and* submitted a CO reading below or meeting the target value were coded as negative. Missing samples not due to equipment problems were coded as missing and were treated as positive for analyses. CO data were summarized for each participant into variables aimed at characterizing abstinence outcomes in two ways: percentage of abstinent samples and longest duration of continuous abstinence. These measures were chosen in order to provide a comprehensive characterization of smoking behavior and are consistent with other studies investigating abstinent outcomes using CM treatment (Dallery et al., 2007; Glenn & Dallery, 2007; Stoops et al., 2009). In addition, given high success rates during the procedure (discussed below), an additional dichotomous outcome variable was created to code for whether or not a

lapse occurred at any point during the procedure. Participants who initiated abstinence on the first day of the quit attempt and maintained continuous abstinence thereafter were considered not to have lapsed.

6.2.2. Predictions of CM outcomes

Predictors of CM outcomes were assessed with logistic regression or spearman correlations for dichotomous and continuous outcome variables, respectively. For logistic regression models, demographic variables, including age and sex were first entered as covariates. Spearman correlations were used instead of linear regression for continuous variables due to non-normal distributions of dependent measures (discussed below). Within this framework, three sets of predictor variables were examined. First, subjective self-report measures were evaluated, including some trait measures (e.g., nicotine dependence) and some state measures (e.g. craving or withdrawal). Change scores between abstinent and non-abstinent conditions were used for state-based predictor variables and total baseline scores were entered for trait-based measures. Change in CO between abstinent and non-abstinent conditions was included as an additional covariate for models examining state-based predictor variables. Next, abstinence-induced changes in anticipatory BOLD activation to monetary and smoking rewards were evaluated as a predictor of CM outcomes. The first eigenvariate was extracted from clusters within the striatal ROI demonstrating significant reward type X abstinence condition interaction, as described in Chapter 5 and shown in Figure 12. Difference scores between abstinent and non-abstinent condition were computed from extracted data for each reward type. Separate models were created for clusters extracted from right and left caudate. Finally, analyses were repeated using absolute levels of anticipatory activation to each reward type during abstinence.

6.3 CONTINGENCY MANAGEMENT RESULTS

6.3.1. Consistency between CO and self-report

Self-reported abstinence was consistent with whether or not target CO level was met for 94.1% of samples submitted by all participations throughout contingency management. Disparities occurred for 5.9% of samples submitted. Of these, 56% of cases involved CO levels that exceeded the target value even though participants self-reported not smoking. Although these were generally coded as non-abstinent and not reinforced, in several instances problems with the CO monitor readings were verified or strongly suspected, such that readings appeared to be artificially high. In these cases, samples were counted as abstinent based on self-report. The remaining 44% involved participants self-reporting smoking despite submitting CO values that met the target value. As noted above, these were coded as non-abstinent and were not reinforced. However, 5 of these samples were incorrectly reinforced due to procedural error. Given that these errors did not result in major disruptions to the overall reinforcement schedule, these were retained and coded as non-abstinent for analyses. One additional sample was entered incorrectly by the participant to indicate a passing CO level, when in fact the sample failed to meet criteria. This was not caught due to procedural error and led to inaccurate reinforcement and a failure to reset the reinforcement schedule, thereby affecting all subsequent samples. Consequently, this participant was excluded from analyses. All exclusion/inclusion decisions and procedures for handling discrepant samples and missing data were made blind to the imaging data.

6.3.2. Missing Samples

Out of 1548 total samples required to be submitted for all subjects throughout the procedure, 109 (7.0%) were missing. All missing samples were treated as non-abstinent for the purposes of reinforcement. However, two subjects were mistakenly reinforced and the schedule was not reset due to procedural error; these subjects were excluded from analyses. Analyses were first conducted with all missing samples coded as non-abstinent. As a secondary follow-up approach, analyses were rerun with missing data manually recoded on the basis of self-report and available data. Specifically, cases where participants did not report smoking and where the 4 previous and subsequent samples were all abstinent were coded as abstinent. Samples without a clear pattern of abstinence or where subjects reported smoking were coded as non-abstinent.

6.3.3. Distribution of CM Outcomes

Overall, participants did remarkably well during the contingency management quit attempt, submitting an average of 30.0 out of 36 abstinent samples, for a mean of 77.7% (SD = 28.7). Distribution of percent abstinence achieved is presented in Figure 18. Longest stretch of continuous abstinence ranged from 1 to 36 samples, with a mean of 21.1 (SD = 13.0) samples. Indeed, 11 participants achieved 100% abstinence, and 14 could be classified as non-lapsers after initiating abstinence on the first day. Recoding missing samples as abstinent based on criteria described above did not substantively change the pattern of results but did result in two additional participants being coded as non-lapsers.

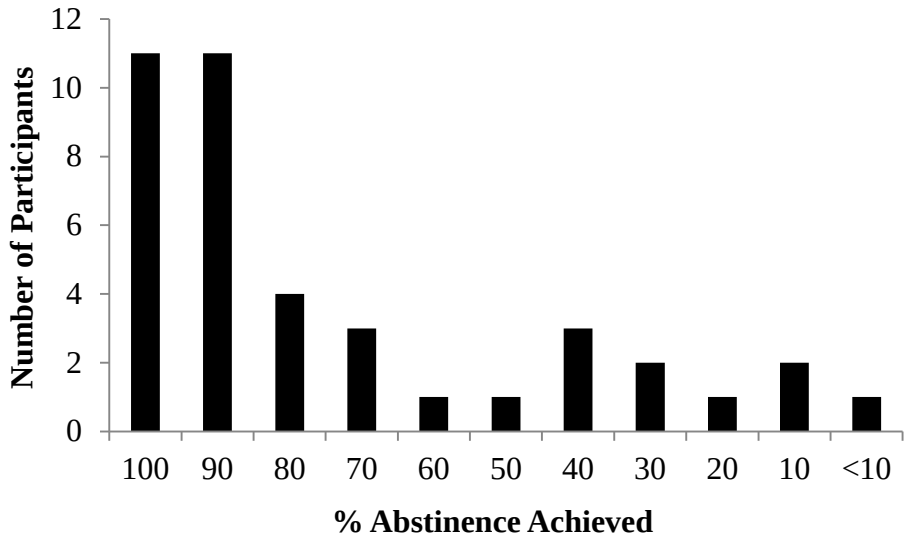


Figure 18. Histogram of percentage abstinence achieved by all participants during contingency management quit attempt.

6.4 PREDICTORS OF CONTINGENCY MANAGEMENT OUTCOMES

6.4.1. Predictors of lapse outcomes

Subjective measures. Demographic variables, including age and sex, were unrelated to lapse outcomes during CM (both *p*'s > 0.50). Measures of nicotine dependence were also unrelated to lapse outcome, although there was a trend toward higher WISDM total scores predicting greater likelihood of lapse ($p = 0.06$; Table 12). Cigarettes smoked per day was also not significantly associated with lapse likelihood, but was in the predicted direction at trend level ($p = 0.06$). Contrary to expectations, greater increase in craving during abstinence compared with non-abstinence was associated with significantly lower likelihood of lapse [Exp(B) = .955, $p < 0.05$]. Increase in withdrawal symptoms was unrelated to lapse outcome. When imputed data was used for missing samples, results were largely unchanged; however, several previously

non-significant variables became significant with the imputed model. Specifically, higher scores on both WISDM and NDSS predicted greater likelihood of lapse [Exp(B) = 1.071 and 1.086, respectively, both *p*'s < 0.05]. Higher number of cigarettes smoked per day also predicted greater likelihood of lapse with the imputed model [Exp(B) = 1.194, $p < 0.05$].

Abstinence-induced changes in reward processing. When controlling for age, sex, and CO change, difference scores from extracted values for money anticipation and puff anticipation from the right caudate added significantly to the model predicting lapse outcomes ($p < 0.05$). Specifically, greater decrease in anticipation of monetary reward during abstinence predicted higher likelihood of lapse [Exp(B) = 11.823, $p < 0.05$] (Figure 19). Greater increase in puff anticipation during abstinence was not significant, but predicted higher lapse likelihood at the trend level [Exp(B) = 5.766, $p = 0.08$]. These predictive associations remained when controlling for the increase in craving during abstinence. Indeed, when all three variables were included in the model, both QSU change score and monetary reward anticipation change scores were significant predictors of lapse (both *p*'s < 0.05), while puff anticipation change remained at the trend level ($p < 0.10$). Extracted values for money anticipation and puff anticipation from the left caudate were not significantly predictive of lapse (both *p*'s > 0.10). However, when increase in craving was also included in the model, monetary reward anticipation change score became significant ($p < 0.05$), with greater decreases in money anticipation during abstinence associated with higher likelihood of lapse. Replicating the findings from the right caudate, greater increases in puff anticipation in the left caudate during abstinence predicted higher lapse likelihood at trend level ($p < 0.10$). Results were unchanged when using the model with imputed missing data.

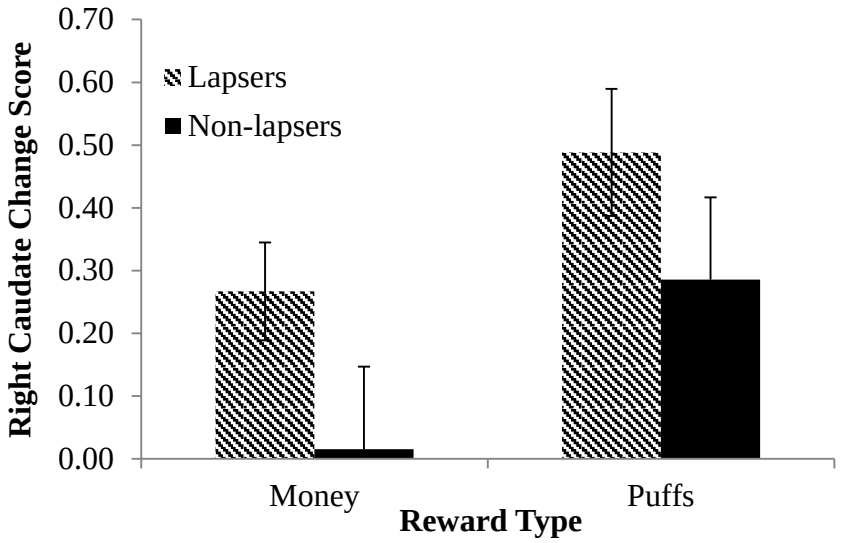
Table 12. Predictors of lapse likelihood during contingency management in logistic regression model, controlling for age, sex, and CO change score.

Variable	*n*	*Exp (B)*	95% Confidence Interval	*p*-value
Fagerstrom Test of Nicotine Dependence*	40	1.257	(.911 – 1.733)	.163
Nicotine Dependence Syndrome Scale*	40	1.058	(.982 – 1.140)	.132
WISDM*	40	1.059	(.998 – 1.124)	.060
Cigarettes smoked per day*	40	1.135	(.993 – 1.297)	.064
QSU-4 Change Score	40	.955	(.918 - .993)	.732
MNWS Change Score	40	1.001	(.996 – 1.005)	.021
Right Caudate Money Change Score	35	11.823	(1.085 – 128.795)	.043
Right Caudate Puff Change Score	35	5.766	(.653 – 30.253)	.083
Left Caudate Money Change Score	35	4.049	(.507 – 32.357)	.187
Left Caudate Puff Change Score	35	4.444	(.653 – 30.253)	.127
Right Caudate Money (Abstinent)*	35	.596	(.093 – 3.805)	.584
Right Caudate Puff (Abstinent)*	35	.703	(.062 – 7.193)	.776
Left Caudate Money (Abstinent)*	35	.800	(.089 – 7.193)	.842
Left Caudate Puff (Abstinent)*	35	.730	(.057 – 9.314)	.808

Abbreviations: WISDM-Wisconsin inventory of smoking dependence motives (CITE); QSU-4-Questionnaire of smoking urges, 4 item version (Toll et al., 2006); MNWS-Minnesota Withdrawal Scale (Hughes & Hatsukami, 1986) Note: Change scores represent difference between abstinence and non-abstinence, with valence reflecting positive direction

*CO change score not included in model

a.



b.

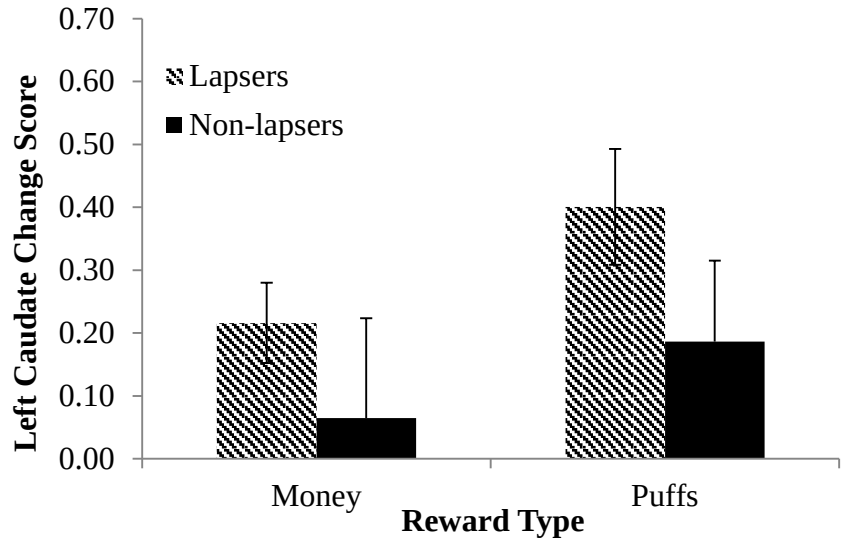


Figure 19. Abstinence-induced changes in striatal anticipatory activation for each reward type for those who did and did not lapse during contingency management quit attempt.

Change in activation in anticipation of monetary and smoking rewards as a function of abstinence for lapsers and non-lapsers during contingency management quit attempt. Change scores reflect decreases in monetary reward anticipation and increases in puff reward anticipation during abstinence relative to non-abstinence, with data extracted from clusters showing significant reward type x condition interaction in the right caudate (a) and left caudate (b).

Reward processing during abstinence. When controlling for age and sex, extracted values for money anticipation and puff anticipation from the right caudate during abstinence did not significantly add to the model predicting lapse outcomes (all *p*'s > 0.50). Extracted values from the left caudate were similarly not predictive. This was quite surprising given that difference scores between non-abstinence and abstinence for monetary reward anticipation in the right caudate had been significant. The lack of even marginal effects during abstinence suggested that variance accounted for by change scores may have been due to individual differences during the non-abstinent state. Thus, although not an original part of the analytic plan, I followed up non-significant findings during abstinence with analyses conducted from the non-abstinent state.

Reward processing during non-abstinence. Again controlling for age and sex, extracted values for money anticipation and puff anticipation from the right caudate during non-abstinence added significantly to the model predicting lapse outcomes ($p < 0.05$). Anticipatory activation to monetary reward during non-abstinence was nearly significant, with higher activation predicting higher likelihood of lapse [Exp(B) = 19.322, $p = 0.052$]. Conversely, higher anticipatory activation to smoking reward during non-abstinence significantly predicted lower lapse likelihood [Exp(B) = .042, $p < 0.05$] (Figure 20). These findings were partially replicated in the left caudate, with extracted values for money anticipation and puff anticipation together significantly adding to the model predicting lapse ($p < 0.05$). Higher anticipatory activation to smoking reward was associated with lower likelihood of lapse [Exp(B) = .043, $p < 0.05$]. Anticipatory activation to monetary reward in the left caudate was non-significant. When using the model with imputed data, monetary reward anticipation in the right caudate became

significant ($p < 0.05$), while smoking reward anticipation became significant only at trend level ($p = .057$). In the left caudate, use of the imputed model led to non-significant findings for both puff and monetary rewards (both p's > .10).

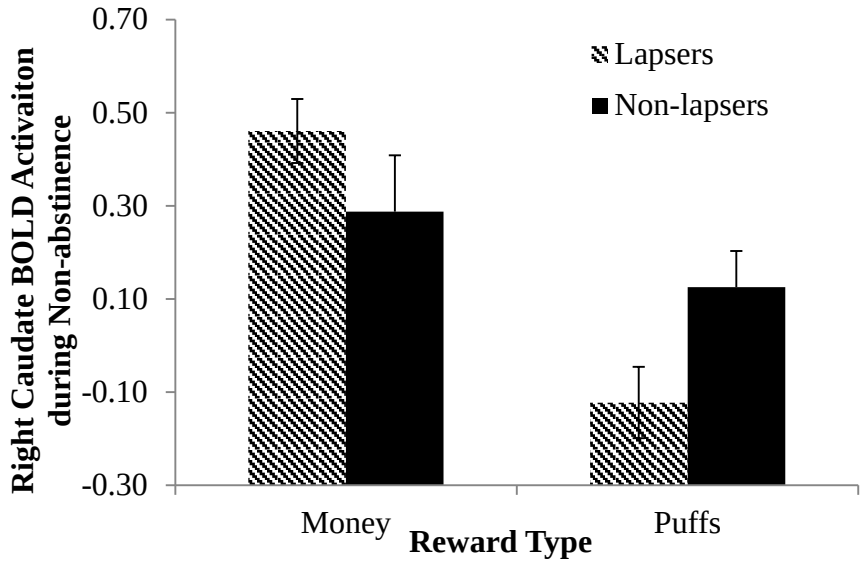


Figure 20. Striatal anticipatory activation to monetary and smoking rewards during non-abstinence for those who did and did not lapse during contingency management quit attempt.

Activation in anticipation of monetary and smoking rewards during non-abstinence for lapsers and non-lapsers during contingency management quit attempt, with data extracted from clusters showing significant reward type x condition interaction in the right caudate.

6.4.2. Predictors of percent abstinence and longest stretch of abstinence

Subjective measures. Spearman correlations between subjective and imaging measures and CM outcomes are presented in Table 13. Higher scores on the NDSS and higher number of cigarettes smoked per day were both associated with lower percentage of abstinent samples but

were unrelated to longest stretch of continuous abstinence. Consistent with predictions of lapse outcome, greater increases in craving during abstinence relative to non-abstinence were associated with higher percentage of abstinence and longer stretches of continuous abstinence. FTND and increases in withdrawal symptoms were unrelated to CM outcomes. As with predictors of lapse outcomes, results were largely unchanged when using the model with imputed missing data, with a few exceptions. Higher scores on NDSS were associated with significantly shorter stretches of abstinence (r = -.332, $p < 0.05$). Similarly, higher scores on the WISDM were associated with lower percentage abstinence (r = -.325, $p < 0.05$) and shorter stretches of continuous abstinence (r = -.355, $p < 0.05$).

Abstinence-induced changes in reward processing. Changes in extracted BOLD signal in anticipation of monetary and smoking reward as a function of abstinence were not associated with percentage abstinence or longest stretch of abstinence during contingency management (all p's > 0.10). This lack of association was consistent across both right and left caudate and when both the conservative and imputed models were used.

Reward processing during abstinence and non-abstinence. Extracted BOLD values from anticipation of monetary and smoking reward during abstinence were not associated with percentage abstinence or longest stretch of abstinence during contingency management (all p's > 0.10). This lack of association was consistent across both right and left caudate and when both the conservative and imputed models were used. Similar non-significant findings were observed for the non-abstinent state.

Table 13. Spearman correlations between subjective and imaging measures and abstinence outcomes during contingency management quit attempt.

Variable	*n*	% Abstinent Samples	Longest Continuous Abstinence
Fagerstrom Test of Nicotine Dependence	40	-.254	-.139
Nicotine Dependence Syndrome Scale	40	-.316*	-.253
WISDM	40	-.283	-.280
Cigarettes smoked per day	40	-.313*	-.160
QSU-4 Change Score	40	.458**	.439**
MNWS Change Score	40	.045	.081
Right Caudate Money Change Score	35	-.166	-.184
Right Caudate Puff Change Score	35	.100	.067
Left Caudate Money Change Score	35	-.092	-.072
Left Caudate Puff Change Score	35	.136	.098
Right Caudate Money (Abstinent)	35	.060	.181
Right Caudate Puff (Abstinent)	35	.220	.169
Left Caudate Money (Abstinent)	35	.003	.075
Left Caudate Puff (Abstinent)	35	.257	.207

Abbreviations: WISDM-Wisconsin inventory of smoking dependence motives (CITE); QSU-4-Questionnaire of smoking urges, 4 item version (Toll et al., 2006); MNWS-Minnesota Withdrawal Scale (Hughes & Hatsukami, 1986); PANAS-Positive and Negative Affect Scale (Watson et al., 1988).

Note: Change scores represent difference between abstinence and non-abstinence, with valence reflecting positive direction

6.5. SUMMARY AND CONCLUSIONS

Individual differences in anticipatory activation to smoking and monetary rewards and their association with abstinence outcomes during a quit attempt were examined using an internet-based contingency management protocol. Results indicated that compliance with the procedure was excellent, and participants tended to achieve generally high levels of abstinence throughout the program. Indeed, frequency of abstinent samples was higher than expected, such that variability in outcomes was somewhat limited. This could have been due to several factors: First, although the reinforcement schedule was based on the existing literature to maximize variability, it is possible that the incentives were high enough to persuade most people to refrain from smoking for a period of three weeks. Changes in economic conditions during recession could have increased the salience of the monetary reinforcement, particularly if rewards were being used for such critical items as paying rent (as some participants admitted to). Increasing restrictions on smoking may have aided participants in abstaining, and liberal inclusion criteria of 5 cigarettes per day (designed for convenience and to increase variability) may have combined to allow participants to quit smoking with relative ease during the designated period. Furthermore, the requirement to achieve 24 hours of abstinence prior to one of the fMRI sessions led to exclusion of 3 participants who could not meet criteria. Thus, the study design may have selected for subjects who were better able to achieve, and potentially maintain, abstinence.

Despite these limitations, several significant associations between predictor variables and abstinence outcomes were observed. Consistent with my primary hypothesis, greater abstinence-induced decreases in monetary reward anticipation in the caudate predicted higher likelihood of lapse after initiating abstinence. This effect was only observed in the right caudate and was not

observed in association with continuous outcome measures. However, this intriguing finding suggested that decrements in processing of non-drug rewards during abstinence relative to non-abstinence may directly impact smoking behavior. Intuitively, it seems likely that participants showing greater decrements in monetary reward processing during abstinence may have been less responsive to incentives for abstinence during CM. However, follow-up analyses examining abstinent and non-abstinent conditions separately suggested an alternative interpretation. Absolute levels of anticipatory activation during abstinence were not predictive of CM outcomes, suggesting that it was not the variation during abstinence itself that mattered. As noted above, this could but due to individual differences in scaling between the two reward types, since relative valuation of rewards was not standardized. Examining difference scores instead of absolute levels of activation during abstinence is one way of controlling for variability that might otherwise have contributed to error.

However, further exploration of variability during the non-abstinent condition suggested that meaningful variation was occurring when looking at absolute levels of activation—just not in the way that was predicted. Higher anticipatory activation to monetary reward and lower anticipatory activation to smoking reward during non-abstinence were both associated with higher lapse likelihood. If non-abstinence is considered as a "baseline" condition, then this result is quite surprising. If anything, the opposite effects might be expected, such that individuals with a higher baseline response to smoking reward and a lower baseline response to monetary reward might be most at risk. However, it is important to note that participants smoked immediately before the non-abstinent scan. Thus, rather than reflecting a baseline condition, it is possible that we are instead observing individual differences in the acute effects of nicotine. Given that acute nicotine has been shown to enhance the reinforcing value of other non-drug rewards (Caggiula et

al., 2009; Donny et al., 2003), then it is possible that those who are experiencing the greatest enhancement effects of nicotine may be most vulnerable to relapse when those effects are removed, possibly due to past learning processes that have more strongly reinforced smoking behavior. While this interpretation cannot be tested directly within the present study, it suggests an important area for future investigation.

In addition to fMRI reward processing variables, several self-report measures significantly predicted CM outcomes. Perhaps most striking and robust, increased craving during abstinence was associated with lower likelihood of lapse, higher percentage of abstinent samples, and longer stretch of continuous abstinence. This finding seems counterintuitive, particularly as several studies have demonstrated associations between increased craving and poorer abstinence outcomes in laboratory-based studies and smoking cessation trials (Baker et al., 2012; Bold, Yoon, Chapman, & McCarthy, 2013; Sweitzer et al., 2012; Van Zundert, Ferguson, Shiffman, & Engels, 2012). However, some controversy exists in the literature regarding the role of subjective craving in predicting relapse, with a recent meta-analysis demonstrating relatively weak and inconsistent findings (Wray, Gass, & Tiffany, 2013). Indeed, some theorists posit that as nicotine dependence develops, smoking behavior becomes increasingly automatized, becoming more stimulus-bound and habit-driven, and requiring less conscious cognitive awareness (Everitt & Robbins, 2013; Tiffany & Carter, 1998). From this viewpoint, craving is not a necessary factor precipitating relapse, as performance of the overlearned habit of smoking is likely to occur without conscious, volitional choice. The present findings raise the possibility that, when given sufficient external incentives to abstain from smoking, increases in craving during abstinence may actually be a protective factor. Although speculative, it is possible that greater conscious awareness of a craving state may have served as

a signal to participants to marshal additional resources to protect against potential lapse, thereby guarding against a habitual return to smoking. While this possibility is intriguing, it is important to note that craving was not actually measured during the CM quit attempt, and thus abstinent scores do not necessarily reflect the experience of craving during smoking cessation. Future studies would be necessary to further explore the relationship between craving, automaticity, and smoking relapse during CM.

In addition to craving, several other measures significantly predicted abstinence outcomes, including WISDM, NDSS, and cigarettes smoked per day. As expected, higher levels of dependence and higher number of cigarettes smoked per day were both associated with poorer abstinence outcomes; however, these were less robust than the craving associations and depended upon which outcome measure and which model was being tested. These findings are consistent with previous smoking cessation studies (Piper et al., 2008) and suggest that the limited variability that was present in the CM outcome data likely reflected meaningful differences in the ability to abstain from smoking when provided with incentives for abstinence. Given limitations of the data, including restricted range of outcomes and potential sources for error (e.g., equipment problems, reinforcement errors, missing samples), replication of previous findings lends credibility to the more novel, preliminary neuroimaging findings discussed above.

Even so, it is important to note that the findings of neuroimaging predictors of abstinence outcomes supporting my primary hypotheses will require replication in a larger sample. The present sample size—although a strength for within-subject comparisons presented in Chapter 5—was somewhat limited for questions of individual differences in smoking cessation outcomes. Futhermore, although multiple comparisons were partially constrained by restricting analyses to data extracted from the *a priori* ROI, more stringent correction for multiple comparisons was not

applied. Given the small sample size and exploratory nature of the question, further control for multiple comparisons would have required limiting analyses to provide only a partial picture of the data or inflating Type II error. Thus, particularly given the relatively inconsistent findings demonstrated here, it is possible that significant results were due to type I error rather than true effects, and further research will be needed to confirm and further clarify the results.

In sum, although limitations were present in the CM outcome data, exploratory analyses provided several suggestive findings that may be potential avenues for future research. Most intriguing is the possibility that greater changes in reward functioning between abstinence and non-abstinence, whether due to stronger abstinence-induced dysregulation or nicotine-induced enhancement effects—is associated with greater vulnerability to relapse during a quit attempt. Summary and implications of these findings, integration with the previous two chapters, and potential future directions are discussed in the next chapter.

7. GENERAL DISCUSSION

7.1. SUMMARY AND IMPLICATIONS

The primary aims of this dissertation were to characterize the neural response to smoking and non-smoking rewards among chronic smokers within the same paradigm, to evaluate the impact of deprivation on the neural response to both smoking and monetary rewards, and to evaluate the association between neural responses to both reward types and the choice to smoke in lieu of alternative reinforcement during a quit attempt. With regard to the first objective, I hypothesized that anticipation and delivery of both smoking and monetary rewards would elicit significant BOLD activation in the striatum and throughout associated reward circuitry. This exploratory hypothesis was supported, demonstrating robust effects of a novel task incorporating both rewards into the same model and suggesting that, when presented within a common framework, smoking and monetary rewards were remarkably similar in the circuitry they engaged. These findings, although not surprising, extended the existing literature by merging what has previously been two relatively separate areas of research and established a framework for examining more nuanced aspects of reward processing that may contribute to nicotine dependence or smoking behavior.

Given the lack of regional specificity for monetary versus smoking rewards, two criticisms could be levied against the first aim of the present study. First, it could be argued that, as rewards presented within the scanner were largely symbolic (i.e., no actual rewards were

delivered until after the scan), similarities in activation patterns were simply an indication that participants were not fully processing the stimuli as distinct, separate reward types. No behavioral correlate was collected in the scanner and subjective ratings of each reward type were not assessed. However, both monetary and smoking reward types robustly activated reward-related circuitry relative to neutral trials, indicating that participants were engaged in the task and processing differences between each trial type. Furthermore, the observed differential response to abstinence for monetary versus smoking rewards provides a strong indication that the task was functioning as intended and monetary and smoking rewards were being separately processed and evaluated. Second, it is possible that the analytic strategy used here was insufficient to detect reward type differences that were actually present. A recent study addressing a similar question found regional specificity in the insula for smoking stimuli compared with other affective stimuli based on extraction of BOLD signal from significant clusters and comparisons of peak activation across the time course (Versace et al., 2011). While it is certainly possible that this approach might have yielded significant findings when comparing reward types, the present analyses were meant to be exploratory and to provide a foundation for subsequent analyses. Follow-up analyses presented in the Appendix B did suggest reward type differences, including greater activation for smoking reward in the mPFC and greater activation to monetary reward in the striatum, but these effects were dependent on deprivation state. These findings provide support for the current approach but reinforce the need for considering factors such as abstinence state for understanding the complexity of reward processing among chronic smokers.

With regard to abstinence, I hypothesized that deprivation from nicotine would lead to dissociated effects for each reward type, with BOLD response to anticipation and delivery of smoking reward increasing and BOLD response anticipation and delivery of monetary reward

decreasing during abstinence relative to non-abstinence. These hypotheses were partially supported, with predicted effects emerging in the striatum and other reward-related regions during the anticipation phase of the task but not during the outcome phase. These findings are consistent with existing theories and behavioral evidence that have observed each of these effects happening separately (Dawkins et al., 2007; Koob & Le Moal, 2008; McBride et al., 2006; McClernon et al., 2009; Sweitzer et al., 2012). However, the present study is the first to provide evidence that these processes are occurring simultaneously, within the same brain regions. It is important to note that, although data extracted from clusters exhibiting a significant reward type by abstinence condition interaction in the striatum indicated a simultaneous decrease in anticipatory activation to monetary reward and increase in anticipatory activation to smoking reward during abstinence, analyses conducted within SPM revealed a significant abstinence effect only for smoking reward. Nonetheless, a clear overall shift occurred in the valuation of smoking rewards relative to monetary rewards as a function of abstinence, with potentially important implications for individuals attempting to quit smoking. Indeed, given the challenges associated with smoking cessation, the alterations in reward processing observed here suggest a novel area of future research that may help to illuminate a pathway of risk.

Finally, I hypothesized that BOLD response to both types of reward—specifically heightened response to smoking reward and blunted response to monetary reward during abstinence and as a change from non-abstinence to abstinence—would be associated with greater difficulty abstaining from smoking when making a quit attempt supported by contingency management. These hypotheses were partially supported: greater abstinence-induced decreases in striatal activation during monetary reward anticipation predicted a higher likelihood of lapse during the quit attempt. However, further exploration of activation patterns during abstinence

and non-abstinence suggested a more complex picture. In particular, higher anticipatory activation to monetary reward and lower anticipatory activation to smoking reward during non-abstinence were associated with greater likelihood of lapse. These findings raise important questions about the driving force behind the changes between non-abstinence and abstinence. Specifically, it is unclear whether observed changes are actually due to deprivation from nicotine, possibly unmasking an underlying reward dysregulation that is not always apparent when smokers are actively smoking, or whether it is the acute effects of smoking just prior to the non-abstinent scan that led to an enhancement of reward functioning. Although the theoretical framework for this dissertation was based on the notion that reward dysregulation among chronic smokers may become more pronounced under conditions of deprivation (Kenny & Markou, 2006; Koob & Le Moal, 2008), evidence also suggests that nicotine serves a reinforcement enhancing role under conditions of acute exposure (Caggiula et al., 2009; Donny et al., 2003). Thus, it is possible that both mechanisms contributed to the differences between abstinence and non-abstinence observed here, and a true "baseline" condition was not achieved. It is interesting to note that previous studies demonstrating nicotine enhancement effects have been largely based on behavioral evidence from nicotine-naïve human and animal subjects (Barr et al., 2008; Donny et al., 2003; Thiel et al., 2009). Thus, the present results suggest potentially important extensions of the existing literature, including demonstration of nicotine enhancement at the neural level among chronic smokers, with implications for smoking behavior. Although speculative at present, the current findings present the intriguing possibility that those most susceptible to nicotine's reinforcement-enhancing effects may be most vulnerable to relapse during a quit attempt, suggesting an important mechanism that could place some individuals at greater risk. While this cannot be clearly differentiated given the current study design, investigation of

enhancement versus deprivation effects may be an important area of future research.

Relatedly, the present study was unable to differentiate between effects of smoking and effects of nicotine per se. Abstinent and non-abstinent conditions differed not only in terms of the amount of recent nicotine exposure but also in terms of the act of smoking itself. This design was intended to maximize differences between conditions and simplify study protocol, but it leads to important caveats in interpretation. Participants were not blinded to their abstinence state, and so it is possible that placebo effects contributed to differences between conditions. Furthermore, evidence suggests that behavioral and sensory aspects of smoking, as well as other constituents of tobacco smoke, play an important role in maintaining smoking behavior (Perkins et al., 2001; Rose, Behm, Westman, & Johnson, 2000; Shahan, Bickel, Madden, & Badger, 1999). Thus, the current study cannot distinguish between effects of nicotine and the other complex factors associated with smoking a cigarette. Future studies employing either regular versus low nicotine content cigarettes or nicotine versus placebo patches are needed to parse out the relative contributions of nicotine versus other factors.

7.2. LIMITATIONS

As noted above, this dissertation had several important strengths. The novel task design allowed for monetary and smoking rewards to be presented within a common framework, thereby merging relatively distinct literatures and allowing two separate theories to be tested simultaneously. Given the complexity of reward processing, this study provided the benefit of a more comprehensive assessment of reward processing, extending beyond the cue reactivity literature and encompassing different reward types, different phases of reward anticipation and

delivery, and different abstinence conditions. Furthermore, the sample size used here was nearly double that of typical fMRI studies in the field addressing similar questions, thereby providing much greater power to detect smaller effects such as the reward type by condition interaction found here.

Despite these strengths, several limitations should also be noted. First, this study was limited by lack of a non-smoking control group, as the inclusion of smoking reward in the task design made use of a comparable task for non-smokers unfeasible. This prevents inference about whether smokers actually exhibit hypersensitivity to smoking reward or hyposensitivity to monetary reward relative to healthy controls as would be expected according to incentive sensitization and opponent-process theories. One other study described above, incorporating both smoking and monetary rewards to address a similar question, included a group of non-dependent, occasional smokers as a control group (Buhler et al., 2010). They found greater striatal anticipatory activation to monetary reward than to smoking reward among non-daily smokers but no differences between reward types among daily, dependent smokers. While the present analyses focused instead on effects of abstinence, a similar approach including a non-dependent control group may have shed further light on the question of enhancement versus deprivation and enriched the overall theoretical discussion of reward dysregulation among chronic smokers.

A second limitation noted above is that relative values of smoking and monetary rewards were not directly equated. This lack of standardization could have affected the results in different ways for each set of analyses. Had smoking reward failed to engage reward-related circuitry in the first set of analyses, it would have been unclear whether this was due to differences in the nature of the reward type or a vastly lower subjective valuation compared with

monetary reward. However, even if the subjective valuation of these rewards was unequal, the within-subjects abstinence condition comparisons conducted in the second set of analyses suggested that the *relative* balance of incentive properties of these rewards shifted as a function of abstinence in favor of heightened incentive motivation for smoking. Thus, changes during abstinence could be detected and interpreted, regardless of the overall starting point. As noted above, lack of standardization could have been more problematic when examining individual differences in reward functioning and associations with abstinence outcomes. While use of difference scores between abstinence and non-abstinence provided some control for inter-individual variability in subjective valuation, this also came with the trade-off of limiting interpretability. Future studies could either directly equate reward types or explicitly measure subjective valuation to reduce this potential confound.

As noted above, several limitations were apparent when analyzing contingency management data. Skewed outcome data and small sample size may have limited the ability to detect effects. In addition, substantial unmeasured variance in terms of intrinsic motivation may have contributed to error. Although participants were all non-treatment seeking at the start of the study, some individuals may have decided as the study progressed to use the cessation trial as an opportunity to quit smoking, particularly after demonstrating that they could abstain for 24 hours prior to the abstinent fMRI scan. Indeed, although combining an fMRI portion of the study with a smoking cessation attempt was a strength of the study, allowing for preliminary investigation of neural predictors of cessation success, the two phases of the study may have influenced each other in unintended ways. For example, it is unclear what effect, if any, the practice of abstaining from smoking for 24 hours prior to the abstinent scan may have had on subsequent cessation success during contingency management. Conversely, it is unclear how the knowledge

of an impending quit attempt may have impacted neural processing of rewards, as previous studies have shown that smoking expectancies and intentions to quit can influence reward processing pathways (Wilson et al., 2008; Wilson, Sayette, & Fiez, 2012). Although a minimum time frame of 3 days was imposed between the second scan and the quit date to minimize carry-over effects, these concerns could not be completely eliminated given the study design. Relatedly, given that the study specifically recruited non-treatment seekers, it is unclear how well the present results will generalize to smokers trying to quit. This could be of particular importance given the implications for smoking cessation and treatment success.

An additional consideration is that, although theoretically guided, analyses of individual differences and predictions of CM outcomes were restricted to the striatal ROI. While this allowed for some constraint on multiple comparisons and alpha inflation, some potentially relevant regions were omitted. For example, insula activation to smoking cues has previously been found to correlate with craving (Tang, Fellows, Small, & Dagher, 2012) and has been shown to be predictive of relapse (Janes et al., 2010). Thus, important effects within this region and other associated areas may have been missed by focusing solely on the striatum. Given preliminary positive findings, future studies could extend analyses to additional interconnected regions.

7.3. FUTURE DIRECTIONS

The findings in this dissertation suggest several important areas for future research. Given the network of reward-related regions shown to be activated by the task and the intriguing findings of dissociated effects of abstinence on anticipation of monetary versus smoking rewards, future

work could use network analysis strategies to examine connectivity across these regions. Such strategies may shed light on potential mechanisms, such as changes in regulatory prefrontal control, that might contribute to the abstinence effects observed here. Future work should also extend the present investigations examining the effect of reward processing on smoking behavior and smoking cessation. Preliminary findings within the present study were promising but require replication given the limitations of the CM data. Furthermore, addressing these questions with treatment seekers who may be using other smoking cessation strategies is important for generalization and could have important implications. For example, it is possible that individuals exhibiting greater shifts in reward processing as a function of abstinence may be most responsive to nicotine replacement or other pharmacotherapy for smoking cessation. Greater understanding of mechanisms contributing to relapse within treatment seeking populations could ultimately help to tailor smoking cessation strategies to target specific vulnerabilities.

Relatedly, future work could examine genetic factors contributing to variation in reward processing among chronic smokers. Polymorphisms of genes within the dopamine system are likely candidates, given the central role of dopamine in reward processing. For example, the A1 allele of the *DRD2/ANKK1 TaqIA* gene has been associated with risk for increased smoking (Comings et al., 1996), faster progression of smoking in adolescents (Audrain-McGovern, Lerman, Wileyto, Rodriguez, & Shields, 2004), and reduced likelihood of abstinence after one year (Styn et al., 2008). Carriers of the A1 allele have previously been shown to exhibit an enhanced BOLD response to monetary rewards in the striatum, ACC, and OFC in the presence of a dopamine agonist (Cohen, Krohn-Grimberghe, Elger, & Weber, 2007), suggesting they may be more susceptible to the neuropharmacological properties of stimulants like nicotine and,

consequently, more likely to experience stronger enhancement effects or develop abstinence-induced reward deficits (Koob & Le Moal, 1997, 2001). Further elucidating the links between genetic markers, neural pathways, and smoking behaviors can ultimately help to improve treatment and prevention efforts.

As noted above, the present findings established strong effects of abstinence versus acute exposure on anticipatory responding to monetary and smoking rewards. However, further work is needed to clarify whether this is due to enhancement effects of nicotine or deprivation effects due to abstinence. To the extent that deprivation does contribute to observed effects, it would also be interesting to examine the duration of effects of deprivation beyond the single 24 hour time point used here to determine whether reward dysregulation recovers after a period of protracted abstinence. Furthermore, future studies could employ a placebo-control design to differentiate effects of smoking from pharmacological effects of nicotine itself. Further investigation of the association between individual differences in these processes and the decision to smoke could also be accomplished through laboratory-based procedures that allow for a cost-effective, targeted assessment of the relative reinforcing value of smoking versus alternative rewards. Indeed, several previous studies have explored smoking lapse and relapse using a variety of laboratory-based models (Chornock, Stitzer, Gross, & Leischow, 1992; Leeman, O'Malley, White, & McKee, 2010; Mueller et al., 2009; Sweitzer, Denlinger, & Donny, 2013), and these could be easily adapted to use in conjunction with fMRI assessment.

The present study focused on monetary and smoking rewards. Another intriguing area of future research is exploration of additional reward types that may by altered among chronic smokers as a function of abstinence. Food reward may be particularly relevant given that studies suggest smoking and food cues activate comparable circuitry (Tang et al., 2012), and smokers

frequently experience weight gain following smoking cessation (Hudmon, Gritz, Clayton, & Nisenbaum, 1999; Killen, Fortmann, & Newman, 1990; Klesges et al., 1997). Increasing research has been focusing on the role of reward pathways in obesity (Tomasi & Volkow, 2013; Volkow, Wang, Fowler, Tomasi, & Baler, 2012), and it is likely that reward dysregulation among chronic smokers may also affect neural response to food rewards. The ability for sensitization to drug reward to generalize to other appetitive stimuli has been proposed by incentive sensitization theory (Robinson & Berridge, 2008), but this has rarely been investigated in humans. Thus, it remains unclear whether food reward may function similarly to monetary reward as an "alternative reinforcer" that elicits an attenuated anticipatory response during abstinence, or if food reward may take on heightened incentive properties similar to smoking reward during abstinence. A recent study found that repeated amphetamine pretreatment resulted in incentive sensitization of food reward in rats (Mendez et al., 2009), suggesting that drug exposure may indeed sensitize the incentive value of food rewards. However, parallel processes have not been evaluated in human smokers. If this sensitization process were occurring, response to food reward may be heightened during abstinence from smoking and may predict choice behavior in laboratory procedures involving food or weight gain following smoking cessation.

A final consideration is that the abstinence-induced alterations in reward processing observed here may be particularly important for individuals with comorbid psychiatric disorders, including depression and attention-deficit hyperactivity disorder (ADHD). Regular tobacco smoking and nicotine dependence are over-represented among individuals with depression or ADHD (Johnson, Rhee, Chase, & Breslau, 2004; Kessler et al., 2006), and differences in reward processing pathways relative to healthy controls have been implicated in both disorders (Epstein

et al., 2006; Forbes et al., 2009; Strohle et al., 2008). Given the central role of anhedonia in depression, it is possible that abstinence-induced attenuations in response to monetary reward may be particularly pronounced among individuals with depression and may place these individuals at greater risk for relapse. Future work could employ the paradigm used here to evaluate reward processing deficits among smokers with depression and other psychiatric disorders.

In conclusion, this dissertation presented a novel approach to evaluating reward processing among chronic smokers by combining monetary and smoking rewards within the same paradigm. Results revealed common circuitry engaged by each reward type, robust effects of abstinence within key reward-related regions, and preliminary evidence that these changes may contribute to the ability to abstain from smoking when given an incentive to do so. These findings extend the current literature on the effects of abstinence on reward processing among chronic smokers and provide a framework for future investigation with important potential implications for treatment and prevention of nicotine dependence.

APPENDIX A

COMPARISONS WITH BASLINE ACTIVATION

Analyses

Within the context of evaluating the circuitry engaged by monetary and smoking rewards, specific trial events were each evaluated separately relative to baseline activation to further probe activation patterns identified with the reward > neutral and win > no win comparisons and to identify the direction of effects contributing to significant differences between task conditions. Comparisons with baseline conditions were restricted to regions demonstrating significant activation when examining overall effects of reward. Significance was tested using FWE correction of $P < 0.05$. More liberal exploratory thresholds of $p < 0.001$ and $p < 0.01$ were also used to identify any subthreshold positive or negative activation which may be contributing to observed effects. Finally, for outcome analyses, the first eigenvariate was extracted from select clusters exhibiting significant money or puff win > no win outcome effects in order to plot activation patterns for each trial type relative to baseline activation. Extracted data were submitted to one-sample *t*-tests for each reward type to test for significant increases or decreases from baseline.

Results

Effects of reward anticipation relative to baseline activation

As noted in section 4.3 above, robust activation was seen throughout reward-related circuitry in response to monetary or smoking reward anticipation relative to neutral trial anticipation. This heightened response could be due to stronger positive activation during reward trials or stronger negative activation during neutral trials. When examined separately relative to baseline activation, monetary reward anticipation was associated with significant positive activation in bilateral occipital cortex, bilateral insula, left hippocampus, and right caudate. Left caudate and medial prefrontal cortex clusters emerged when relaxing significance threshold to $p < 0.001$, uncorrected (Figure 21a, Table 14). When examining smoking reward anticipation relative to baseline activation using FWE correction, only bilateral occipital cortex and bilateral insula were significant. Additional areas of medial prefrontal cortex and left hippocampus emerged at $p < 0.001$ (Figure 21b, Table 15). Positive activation within bilateral caudate was only evident at $p < 0.01$ (data not shown). For neutral trials, positive activation relative to baseline was only observed in bilateral occipital cortex, both when using FWE correction and at $p < 0.001$. A small additional cluster of positive activation (67 voxels) was observed in the right insula at $p < 0.01$ (data not shown), suggesting that significant differences between reward anticipation and neutral trials in this area are the result of highly positive activation during reward anticipation rather than negative activation during neutral condition. No areas of negative activation were observed for neutral trials relative to baseline with FWE correction or $p < 0.001$. Small clusters of negative activation emerged in medial prefrontal cortex and right thalamus at a significance threshold of $p < 0.01$ (Figure 21c), suggesting that

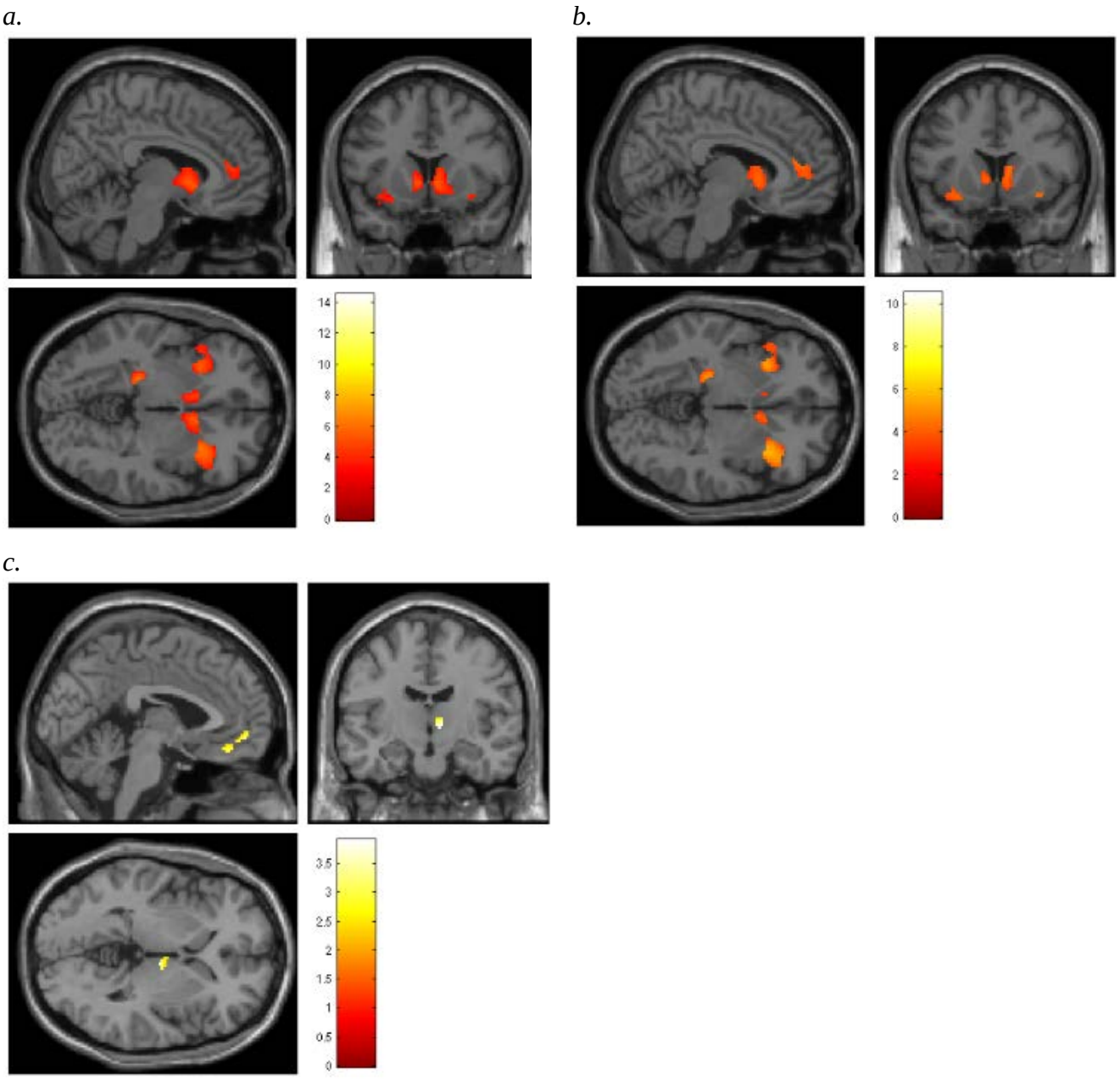


Figure 21: Activation associated with reward anticipation relative to baseline activation, analyzed separately by trial type.

Activation associated with reward anticipation relative to baseline, collapsed across abstinence condition, masked for money or puff reward > neutral anticipation. *a.* Monetary reward > baseline, $p < 0.001$, uncorrected. Slices shown at x = 8, y = 12, z = -4. *b.* Smoking reward > baseline, $p < 0.001$, uncorrected. Slices shown at x = 8, y = 12, z = -4. *c.* Neutral reward < baseline, $p < 0.01$, uncorrected. Slices shown at x = -2, y = -12, z = 0. Medial prefrontal cortex: 0, 54, -8; $T = 3.24$, 44 voxels, and -2, 40, -18; $T = 2.98$, 22 voxels. Right thalamus: 8, -12, 0; $T = 3.90$, 31 voxels.

Table 14. Suprathreshold clusters associated with monetary reward anticipation > baseline, masked for areas showing significant effect of money or puff reward > neutral anticipation.

	Voxels	Location			T	Brain areas
		x	y	Z	(df = 222)	
1	405	32	20	-6	5.84	Right insula, right inferior frontal gyrus
2	309	-30	20	-6	5.38	Left insula, left inferior frontal gyrus
3	323	8	10	0	5.32	Right caudate head
4	276	12	42	14	4.57	Medial prefrontal cortex
5	178	-6	10	0	5.16	Left caudate head
6	94	-22	-28	0	5.55	Left hippocampus
7	49	-26	-88	12	12.48	Left middle occipital gyrus
8	36	32	-88	14	14.52	Right middle occipital gyrus

Table 15. Suprathreshold clusters associated with smoking reward anticipation > baseline, masked for areas showing significant effect of money or puff reward > neutral anticipation.

	Voxels	Location			T	Brain areas
		x	y	Z	(df = 222)	
1	401	12	42	14	4.54	Medial prefrontal cortex
2	384	36	20	-6	5.82	Right insula, right inferior frontal gyrus
3	292	-30	20	-12	5.57	Left insula, left inferior frontal gyrus
4	76	-22	-28	0	5.73	Left hippocampus
5	49	-32	-88	16	8.81	Left middle occipital gyrus
6	36	30	-88	14	10.50	Right middle occipital gyrus

Note: Location refers to Montreal Neurological Institute (MNI) coordinates for peak voxel of each cluster. Significance threshold set at $p < 0.001$, uncorrected.

effects of reward anticipation relative to neutral trials in mPFC may be driven, in part, by slightly negative activation during the anticipation phase of neutral trials.

Effects of reward win and no win outcomes relative to baseline activation

As noted in section 4.4 above, win trials strongly activated bilateral striatum and posterior cingulate cortex, along with regions of posterior parietal cortex, relative to no win trials. While significant effects of win > no win trials in reward-related circuitry are presumably the result of a positive response to win trials, it is also possible that a negative response may have occurred, particularly in the ventral striatum, in response to no win trials. Therefore, win and no win trials were examined separately for each reward type relative to baseline activation, masked for regions showing a positive win > no win contrast for both reward types combined. When using FWE correction, small clusters of bilateral caudate were evident for both reward types, along with right inferior parietal lobule. Left inferior parietal lobule could be seen for monetary win relative to baseline. At a significance threshold of $p < 0.001$, both monetary and smoking win outcomes were associated with significant positive activation across all of the regions contained within the mask (Figure 22, Tables 16 and 17). Furthermore, peak voxels within each cluster were remarkably similar for smoking and monetary rewards, indicating a nearly identical response for each reward type. Of note, bilateral striatum activation appeared to be restricted to anterior portions of caudate head, in contrast with win > no win comparisons which was evident across larger regions of ventral striatum. Monetary and smoking no win trials were both associated with similar positive activations in posterior parietal cortex when applying FWE correction. Slight positive activations could be observed in anterior portions of bilateral caudate when loosening correction to $p < 0.01$, uncorrected.

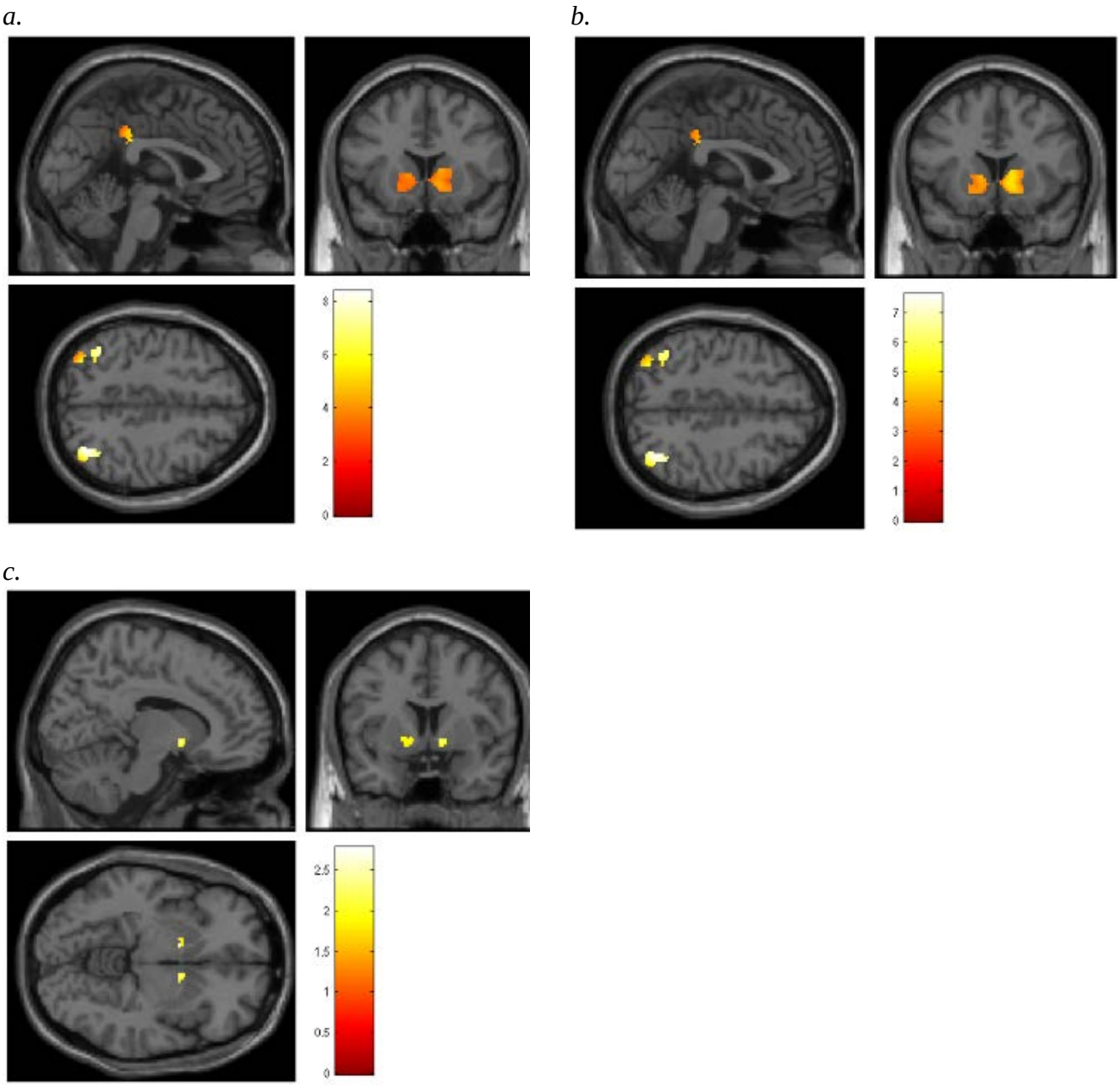


Figure 22: Activation associated with reward outcomes relative to baseline activation, analyzed separately by trial type and outcome.

Activation associated with reward outcomes relative to baseline, collapsed across abstinence condition, masked for money or puff win > no win outcome. *a.* Monetary win > baseline, $p < 0.001$, uncorrected. Slices shown at x = 0, y = 14, z = 46. *b.* Smoking win > baseline, $p < 0.001$, uncorrected. Slices shown at x = 0, y = 14, z = 46. *c.* Money no win < baseline, $p < 0.05$, uncorrected. Slices shown at x = 12, y = 6, z = -6. Right ventral striatum: 12, 4, -6; $T = 2.35$, 20 voxels. Left ventral striatum: -14, 4, -8; $T = 2.78$, 21 voxels.

Table 16. Suprathreshold clusters associated with money win > baseline, masked for areas showing significant effect of money or puff win > no win outcome.

	Voxels	Location			T	Brain areas
		x	y	z	(df = 222)	
1	217	12	18	-4	5.43	Right anterior caudate head
2	168	-12	22	-4	5.36	Left anterior caudate head
3	176	36	-66	46	8.38	Right inferior parietal lobule/angular cortex
4	67	0	-32	30	5.12	Posterior cingulate cortex
5	33	-32	-70	46	5.49	Left superior parietal lobule/precuneus
6	46	-40	-56	42	8.07	Left inferior parietal lobule
7	24	-48	40	16	5.66	Left middle frontal gyrus, inferior frontal gyrus

Table 17. Suprathreshold clusters associated with smoking win > baseline, masked for areas showing significant effect of money or puff win > no win outcome.

	Voxels	Location			T	Brain areas
		x	y	z	(df = 222)	
1	248	10	18	-4	5.33	Right anterior caudate head
2	179	-12	22	-6	5.02	Left anterior caudate head
3	176	38	-66	48	7.60	Right inferior parietal lobule/angular cortex
4	40	0	-32	30	4.10	Posterior cingulate cortex
5	37	-32	-70	46	5.23	Left superior parietal lobule/precuneus
6	46	-38	-58	42	6.97	Left inferior parietal lobule
7	24	-44	50	4	4.65	Left middle frontal gyrus, inferior frontal gyrus

Note: Location refers to Montreal Neurological Institute (MNI) coordinates for peak voxel of each cluster. Significance threshold set at $p < 0.001$, uncorrected.

When examining negative activations for no win trials (i.e. no win < baseline), a very small effect was evident in bilateral ventral striatum for monetary no win trials (Figure 22c). This effect was only evident at a threshold of $p < 0.05$, and was not observed at any threshold for smoking no win outcomes. This suggests that deactivation in ventral striatum may be contributing, in part, to significant contrasts between monetary win and no win outcomes. Examination of extracted eigenvariates from right and left striatum clusters (shown in Figure 10) confirmed this observation. Extracted data are plotted in Figure 23. Both money and smoking wins were associated with significant increases in activation relative to baseline (confirmed through one-sample *t*-tests on extracted data). Only money no win was associated with a significant decrease in activation relative to baseline, whereas puff no win outcomes did not differ from baseline.

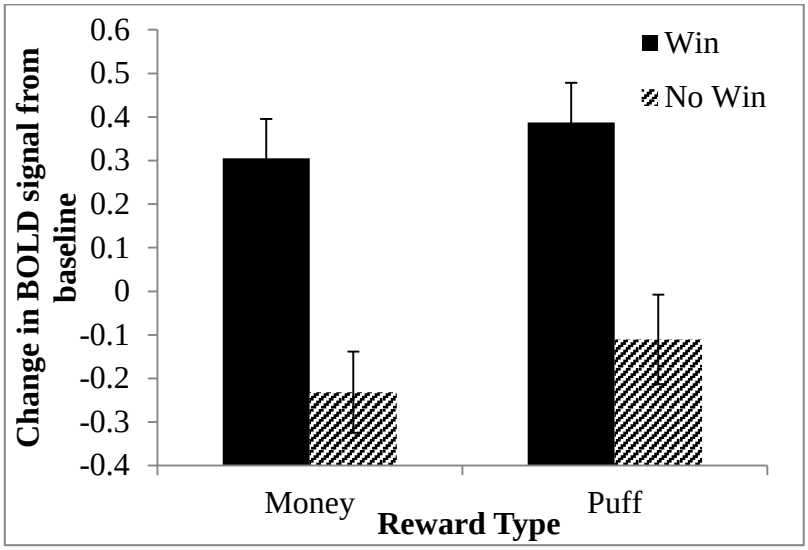


Figure 23. Right striatal BOLD activation in response to monetary and smoking reward win and no win outcomes, plotted separately relative to baseline activation.

BOLD values for each reward outcome type (money win, money no win, smoking win, and smoking no win) relative to baseline activation, extracted from right ventral striatum/caudate cluster showing significant money or puff win > no win activation. Money win and puff win outcomes both exhibit significant positive activations relative to baseline (t = 4.506 and 6.229, respectively, both p's < 0.001. Money no win outcome showed a significant deactivation relative to baseline (t = -3.276, p < 0.01), while activation in response to puff no win outcome did not differ significantly from baseline. Results were replicated on data extracted from left ventral striatum/caudate.

APPENDIX B

COMPARISONS OF MONETARY VERSUS SMOKING REWARDS WITHIN EACH ABSTINENCE CONDITION

Analyses

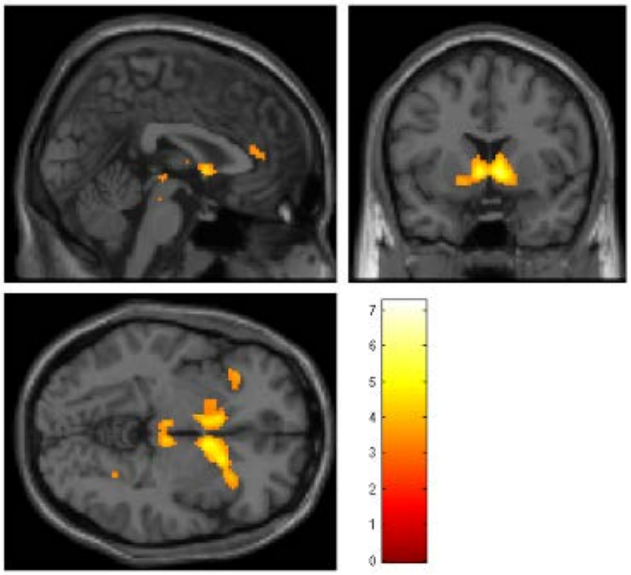
Within the context of examining effects of abstinence described in section, follow-up analyses were conducted to test contrasts between smoking and monetary rewards separately for abstinent and non-abstinent conditions. This served to extend the reward type comparisons conducted in Chapter 4, allowing for further exploration of differences between reward types when separated by abstinence condition. Comparisons were conducted within the ANOVA framework described in section 5.2. Threshold for significance was set at $p < 0.001$, uncorrected, 20 voxel extent.

Results

Anticipation phase

During non-abstinence, response to anticipation of monetary reward > smoking reward was significantly greater throughout reward-related circuitry, including bilateral caudate, right and left anterior insula, bilateral occipital lobe, and a small region of ACC, as well as several other clusters throughout temporal and frontal lobes (Figure 24a, Table 18). The same comparison during abstinence revealed only bilateral occipital cortex (-26, -88, 12, T = 5.33, 72 voxels; 34, -88, 14, T = 4.85, 76 voxels) and a small cluster in left post-central gyrus (-32, -32, 46, T = 3.49, 20 voxels).

a.



b.

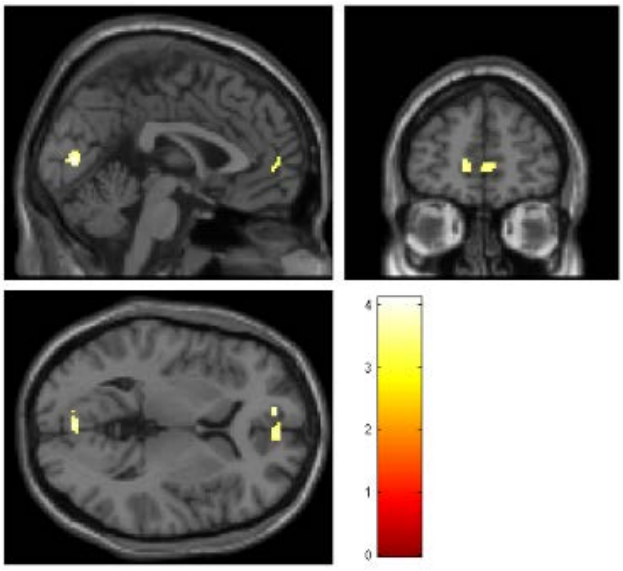


Figure 24. Direct comparisons of monetary and smoking reward anticipation, analyzed separately during abstinent and non-abstinent conditions.

Comparisons of monetary versus smoking reward anticipation separated by abstinence condition, $p < 0.001$, 20 voxel extent threshold. *a.* Activation associated with money > smoking anticipation during non-abstinent condition. Slices shown at x = 2, y = 8, z = -4. *b.* Activation associated with smoking > monetary anticipation during abstinent condition. Slices shown at x = 0, y = 52, z = 4.

Table 18. Suprathreshold clusters associated with monetary reward > smoking reward anticipation during non-abstinence.

	Voxels	Location			T	Brain areas
		x	y	z	(df = 144)	
1	1090	8	8	0	5.75	Bilateral caudate head, right inferior frontal gyrus, right anterior insula
2	381	34	-88	14	7.25	Right occipital lobe
3	236	8	-24	-18	4.49	Brainstem
4	163	-26	-88	12	6.89	Left occipital lobe
5	69	-36	24	-8	4.31	Left inferior frontal gyrus
6	43	-54	-46	16	4.21	Left superior temporal gyrus
7	24	28	-48	-8	4.05	Right parahippocampal gyrus
8	32	-48	-2	48	3.82	Left middle frontal gyrus, precentral gyrus
9	21	-44	-10	56	3.60	Left middle frontal gyrus, precentral gyrus
10	33	2	40	12	3.59	Anterior cingulate cortex

Table 19. Suprathreshold clusters associated with smoking reward > monetary reward anticipation during abstinence.

	Voxels	Location			T	Brain areas
		x	y	z	(df = 144)	
1	89	-10	54	4	4.11	Medial frontal gyrus
2	85	-2	-80	8	3.98	Cuneus
3	24	-56	-48	-2	3.73	Middle temporal gyrus
4	20	-42	-68	48	3.48	Superior parietal lobule

Note: Location refers to Montreal Neurological Institute (MNI) coordinates for peak voxel of each cluster. Significance threshold set at $p < 0.001$, uncorrected across the whole-brain, with 20 voxel extent threshold.

Comparison of smoking > monetary reward anticipation during abstinence revealed significantly greater activation in a region of the medial prefrontal cortex and cuneus, along with small clusters in the middle temporal gyrus and superior parietal lobule (Figure 24 b, Table 19). The same contrast during non-abstinence revealed only a small cluster of significant activation in the middle temporal gyrus (-36, -62, 18, T = 4.16, 21 voxels).

Outcome phase

Monetary versus smoking reward outcomes were compared separately for abstinent and non-abstinent conditions. During non-abstinence, response to monetary win > no win outcomes was significantly greater than response to smoking win > no win outcomes in a small cluster of the left DS, including caudate head and body, and in a region of the right precuneus (Figure 25). No significant differences were found between monetary and smoking outcomes during abstinence.

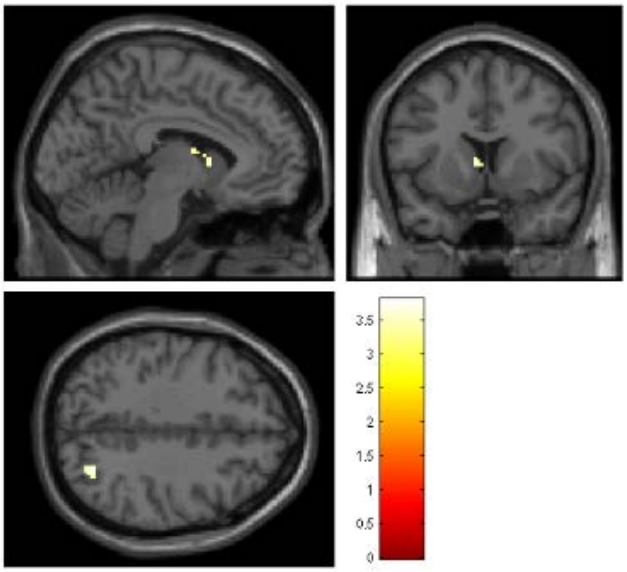


Figure 25. Direct comparisons of monetary and smoking reward win > no win outcomes, analyzed separately during abstinent and non-abstinent conditions.

Activation associated with money > smoking reward outcome (based on win > no win contrasts) during non-abstinent condition, $p < 0.001$, 20 voxel extent threshold. Slices shown at x = -6, y = 10, z = 40. Right precuneus: 28, -68, 40; $T = 3.81$, 53 voxels. Left caudate head/body: -4, 8, 6; $T = 3.52$, 28 voxels.

BIBLIOGRAPHY

Addicott, M. A., Baranger, D. A., Kozink, R. V., Smoski, M. J., Dichter, G. S., & McClernon, F. J. (2012). Smoking withdrawal is associated with increases in brain activation during decision making and reward anticipation: a preliminary study. [Research Support, N.I.H., Extramural]. *Psychopharmacology (Berl), 219*(2), 563-573. doi: 10.1007/s00213-011-24043

Alessi, S. M., Badger, G. J., & Higgins, S. T. (2004). An experimental examination of the initial weeks of abstinence in cigarette smokers. *Exp Clin Psychopharmacol, 12*(4), 276-287. doi: 2004-20800-008 [pii] 10.1037/1064-1297.12.4.276

Anderson, A. K., & Sobel, N. (2003). Dissociating intensity from valence as sensory inputs to emotion. *Neuron, 39*(4), 581-583. doi: S089662730300504X [pii]

Apicella, P., Ljungberg, T., Scarnati, E., & Schultz, W. (1991). Responses to reward in monkey dorsal and ventral striatum. *Exp Brain Res, 85*(3), 491-500.

Attwood, A. S., Penton-Voak, I. S., & Munafo, M. R. (2009). Effects of acute nicotine administration on ratings of attractiveness of facial cues. *Nicotine Tob Res, 11*(1), 44-48. doi: ntn006 [pii] 10.1093/ntr/ntn006

Audrain-McGovern, J., Lerman, C., Wileyto, E. P., Rodriguez, D., & Shields, P. G. (2004). Interacting effects of genetic predisposition and depression on adolescent smoking progression. *Am J Psychiatry, 161*(7), 1224-1230.

Azizian, A., Monterosso, J., O'Neill, J., & London, E. D. (2009). Magnetic resonance imaging studies of cigarette smoking. [Review]. *Handb Exp Pharmacol*(192), 113-143. doi: 10.1007/978-3-540-69248-5_5

Bailey, S. R., Goedeker, K. C., & Tiffany, S. T. (2009). The impact of cigarette deprivation and cigarette availability on cue-reactivity in smokers. *Addiction, 105*(2), 364-372. doi: ADD2760 [pii]10.1111/j.1360-0443.2009.02760.x

Baker, T. B., Piper, M. E., Schlam, T. R., Cook, J. W., Smith, S. S., Loh, W. Y., & Bolt, D. (2012). Are tobacco dependence and withdrawal related amongst heavy smokers? Relevance to conceptualizations of dependence. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.]. *J Abnorm Psychol, 121*(4), 909-921. doi: 10.1037/a0027889

Barr, R. S., Pizzagalli, D. A., Culhane, M. A., Goff, D. C., & Evins, A. E. (2008). A single dose of nicotine enhances reward responsiveness in nonsmokers: implications for development of dependence. *Biol Psychiatry, 63*(11), 1061-1065. doi: S0006-3223(07)00890-6 [pii]10.1016/j.biopsych.2007.09.015

Barrett, S. P. (2010). The effects of nicotine, denicotinized tobacco, and nicotine-containing tobacco on cigarette craving, withdrawal, and self-administration in male and female smokers. *Behav Pharmacol, 21*(2), 144-152. doi: 10.1097/FBP.0b013e328337be68

Bassareo, V., & Di Chiara, G. (1999). Modulation of feeding-induced activation of mesolimbic dopamine transmission by appetitive stimuli and its relation to motivational state. *Eur J Neurosci, 11*(12), 4389-4397. doi: ejn843 [pii]

Beck, A., Schlagenhauf, F., Wustenberg, T., Hein, J., Kienast, T., Kahnt, T., . . . Wrase, J. (2009). Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics. *Biol Psychiatry, 66*(8), 734-742. doi: S0006-3223(09)00567-8 [pii]10.1016/j.biopsych.2009.04.035

Berridge, K. C., Robinson, T. E., & Aldridge, J. W. (2009). Dissecting components of reward: 'liking', 'wanting', and learning. *Curr Opin Pharmacol, 9*(1), 65-73. doi: S1471-4892(08)00212-9 [pii] 10.1016/j.coph.2008.12.014

Besheer, J., & Bevins, R. A. (2003). Impact of nicotine withdrawal on novelty reward and related behaviors. *Behav Neurosci, 117*(2), 327-340.

Bold, K. W., Yoon, H., Chapman, G. B., & McCarthy, D. E. (2013). Factors Predicting Smoking in a Laboratory-Based Smoking-Choice Task. *Exp Clin Psychopharmacol*. doi: 10.1037/a0031559

Braus, D. F., Wrase, J., Grusser, S., Hermann, D., Ruf, M., Flor, H., . . . Heinz, A. (2001). Alcohol-associated stimuli activate the ventral striatum in abstinent alcoholics. *J Neural Transm, 108*(7), 887-894.

Breiter, H. C., Aharon, I., Kahneman, D., Dale, A., & Shizgal, P. (2001). Functional imaging of neural responses to expectancy and experience of monetary gains and losses. *Neuron, 30*(2), 619-639. doi: S0896-6273(01)00303-8 [pii]

Brody, A. L. (2006). Functional brain imaging of tobacco use and dependence. *J Psychiatr Res, 40*(5), 404-418. doi: S0022-3956(05)00059-2 [pii]10.1016/j.jpsychires.2005.04.012

Brody, A. L., Mandelkern, M. A., London, E. D., Childress, A. R., Lee, G. S., Bota, R. G., . . . Jarvik, M. E. (2002). Brain metabolic changes during cigarette craving. *Arch Gen Psychiatry, 59*(12), 1162-1172. doi: yoa10040 [pii]

Brody, A. L., Olmstead, R. E., London, E. D., Farahi, J., Meyer, J. H., Grossman, P., . . . Mandelkern, M. A. (2004). Smoking-induced ventral striatum dopamine release. *Am J Psychiatry, 161*(7), 1211-1218.

Buhler, M., Vollstadt-Klein, S., Kobiella, A., Budde, H., Reed, L. J., Braus, D. F., . . . Smolka, M. N. (2010). Nicotine dependence is characterized by disordered reward processing in a network driving motivation. *Biol Psychiatry, 67*(8), 745-752. doi: S0006-3223(09)01317-1 [pii]10.1016/j.biopsych.2009.10.029

Caggiula, A. R., Donny, E. C., Palmatier, M. I., Liu, X., Chaudhri, N., & Sved, A. F. (2009). The role of nicotine in smoking: a dual-reinforcement model. *Nebr Symp Motiv, 55*, 91-109.

Calder, A. J., Lawrence, A. D., & Young, A. W. (2001). Neuropsychology of fear and loathing. *Nat Rev Neurosci, 2*(5), 352-363. doi: 10.1038/3507258435072584 [pii]

Cardinal, R. N., Parkinson, J. A., Lachenal, G., Halkerston, K. M., Rudarakanchana, N., Hall, J., . . . Everitt, B. J. (2002). Effects of selective excitotoxic lesions of the nucleus accumbens core, anterior cingulate cortex, and central nucleus of the amygdala on autoshaping performance in rats. *Behav Neurosci, 116*(4), 553-567.

Chaudhri, N., Caggiula, A. R., Donny, E. C., Palmatier, M. I., Liu, X., & Sved, A. F. (2006). Complex interactions between nicotine and nonpharmacological stimuli reveal multiple roles for nicotine in reinforcement. *Psychopharmacology (Berl), 184*(3-4), 353-366.

Chornock, W. M., Stitzer, M. L., Gross, J., & Leischow, S. (1992). Experimental model of smoking re-exposure: effects on relapse. [Clinical Trial Randomized Controlled Trial Research Support, U.S. Gov't, P.H.S.]. *Psychopharmacology (Berl), 108*(4), 495-500.

Cohen, M. X., Krohn-Grimberghe, A., Elger, C. E., & Weber, B. (2007). Dopamine gene predicts the brain's response to dopaminergic drug. *Eur J Neurosci, 26*(12), 3652-3660.

Comings, D. E., Ferry, L., Bradshaw-Robinson, S., Burchette, R., Chiu, C., & Muhleman, D. (1996). The dopamine D2 receptor (DRD2) gene: a genetic risk factor in smoking. *Pharmacogenetics, 6*(1), 73-79.

Cook, J., Spring, B., McChargue, D., & Doran, N. (2010). Effects of anhedonia on days to relapse among smokers with a history of depression: a brief report. *Nicotine Tob Res, 12*(9), 978-982. doi: ntq118 [pii]10.1093/ntr/ntq118

Cook, J. W., Spring, B., McChargue, D., & Hedeker, D. (2004). Hedonic capacity, cigarette craving, and diminished positive mood. *Nicotine Tob Res, 6*(1), 39-47.

Corrigall, W. A., & Coen, K. M. (1991). Selective dopamine antagonists reduce nicotine self-administration. *Psychopharmacology, 104*(2), 171-176.

Corrigall, W. A., Franklin, K. B., Coen, K. M., & Clarke, P. B. (1992). The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. *Psychopharmacology, 107*(2-3), 285-289.

Dallery, J., & Glenn, I. M. (2005). Effects of an Internet-based voucher reinforcement program for smoking abstinence: a feasibility study. *J Appl Behav Anal, 38*(3), 349-357. doi: 10.1901/jaba.2005.150-04

Dallery, J., Glenn, I. M., & Raiff, B. R. (2007). An Internet-based abstinence reinforcement treatment for cigarette smoking. *Drug Alcohol Depend, 86*(2-3), 230-238. doi: S0376-8716(06)00236-5 [pii]10.1016/j.drugalcdep.2006.06.013

David, S. P., Munafo, M. R., Johansen-Berg, H., Mackillop, J., Sweet, L. H., Cohen, R. A., . . . Walton, R. T. (2007). Effects of Acute Nicotine Abstinence on Cue-elicited Ventral Striatum/Nucleus Accumbens Activation in Female Cigarette Smokers: A Functional Magnetic Resonance Imaging Study. *Brain Imaging Behav, 1*(3-4), 43-57. doi: 10.1007/s11682-007-9004-1

David, S. P., Munafo, M. R., Johansen-Berg, H., Smith, S. M., Rogers, R. D., Matthews, P. M., & Walton, R. T. (2005). Ventral striatum/nucleus accumbens activation to smoking-related pictorial cues in smokers and nonsmokers: a functional magnetic resonance imaging study. *Biol Psychiatry, 58*(6), 488-494.

Dawkins, L., Acaster, S., & Powell, J. H. (2007). The effects of smoking and abstinence on experience of happiness and sadness in response to positively valenced, negatively valenced, and neutral film clips. *Addict Behav, 32*(2), 425-431.

Dawkins, L., Powell, J. H., West, R., Powell, J., & Pickering, A. (2006). A double-blind placebo controlled experimental study of nicotine: I--effects on incentive motivation. *Psychopharmacology (Berl), 189*(3), 355-367.

Delgado, M. R. (2007). Reward-related responses in the human striatum. *Ann N Y Acad Sci, 1104*, 70-88. doi: annals.1390.002 [pii] 10.1196/annals.1390.002

Delgado, M. R., Locke, H. M., Stenger, V. A., & Fiez, J. A. (2003). Dorsal striatum responses to reward and punishment: effects of valence and magnitude manipulations. *Cogn Affect Behav Neurosci, 3*(1), 27-38.

Delgado, M. R., Nystrom, L. E., Fissell, C., Noll, D. C., & Fiez, J. A. (2000). Tracking the hemodynamic responses to reward and punishment in the striatum. *J Neurophysiol, 84*(6), 3072-3077.

Di Ciano, P., & Everitt, B. J. (2004). Direct interactions between the basolateral amygdala and nucleus accumbens core underlie cocaine-seeking behavior by rats. *J Neurosci, 24*(32), 7167-7173. doi: 10.1523/JNEUROSCI.1581-04.200424/32/7167 [pii]

Diekhof, E. K., Kaps, L., Falkai, P., & Gruber, O. (2012). The role of the human ventral striatum and the medial orbitofrontal cortex in the representation of reward magnitude - an activation likelihood estimation meta-analysis of neuroimaging studies of passive reward expectancy and outcome processing. *Neuropsychologia, 50*(7), 1252-1266. doi: S0028-3932(12)00077-2 [pii] 10.1016/j.neuropsychologia.2012.02.007

Domino, E. F., & Tsukada, H. (2009). Nicotine sensitization of monkey striatal dopamine release. *Eur J Pharmacol, 607*(1-3), 91-95. doi: S0014-2999(09)00142-3 [pii] 10.1016/j.ejphar.2009.02.011

Donny, E. C., Chaudhri, N., Caggiula, A. R., Evans-Martin, F. F., Booth, S., Gharib, M. A., . . . Sved, A. F. (2003). Operant responding for a visual reinforcer in rats is enhanced by noncontingent nicotine: implications for nicotine self-administration and reinforcement. *Psychopharmacology (Berl), 169*(1), 68-76.

Donny, E. C., & Dierker, L. C. (2007). The absence of DSM-IV nicotine dependence in moderate-to-heavy daily smokers. *Drug Alcohol Depend, 89*(1), 93-96. doi: S0376-8716(06)00457-1 [pii]10.1016/j.drugalcdep.2006.11.019

Donny, E. C., Griffin, K. M., Shiffman, S., & Sayette, M. A. (2008). The relationship between cigarette use, nicotine dependence, and craving in laboratory volunteers. *Nicotine Tob Res, 10*(3), 447-455. doi: 791303121 [pii] 10.1080/14622200801901906

Dunn, K. E., Sigmon, S. C., Thomas, C. S., Heil, S. H., & Higgins, S. T. (2008). Voucher-based contingent reinforcement of smoking abstinence among methadone-maintained patients: a pilot study. *J Appl Behav Anal, 41*(4), 527-538.

Duvauchelle, C. L., Ikegami, A., Asami, S., Robens, J., Kressin, K., & Castaneda, E. (2000). Effects of cocaine context on NAcc dopamine and behavioral activity after repeated intravenous cocaine administration. *Brain Res, 862*(1-2), 49-58. doi: S0006-8993(00)02091-6 [pii]

Elliott, R., Dolan, R. J., & Frith, C. D. (2000). Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. *Cereb Cortex, 10*(3), 308-317.

Elliott, R., Newman, J. L., Longe, O. A., & Deakin, J. F. (2003). Differential response patterns in the striatum and orbitofrontal cortex to financial reward in humans: a parametric functional magnetic resonance imaging study. *J Neurosci, 23*(1), 303-307. doi: 23/1/303 [pii]

Engelmann, J. M., Versace, F., Robinson, J. D., Minnix, J. A., Lam, C. Y., Cui, Y., . . . Cinciripini, P. M. (2012). Neural substrates of smoking cue reactivity: a meta-analysis of fMRI studies. [Meta-Analysis Research Support, N.I.H., Extramural]. *Neuroimage, 60*(1), 252-262. doi: 10.1016/j.neuroimage.2011.12.024

Epping-Jordan, M. P., Watkins, S. S., Koob, G. F., & Markou, A. (1998). Dramatic decreases in brain reward function during nicotine withdrawal. *Nature, 393*(6680), 76-79. doi: 10.1038/30001

Epstein, J., Pan, H., Kocsis, J. H., Yang, Y., Butler, T., Chusid, J., . . . Silbersweig, D. A. (2006). Lack of ventral striatal response to positive stimuli in depressed versus normal subjects. *Am J Psychiatry, 163*(10), 1784-1790.

Everitt, B. J., & Robbins, T. W. (2013). From the ventral to the dorsal striatum: Devolving views of their roles in drug addiction. *Neurosci Biobehav Rev*. doi: 10.1016/j.neubiorev.2013.02.010

Fehr, C., Yakushev, I., Hohmann, N., Buchholz, H. G., Landvogt, C., Deckers, H., . . . Schreckenberger, M. (2008). Association of low striatal dopamine d2 receptor availability with nicotine dependence similar to that seen with other drugs of abuse. *Am J Psychiatry, 165*(4), 507-514. doi: appi.ajp.2007.07020352 [pii] 10.1176/appi.ajp.2007.07020352

Ferguson, S. G., & Shiffman, S. (2009). The relevance and treatment of cue-induced cravings in tobacco dependence. *J Subst Abuse Treat, 36*(3), 235-243. doi: S0740-5472(08)00099-8 [pii]10.1016/j.jsat.2008.06.005

Forbes, E. E., Hariri, A. R., Martin, S. L., Silk, J. S., Moyles, D. L., Fisher, P. M., . . . Dahl, R. E. (2009). Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *Am J Psychiatry, 166*(1), 64-73. doi: appi.ajp.2008.07081336 [pii]10.1176/appi.ajp.2008.07081336

Forbes, E. E., Olino, T. M., Ryan, N. D., Birmaher, B., Axelson, D., Moyles, D. L., & Dahl, R. E. (2010). Reward-related brain function as a predictor of treatment response in adolescents with major depressive disorder. *Cogn Affect Behav Neurosci, 10*(1), 107-118. doi: 10/1/107 [pii] 10.3758/CABN.10.1.107

Forbes, E. E., Ryan, N. D., Phillips, M. L., Manuck, S. B., Worthman, C. M., Moyles, D. L., . . . Dahl, R. E. (2010). Healthy adolescents' neural response to reward: associations with puberty, positive affect, and depressive symptoms. *J Am Acad Child Adolesc Psychiatry, 49*(2), 162-172 e161-165. doi: 00004583-201002000-00010 [pii]

Franklin, T. R., Wang, Z., Wang, J., Sciortino, N., Harper, D., Li, Y., . . . Childress, A. R. (2007). Limbic activation to cigarette smoking cues independent of nicotine withdrawal: a perfusion fMRI study. *Neuropsychopharmacology, 32*(11), 2301-2309. doi: 1301371 [pii]10.1038/sj.npp.1301371

Friston, K. J., Holmes, A. P., Poline, J. B., Grasby, P. J., Williams, S. C., Frackowiak, R. S., & Turner, R. (1995). Analysis of fMRI time-series revisited. [Research Support, Non-U.S. Gov't]. *Neuroimage, 2*(1), 45-53. doi: 10.1006/nimg.1995.1007

Froeliger, B., Modlin, L., Wang, L., Kozink, R. V., & McClernon, F. J. (2012). Nicotine withdrawal modulates frontal brain function during an affective Stroop task. [Comparative Study Randomized Controlled Trial Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Psychopharmacology (Berl), 220*(4), 707-718. doi: 10.1007/s00213-011-2522-y

Froeliger, B., Modlin, L. A., Kozink, R. V., Wang, L., Garland, E. L., Addicott, M. A., & McClernon, F. J. (2013). Frontoparietal attentional network activation differs between smokers and nonsmokers during affective cognition. *Psychiatry Res, 211*(1), 57-63. doi: 10.1016/j.pscychresns.2012.05.002

Garavan, H., Pankiewicz, J., Bloom, A., Cho, J. K., Sperry, L., Ross, T. J., . . . Stein, E. A. (2000). Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. *Am J Psychiatry, 157*(11), 1789-1798.

Gianaros, P. J., Manuck, S. B., Sheu, L. K., Kuan, D. C., Votruba-Drzal, E., Craig, A. E., & Hariri, A. R. (2011). Parental education predicts corticostriatal functionality in adulthood. [Research Support, N.I.H., Extramural]. *Cereb Cortex, 21*(4), 896-910. doi: 10.1093/cercor/bhq160

Glenn, I. M., & Dallery, J. (2007). Effects of internet-based voucher reinforcement and a transdermal nicotine patch on cigarette smoking. *J Appl Behav Anal, 40*(1), 1-13.

Gloria, R., Angelos, L., Schaefer, H. S., Davis, J. M., Majeskie, M., Richmond, B. S., . . . Baker, T. B. (2009). An fMRI investigation of the impact of withdrawal on regional brain activity during nicotine anticipation. *Psychophysiology, 46*(4), 681-693. doi: PSYP823 [pii] 10.1111/j.1469-8986.2009.00823.x

Goldstein, R. Z., Alia-Klein, N., Tomasi, D., Zhang, L., Cottone, L. A., Maloney, T., . . . Volkow, N. D. (2007). Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? *Am J Psychiatry, 164*(1), 43-51. doi: 164/1/43 [pii] 10.1176/appi.ajp.164.1.43

Goldstein, R. Z., Tomasi, D., Alia-Klein, N., Honorio Carrillo, J., Maloney, T., Woicik, P. A., . . . Volkow, N. D. (2009). Dopaminergic response to drug words in cocaine addiction. *J Neurosci, 29*(18), 6001-6006. doi: 29/18/6001 [pii] 10.1523/JNEUROSCI.4247-08.2009

Groenewegen, H. J., & Trimble, M. (2007). The ventral striatum as an interface between the limbic and motor systems. *CNS Spectr, 12*(12), 887-892.

Grusser, S. M., Wrase, J., Klein, S., Hermann, D., Smolka, M. N., Ruf, M., . . . Heinz, A. (2004). Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology (Berl), 175*(3), 296-302. doi: 10.1007/s00213-004-1828-4

Haber, S., & McFarland, N. R. (2001). The place of the thalamus in frontal cortical-basal ganglia circuits. *Neuroscientist, 7*(4), 315-324.

Haber, S. N., & Knutson, B. (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology, 35*(1), 4-26. doi: npp2009129 [pii]10.1038/npp.2009.129

Haber, S. N., Kunishio, K., Mizobuchi, M., & Lynd-Balta, E. (1995). The orbital and medial prefrontal circuit through the primate basal ganglia. *J Neurosci, 15*(7 Pt 1), 4851-4867.

Hamann, S., & Mao, H. (2002). Positive and negative emotional verbal stimuli elicit activity in the left amygdala. *Neuroreport, 13*(1), 15-19.

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K. O. (1991). The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict, 86*(9), 1119-1127.

Heinz, A., Siessmeier, T., Wrase, J., Hermann, D., Klein, S., Grusser, S. M., . . . Bartenstein, P. (2004). Correlation between dopamine D(2) receptors in the ventral striatum and central processing of alcohol cues and craving. *Am J Psychiatry, 161*(10), 1783-1789. doi: 161/10/1783 [pii] 10.1176/appi.ajp.161.10.1783

Heinz, A., Wrase, J., Kahnt, T., Beck, A., Bromand, Z., Grusser, S. M., . . . Mann, K. (2007). Brain activation elicited by affectively positive stimuli is associated with a lower risk of relapse in detoxified alcoholic subjects. *Alcohol Clin Exp Res, 31*(7), 1138-1147. doi: ACER406 [pii] 10.1111/j.1530-0277.2007.00406.x

Higgins, S. T., Heil, S. H., Solomon, L. J., Bernstein, I. M., Lussier, J. P., Abel, R. L., . . . Badger, G. J. (2004). A pilot study on voucher-based incentives to promote abstinence from cigarette smoking during pregnancy and postpartum. *Nicotine Tob Res, 6*(6), 1015-1020.

Hikosaka, K., & Watanabe, M. (2000). Delay activity of orbital and lateral prefrontal neurons of the monkey varying with different rewards. *Cereb Cortex, 10*(3), 263-271.

Hommer, D. W., Knutson, B., Fong, G. W., Bennett, S., Adams, C. M., & Varnera, J. L. (2003). Amygdalar recruitment during anticipation of monetary rewards: an event-related fMRI study. *Ann N Y Acad Sci, 985*, 476-478.

Hudmon, K. S., Gritz, E. R., Clayton, S., & Nisenbaum, R. (1999). Eating orientation, postcessation weight gain, and continued abstinence among female smokers receiving an unsolicited smoking cessation intervention. [Clinical Trial Randomized Controlled Trial Research Support, U.S. Gov't, P.H.S.]. *Health Psychol, 18*(1), 29-36.

Hughes, J. R., & Hatsukami, D. (1986). Signs and symptoms of tobacco withdrawal. [Clinical Trial Randomized Controlled Trial Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Arch Gen Psychiatry, 43*(3), 289-294.

Janes, A. C., Nickerson, L. D., Frederick Bde, B., & Kaufman, M. J. (2012). Prefrontal and limbic resting state brain network functional connectivity differs between nicotine-dependent smokers and non-smoking controls. *Drug Alcohol Depend, 125*(3), 252-259. doi: S0376-8716(12)00072-5 [pii] 10.1016/j.drugalcdep.2012.02.020

Janes, A. C., Pizzagalli, D. A., Richardt, S., de, B. F. B., Chuzi, S., Pachas, G., . . . Kaufman, M. J. (2010). Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. *Biol Psychiatry, 67*(8), 722-729. doi: S0006-3223(10)00010-7 [pii] 10.1016/j.biopsych.2009.12.034

Johnson, E. O., Rhee, S. H., Chase, G. A., & Breslau, N. (2004). Comorbidity of depression with levels of smoking: an exploration of the shared familial risk hypothesis. [Research Support, U.S. Gov't, P.H.S.]. *Nicotine Tob Res, 6*(6), 1029-1038.

Johnson, R. A., & Gerstein, D. R. (1998). Initiation of use of alcohol, cigarettes, marijuana, cocaine, and other substances in US birth cohorts since 1919. [see comments]. *American Journal of Public Health, 88*(1), 27-33.

Kalivas, P. W., & Stewart, J. (1991). Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. *Brain Res Brain Res Rev, 16*(3), 223-244.

Kalivas, P. W., & Volkow, N. D. (2005). The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry, 162*(8), 1403-1413.

Kenny, P. J., & Markou, A. (2006). Nicotine self-administration acutely activates brain reward systems and induces a long-lasting increase in reward sensitivity. *Neuropsychopharmacology, 31*(6), 1203-1211. doi: 1300905 [pii]10.1038/sj.npp.1300905

Kessler, R. C., Adler, L., Barkley, R., Biederman, J., Conners, C. K., Demler, O., . . . Zaslavsky, A. M. (2006). The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. [Comparative Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Am J Psychiatry, 163*(4), 716-723. doi: 10.1176/appi.ajp.163.4.716

Killen, J. D., Fortmann, S. P., & Newman, B. (1990). Weight change among participants in a large sample minimal contact smoking relapse prevention trial. [Clinical Trial Comparative Study Randomized Controlled Trial Research Support, U.S. Gov't, P.H.S.]. *Addict Behav, 15*(4), 323-332.

Kiyatkin, E. A., & Stein, E. A. (1996). Conditioned changes in nucleus accumbens dopamine signal established by intravenous cocaine in rats. *Neurosci Lett, 211*(2), 73-76. doi: 0304-3940(96)12731-2 [pii]

Klesges, R. C., Winders, S. E., Meyers, A. W., Eck, L. H., Ward, K. D., Hultquist, C. M., . . . Shadish, W. R. (1997). How much weight gain occurs following smoking cessation? A comparison of weight gain using both continuous and point prevalence abstinence. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *J Consult Clin Psychol, 65*(2), 286-291.

Knutson, B., Fong, G. W., Adams, C. M., Varner, J. L., & Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport, 12*(17), 3683-3687.

Knutson, B., & Wimmer, G. E. (2007). Splitting the difference: how does the brain code reward episodes? *Ann N Y Acad Sci, 1104*, 54-69. doi: annals.1390.020 [pii]10.1196/annals.1390.020

Koepp, M. J., Gunn, R. N., Lawrence, A. D., Cunningham, V. J., Dagher, A., Jones, T., . . . Grasby, P. M. (1998). Evidence for striatal dopamine release during a video game. *Nature, 393*(6682), 266-268. doi: 10.1038/30498

Kollins, S. H., English, J. S., Roley, M. E., O'Brien, B., Blair, J., Lane, S. D., & McClernon, F. J. (2012). Effects of smoking abstinence on smoking-reinforced responding, withdrawal, and cognition in adults with and without attention deficit hyperactivity disorder. *Psychopharmacology (Berl)*. doi: 10.1007/s00213-012-2937-0

Koob, G. F., & Le Moal, M. (1997). Drug abuse: hedonic homeostatic dysregulation. *Science, 278*(5335), 52-58.

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

Koob, G. F., & Le Moal, M. (2005). Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. *Nat Neurosci, 8*(11), 1442-1444.

Koob, G. F., & Le Moal, M. (2008). Review. Neurobiological mechanisms for opponent motivational processes in addiction. *Philos Trans R Soc Lond B Biol Sci, 363*(1507), 3113-3123. doi: C54412M472226253 [pii]10.1098/rstb.2008.0094

Kringelbach, M. L. (2005). The human orbitofrontal cortex: linking reward to hedonic experience. *Nat Rev Neurosci, 6*(9), 691-702.

Kushnir, V., Menon, M., Balducci, X. L., Selby, P., Busto, U., & Zawertailo, L. (2010). Enhanced smoking cue salience associated with depression severity in nicotine-dependent individuals: a preliminary fMRI study. *Int J Neuropsychopharmacol*, 1-12. doi: S1461145710000696 [pii] 10.1017/S1461145710000696

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annu Rev Neurosci, 23*, 155-184. doi: 10.1146/annurev.neuro.23.1.155

Leeman, R. F., O'Malley, S. S., White, M. A., & McKee, S. A. (2010). Nicotine and food deprivation decrease the ability to resist smoking. [Randomized Controlled Trial Research Support, N.I.H., ExtramuralResearch Support, Non-U.S. Gov't]. *Psychopharmacology (Berl), 212*(1), 25-32. doi: 10.1007/s00213-010-1902-z

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *NeuroImage, 19*, 1233-1239.

Martin-Soelch, C., Chevalley, A. F., Kunig, G., Missimer, J., Magyar, S., Mino, A., . . . Leenders, K. L. (2001). Changes in reward-induced brain activation in opiate addicts. *Eur J Neurosci, 14*(8), 1360-1368. doi: 1753 [pii]

Martin-Soelch, C., Missimer, J., Leenders, K. L., & Schultz, W. (2003). Neural activity related to the processing of increasing monetary reward in smokers and nonsmokers. *Eur J Neurosci, 18*(3), 680-688. doi: 2791 [pii]

Martin-Solch, C., Magyar, S., Kunig, G., Missimer, J., Schultz, W., & Leenders, K. L. (2001). Changes in brain activation associated with reward processing in smokers and nonsmokers. A positron emission tomography study. *Exp Brain Res, 139*(3), 278-286.

McBride, D., Barrett, S. P., Kelly, J. T., Aw, A., & Dagher, A. (2006). Effects of expectancy and abstinence on the neural response to smoking cues in cigarette smokers: an fMRI study. *Neuropsychopharmacology, 31*(12), 2728-2738. doi: 10.1038/sj.npp.1301075

McClernon, F. J., Hiott, F. B., Huettel, S. A., & Rose, J. E. (2005). Abstinence-induced changes in self-report craving correlate with event-related FMRI responses to smoking cues. *Neuropsychopharmacology, 30*(10), 1940-1947.

McClernon, F. J., Kozink, R. V., Lutz, A. M., & Rose, J. E. (2009). 24-h smoking abstinence potentiates fMRI-BOLD activation to smoking cues in cerebral cortex and dorsal striatum. *Psychopharmacology (Berl), 204*(1), 25-35. doi: 10.1007/s00213-008-1436-9

McClernon, F. J., Kozink, R. V., & Rose, J. E. (2008). Individual differences in nicotine dependence, withdrawal symptoms, and sex predict transient fMRI-BOLD responses to smoking cues. *Neuropsychopharmacology, 33*(9), 2148-2157.

McClure, S. M., York, M. K., & Montague, P. R. (2004). The neural substrates of reward processing in humans: the modern role of FMRI. *Neuroscientist, 10*(3), 260-268. doi: 10.1177/1073858404263526

McFarland, K., Lapish, C. C., & Kalivas, P. W. (2003). Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *J Neurosci, 23*(8), 3531-3537. doi: 23/8/3531 [pii]

McKee, S. A., Weinberger, A. H., Shi, J., Tetrault, J., & Coppola, S. (2012). Developing and validating a human laboratory model to screen medications for smoking cessation. [Research Support, N.I.H., Extramural]. *Nicotine Tob Res, 14*(11), 1362-1371. doi: 10.1093/ntr/nts090

Mendez, I. A., Williams, M. T., Bhavsar, A., Lu, A. P., Bizon, J. L., & Setlow, B. (2009). Long-lasting sensitization of reward-directed behavior by amphetamine. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Behav Brain Res, 201*(1), 74-79. doi: 10.1016/j.bbr.2009.01.034

Meredith, S. E., Grabinski, M. J., & Dallery, J. Internet-based group contingency management to promote abstinence from cigarette smoking: A feasibility study. *Drug Alcohol Depend*. doi: S0376-8716(11)00096-2 [pii] 10.1016/j.drugalcdep.2011.02.012

Mueller, E. T., Landes, R. D., Kowal, B. P., Yi, R., Stitzer, M. L., Burnett, C. A., & Bickel, W. K. (2009). Delay of smoking gratification as a laboratory model of relapse: effects of incentives for not smoking, and relationship with measures of executive function. [Research Support, N.I.H., Extramural]. *Behav Pharmacol, 20*(5-6), 461-473. doi: 10.1097/FBP.0b013e3283305ec7

Naqvi, N. H., Rudrauf, D., Damasio, H., & Bechara, A. (2007). Damage to the insula disrupts addiction to cigarette smoking. [Research Support, N.I.H., Extramural]. *Science, 315*(5811), 531-534. doi: 10.1126/science.1135926

Nestor, L., McCabe, E., Jones, J., Clancy, L., & Garavan, H. (2011). Differences in "bottom-up" and "top-down" neural activity in current and former cigarette smokers: Evidence for neural substrates which may promote nicotine abstinence through increased cognitive control. [Research Support, Non-U.S. Gov't]. *Neuroimage, 56*(4), 2258-2275. doi: 10.1016/j.neuroimage.2011.03.054

O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., & Dolan, R. J. (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. [Research Support, Non-U.S. Gov't]. *Science, 304*(5669), 452-454. doi: 10.1126/science.1094285

O'Doherty, J., Kringelbach, M. L., Rolls, E. T., Hornak, J., & Andrews, C. (2001). Abstract reward and punishment representations in the human orbitofrontal cortex. *Nat Neurosci, 4*(1), 95-102. doi: 10.1038/82959

O'Doherty, J. P. (2004). Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Curr Opin Neurobiol, 14*(6), 769-776. doi: S0959-4388(04)00168-0 [pii] 10.1016/j.conb.2004.10.016

O'Doherty, J. P., Deichmann, R., Critchley, H. D., & Dolan, R. J. (2002). Neural responses during anticipation of a primary taste reward. *Neuron, 33*(5), 815-826. doi: S0896627302006037 [pii]

Perkins, K. A. (2009). Does smoking cue-induced craving tell us anything important about nicotine dependence? *Addiction, 104*(10), 1610-1616. doi: ADD2550 [pii] 10.1111/j.1360-0443.2009.02550.x

Perkins, K. A., Gerlach, D., Vender, J., Grobe, J., Meeker, J., & Hutchison, S. (2001). Sex differences in the subjective and reinforcing effects of visual and olfactory cigarette smoke stimuli. [Comparative Study Research Support, U.S. Gov't, P.H.S.]. *Nicotine Tob Res, 3*(2), 141-150. doi: 10.1080/14622200110043059

Peters, J., Bromberg, U., Schneider, S., Brassen, S., Menz, M., Banaschewski, T., . . . Buchel, C. (2011). Lower ventral striatal activation during reward anticipation in adolescent smokers. [Research Support, Non-U.S. Gov't]. *Am J Psychiatry, 168*(5), 540-549. doi: 10.1176/appi.ajp.2010.10071024

Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003). Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry, 54*(5), 504-514.

Phillips, P. E., Stuber, G. D., Heien, M. L., Wightman, R. M., & Carelli, R. M. (2003). Subsecond dopamine release promotes cocaine seeking. *Nature, 422*(6932), 614-618. doi: 10.1038/nature01476 nature01476 [pii]

Piper, M. E., McCarthy, D. E., Bolt, D. M., Smith, S. S., Lerman, C., Benowitz, N., . . . Baker, T. B. (2008). Assessing dimensions of nicotine dependence: an evaluation of the Nicotine Dependence Syndrome Scale (NDSS) and the Wisconsin Inventory of Smoking Dependence Motives (WISDM). [Evaluation Studies Research Support, N.I.H., Extramural]. *Nicotine Tob Res, 10*(6), 1009-1020. doi: 10.1080/14622200802097563

Piper, M. E., Piasecki, T. M., Federman, E. B., Bolt, D. M., Smith, S. S., Fiore, M. C., & Baker, T. B. (2004). A multiple motives approach to tobacco dependence: the Wisconsin Inventory of Smoking Dependence Motives (WISDM-68). [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Validation Studies]. *J Consult Clin Psychol, 72*(2), 139-154. doi: 10.1037/0022-006X.72.2.139

Powell, J., Dawkins, L., & Davis, R. E. (2002). Smoking, reward responsiveness, and response inhibition: tests of an incentive motivational model. *Biol Psychiatry, 51*(2), 151-163.

Powell, J. H., Pickering, A. D., Dawkins, L., West, R., & Powell, J. F. (2004). Cognitive and psychological correlates of smoking abstinence, and predictors of successful cessation. *Addict Behav, 29*(7), 1407-1426.

Ray, J. P., & Price, J. L. (1993). The organization of projections from the mediodorsal nucleus of the thalamus to orbital and medial prefrontal cortex in macaque monkeys. *J Comp Neurol, 337*(1), 1-31. doi: 10.1002/cne.903370102

Reynolds, B., Dallery, J., Shroff, P., Patak, M., & Leraas, K. (2008). A web-based contingency management program with adolescent smokers. *J Appl Behav Anal, 41*(4), 597-601.

Robbins, T. W., & Everitt, B. J. (1992). Functions of dopamine in the dorsal and ventral striatum. *Seminars in Neuroscience, 4*(2), 119-127.

Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Brain Res Rev, 18*(3), 247-291.

Robinson, T. E., & Berridge, K. C. (2008). Review. The incentive sensitization theory of addiction: some current issues. [Research Support, N.I.H., ExtramuralReview]. *Philos Trans R Soc Lond B Biol Sci, 363*(1507), 3137-3146. doi: 10.1098/rstb.2008.0093

Robinson, T. E., & Kolb, B. (2004). Structural plasticity associated with exposure to drugs of abuse. *Neuropharmacology, 47 Suppl 1*, 33-46.

Roesch, M. R., Calu, D. J., Esber, G. R., & Schoenbaum, G. (2010). All that glitters ... dissociating attention and outcome expectancy from prediction errors signals. *J Neurophysiol, 104*(2), 587-595. doi: jn.00173.2010 [pii]10.1152/jn.00173.2010

Roesch, M. R., & Olson, C. R. (2003). Impact of expected reward on neuronal activity in prefrontal cortex, frontal and supplementary eye fields and premotor cortex. *J Neurophysiol, 90*(3), 1766-1789. doi: 10.1152/jn.00019.200300019.2003 [pii]

Roesch, M. R., & Olson, C. R. (2004). Neuronal activity related to reward value and motivation in primate frontal cortex. *Science, 304*(5668), 307-310. doi: 10.1126/science.1093223304/5668/307 [pii]

Roll, J. M., & Higgins, S. T. (2000). A within-subject comparison of three different schedules of reinforcement of drug abstinence using cigarette smoking as an exemplar. *Drug Alcohol Depend, 58*(1-2), 103-109. doi: S0376-8716(99)00073-3 [pii]

Roll, J. M., Higgins, S. T., & Badger, G. J. (1996). An experimental comparison of three different schedules of reinforcement of drug abstinence using cigarette smoking as an exemplar. *J Appl Behav Anal, 29*(4), 495-504; quiz 504-495. doi: 10.1901/jaba.1996.29-495

Rolls, E. T. (2000). The orbitofrontal cortex and reward. *Cereb Cortex, 10*(3), 284-294.

Rolls, E. T., Thorpe, S. J., & Maddison, S. P. (1983). Responses of striatal neurons in the behaving monkey. 1. Head of the caudate nucleus. [Research Support, Non-U.S. Gov't]. *Behav Brain Res, 7*(2), 179-210.

Rose, E. J., Ross, T. J., Salmeron, B. J., Lee, M., Shakleya, D. M., Huestis, M., & Stein, E. A. (2012). Chronic exposure to nicotine is associated with reduced reward-related activity in the striatum but not the midbrain. [Randomized Controlled Trial Research Support, N.I.H., Intramural]. *Biol Psychiatry, 71*(3), 206-213. doi: 10.1016/j.biopsych.2011.09.013

Rose, J. E., Behm, F. M., Westman, E. C., & Johnson, M. (2000). Dissociating nicotine and nonnicotine components of cigarette smoking. [Research Support, U.S. Gov't, P.H.S.]. *Pharmacol Biochem Behav, 67*(1), 71-81.

Rushworth, M. F., & Behrens, T. E. (2008). Choice, uncertainty and value in prefrontal and cingulate cortex. *Nat Neurosci, 11*(4), 389-397. doi: nn2066 [pii] 10.1038/nn2066

Schoenbaum, G., Setlow, B., & Ramus, S. J. (2003). A systems approach to orbitofrontal cortex function: recordings in rat orbitofrontal cortex reveal interactions with different learning systems. *Behav Brain Res, 146*(1-2), 19-29. doi: S0166432803003358 [pii]

Schuh, K. J., & Stitzer, M. L. (1995). Desire to smoke during spaced smoking intervals. [Clinical Trial Randomized Controlled Trial Research Support, U.S. Gov't, P.H.S.]. *Psychopharmacology (Berl), 120*(3), 289-295.

Schultz, W. (2000). Multiple reward signals in the brain. *Nat Rev Neurosci, 1*(3), 199-207. doi: 10.1038/35044563

Schultz, W., & Dickinson, A. (2000). Neuronal coding of prediction errors. *Annu Rev Neurosci, 23*, 473-500. doi: 10.1146/annurev.neuro.23.1.473

Sescousse, G., Caldu, X., Segura, B., & Dreher, J. C. (2013). Processing of primary and secondary rewards: A quantitative meta-analysis and review of human functional neuroimaging studies. *Neurosci Biobehav Rev*. doi: S0149-7634(13)00037-7 [pii] 10.1016/j.neubiorev.2013.02.002

Shahan, T. A., Bickel, W. K., Madden, G. J., & Badger, G. J. (1999). Comparing the reinforcing efficacy of nicotine containing and de-nicotinized cigarettes: a behavioral economic analysis. [Research Support, U.S. Gov't, P.H.S.]. *Psychopharmacology (Berl), 147*(2), 210-216.

Shiffman, S., Waters, A., & Hickcox, M. (2004). The nicotine dependence syndrome scale: a multidimensional measure of nicotine dependence. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Nicotine Tob Res, 6*(2), 327-348. doi: 10.1080/14622200420002024 81

Skjei, K. L., & Markou, A. (2003). Effects of repeated withdrawal episodes, nicotine dose, and duration of nicotine exposure on the severity and duration of nicotine withdrawal in rats. *Psychopharmacology (Berl), 168*(3), 280-292.

Stoops, W. W., Dallery, J., Fields, N. M., Nuzzo, P. A., Schoenberg, N. E., Martin, C. A., . . . Wong, C. J. (2009). An internet-based abstinence reinforcement smoking cessation intervention in rural smokers. *Drug Alcohol Depend, 105*(1-2), 56-62. doi: S0376-8716(09)00227-0 [pii] 10.1016/j.drugalcdep.2009.06.010

Strohle, A., Stoy, M., Wrase, J., Schwarzer, S., Schlagenhauf, F., Huss, M., . . . Heinz, A. (2008). Reward anticipation and outcomes in adult males with attention-deficit/hyperactivity disorder. *Neuroimage, 39*(3), 966-972. doi: 10.1016/j.neuroimage.2007.09.044

Styn, M. A., Nukui, T., Romkes, M., Perkins, K., Land, S. R., & Weissfeld, J. L. (2008). The impact of genetic variation in DRD2 and SLC6A3 on smoking cessation in a cohort of participants 1 year after enrollment in a lung cancer screening study. *Am J Med Genet B Neuropsychiatr Genet*.

Sweitzer, M. M., Denlinger, R. L., & Donny, E. C. (2013). Dependence and withdrawal-induced craving predict abstinence in an incentive-based model of smoking relapse. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.]. *Nicotine Tob Res, 15*(1), 36-43. doi: 10.1093/ntr/nts080

Sweitzer, M. M., Donny, E. C., & Hariri, A. R. (2012). Imaging genetics and the neurobiological basis of individual differences in vulnerability to addiction. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Drug Alcohol Depend, 123 Suppl 1*, S59-71. doi: 10.1016/j.drugalcdep.2012.01.017

Takahashi, H., Fujimura, Y., Hayashi, M., Takano, H., Kato, M., Okubo, Y., . . . Suhara, T. (2008). Enhanced dopamine release by nicotine in cigarette smokers: a double-blind, randomized, placebo-controlled pilot study. *Int J Neuropsychopharmacol, 11*(3), 413-417.

Tang, D. W., Fellows, L. K., Small, D. M., & Dagher, A. (2012). Food and drug cues activate similar brain regions: a meta-analysis of functional MRI studies. [Meta-Analysis]. *Physiol Behav, 106*(3), 317-324. doi: 10.1016/j.physbeh.2012.03.009

Thiel, K. J., Sanabria, F., & Neisewander, J. L. (2009). Synergistic interaction between nicotine and social rewards in adolescent male rats. *Psychopharmacology (Berl), 204*(3), 391-402. doi: 10.1007/s00213-009-1470-2

Thut, G., Schultz, W., Roelcke, U., Nienhusmeier, M., Missimer, J., Maguire, R. P., & Leenders, K. L. (1997). Activation of the human brain by monetary reward. *Neuroreport, 8*(5), 1225-1228.

Tidey, J. W., O'Neill, S. C., & Higgins, S. T. (2002). Contingent monetary reinforcement of smoking reductions, with and without transdermal nicotine, in outpatients with schizophrenia. *Exp Clin Psychopharmacol, 10*(3), 241-247.

Tiffany, S. T., & Carter, B. L. (1998). Is craving the source of compulsive drug use? *J Psychopharmacol, 12*(1), 23-30.

Toll, B. A., Katulak, N. A., & McKee, S. A. (2006). Investigating the factor structure of the Questionnaire on Smoking Urges-Brief (QSU-Brief). [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.]. *Addict Behav, 31*(7), 1231-1239. doi: 10.1016/j.addbeh.2005.09.008

Tomasi, D., & Volkow, N. D. (2013). Striatocortical pathway dysfunction in addiction and obesity: differences and similarities. [Research Support, N.I.H., Extramural]. *Crit Rev Biochem Mol Biol, 48*(1), 1-19. doi: 10.3109/10409238.2012.735642

Van Zundert, R. M., Ferguson, S. G., Shiffman, S., & Engels, R. (2012). Dynamic effects of craving and negative affect on adolescent smoking relapse. *Health Psychol, 31*(2), 226-234. doi: 2011-21629-001 [pii] 10.1037/a0025204

Vanderschuren, L. J., Di Ciano, P., & Everitt, B. J. (2005). Involvement of the dorsal striatum in cue-controlled cocaine seeking. *J Neurosci, 25*(38), 8665-8670. doi: 25/38/8665 [pii] 10.1523/JNEUROSCI.0925-05.2005

Vanderschuren, L. J., & Kalivas, P. W. (2000). Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. *Psychopharmacology (Berl), 151*(2-3), 99-120.

Versace, F., Engelmann, J. M., Jackson, E. F., Costa, V. D., Robinson, J. D., Lam, C. Y., . . . Cinciripini, P. M. (2011). Do brain responses to emotional images and cigarette cues differ? An fMRI study in smokers. *Eur J Neurosci, 34*(12), 2054-2063. doi: 10.1111/j.1460-9568.2011.07915.x

Vezina, P. (2004). Sensitization of midbrain dopamine neuron reactivity and the self-administration of psychomotor stimulant drugs. *Neurosci Biobehav Rev, 27*(8), 827-839. doi: 10.1016/j.neubiorev.2003.11.001 S0149763403001398 [pii]

Vezina, P., McGehee, D. S., & Green, W. N. (2007). Exposure to nicotine and sensitization of nicotine-induced behaviors. *Prog Neuropsychopharmacol Biol Psychiatry, 31*(8), 1625-1638. doi: S0278-5846(07)00313-2 [pii] 10.1016/j.pnpbp.2007.08.038

Volkow, N. D., & Fowler, J. S. (2000). Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cereb Cortex, 10*(3), 318-325.

Volkow, N. D., Fowler, J. S., & Wang, G. J. (2003). The addicted human brain: insights from imaging studies. *J Clin Invest, 111*(10), 1444-1451.

Volkow, N. D., Fowler, J. S., & Wang, G. J. (2004). The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. *Neuropharmacology, 47 Suppl 1*, 3-13.

Volkow, N. D., Fowler, J. S., Wang, G. J., Hitzemann, R., Logan, J., Schlyer, D. J., . . . Wolf, A. P. (1993). Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse, 14*(2), 169-177. doi: 10.1002/syn.890140210

Volkow, N. D., Wang, G. J., Fowler, J. S., Tomasi, D., & Baler, R. (2012). Food and drug reward: overlapping circuits in human obesity and addiction. *Curr Top Behav Neurosci, 11*, 1-24. doi: 10.1007/7854_2011_169

Volkow, N. D., Wang, G. J., Telang, F., Fowler, J. S., Logan, J., Childress, A. R., . . . Wong, C. (2006). Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *J Neurosci, 26*(24), 6583-6588. doi: 26/24/6583 [pii] 10.1523/JNEUROSCI.1544-06.2006

Volkow, N. D., Wang, G. J., Telang, F., Fowler, J. S., Logan, J., Jayne, M., . . . Wong, C. (2007). Profound decreases in dopamine release in striatum in detoxified alcoholics: possible orbitofrontal involvement. *J Neurosci, 27*(46), 12700-12706. doi: 27/46/12700 [pii] 10.1523/JNEUROSCI.3371-07.2007

Vorel, S. R., Liu, X., Hayes, R. J., Spector, J. A., & Gardner, E. L. (2001). Relapse to cocaine-seeking after hippocampal theta burst stimulation. *Science, 292*(5519), 1175-1178. doi: 10.1126/science.1058043 292/5519/1175 [pii]

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol, 54*(6), 1063-1070.

Weaver, M. T., Sweitzer, M., Coddington, S., Sheppard, J., Verdecchia, N., Caggiula, A. R., . . . Donny, E. C. (2012). Precipitated withdrawal from nicotine reduces reinforcing effects of a visual stimulus for rats. [Research Support, N.I.H., Extramural]. *Nicotine Tob Res, 14*(7), 824-832. doi: 10.1093/ntr/ntr293

Weiss, F., Maldonado-Vlaar, C. S., Parsons, L. H., Kerr, T. M., Smith, D. L., & Ben-Shahar, O. (2000). Control of cocaine-seeking behavior by drug-associated stimuli in rats: effects on recovery of extinguished operant-responding and extracellular dopamine levels in amygdala and nucleus accumbens. *Proc Natl Acad Sci U S A, 97*(8), 4321-4326. doi: 97/8/4321 [pii]

Wilson, S. J., Sayette, M. A., Delgado, M. R., & Fiez, J. A. (2005). Instructed smoking expectancy modulates cue-elicited neural activity: a preliminary study. *Nicotine Tob Res, 7*(4), 637-645. doi: GJ72024027671722 [pii] 10.1080/14622200500185520

Wilson, S. J., Sayette, M. A., Delgado, M. R., & Fiez, J. A. (2008). Effect of smoking opportunity on responses to monetary gain and loss in the caudate nucleus. *J Abnorm Psychol, 117*(2), 428-434. doi: 2008-05639-018 [pii] 10.1037/0021-843X.117.2.428

Wilson, S. J., Sayette, M. A., & Fiez, J. A. (2004). Prefrontal responses to drug cues: a neurocognitive analysis. *Nat Neurosci, 7*(3), 211-214. doi: 10.1038/nn1200 nn1200 [pii]

Wilson, S. J., Sayette, M. A., & Fiez, J. A. (2012). Quitting-unmotivated and quitting-motivated cigarette smokers exhibit different patterns of cue-elicited brain activation when anticipating an opportunity to smoke. [Research Support, N.I.H., Extramural]. *J Abnorm Psychol, 121*(1), 198-211. doi: 10.1037/a0025112

Wong, D. F., Kuwabara, H., Schretlen, D. J., Bonson, K. R., Zhou, Y., Nandi, A., . . . London, E. D. (2006). Increased occupancy of dopamine receptors in human striatum during cue-elicited cocaine craving. *Neuropsychopharmacology, 31*(12), 2716-2727. doi: 1301194 [pii] 10.1038/sj.npp.1301194

Worsley, K. J., & Friston, K. J. (1995). Analysis of fMRI time-series revisited--again. [Comment Research Support, Non-U.S. Gov't]. *Neuroimage, 2*(3), 173-181. doi: 10.1006/nimg.1995.1023

Wrase, J., Grusser, S. M., Klein, S., Diener, C., Hermann, D., Flor, H., . . . Heinz, A. (2002). Development of alcohol-associated cues and cue-induced brain activation in alcoholics. *Eur Psychiatry, 17*(5), 287-291. doi: S0924933802006764 [pii]

Wrase, J., Schlagenhauf, F., Kienast, T., Wustenberg, T., Bermpohl, F., Kahnt, T., . . . Heinz, A. (2007). Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. *Neuroimage, 35*(2), 787-794. doi: S1053-8119(06)01159-1 [pii] 10.1016/j.neuroimage.2006.11.043

Wray, J. M., Gass, J. C., & Tiffany, S. T. (2013). A Systematic Review of the Relationships Between Craving and Smoking Cessation. *Nicotine Tob Res*. doi: 10.1093/ntr/nts268

Xu, X., Wang, J., Aron, A., Lei, W., Westmaas, J. L., & Weng, X. (2012). Intense passionate love attenuates cigarette cue-reactivity in nicotine-deprived smokers: an FMRI study. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.]. *PLoS One, 7*(7), e42235. doi: 10.1371/journal.pone.0042235

Zald, D. H., Boileau, I., El-Dearedy, W., Gunn, R., McGlone, F., Dichter, G. S., & Dagher, A. (2004). Dopamine transmission in the human striatum during monetary reward tasks. *J Neurosci, 24*(17), 4105-4112. doi: 10.1523/JNEUROSCI.4643-03.2004 24/17/4105 [pii]

Zarahn, E., Aguirre, G. K., & D'Esposito, M. (1997). Empirical analyses of BOLD fMRI statistics. I. Spatially unsmoothed data collected under null-hypothesis conditions. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Neuroimage, 5*(3), 179-197.

Zijlstra, F., Veltman, D. J., Booij, J., van den Brink, W., & Franken, I. H. (2009). Neurobiological substrates of cue-elicited craving and anhedonia in recently abstinent opioid-dependent males. *Drug Alcohol Depend, 99*(1-3), 183-192. doi: S0376-8716(08)00254-8 [pii] 10.1016/j.drugalcdep.2008.07.012