ABSTRACT

Title of Document: CORTICOLIMBIC FUNCTIONING, NICOTINE DEPENDENCE CHARACTERISTICS, AND SMOKING LAPSE HISTORY: AN FMRI STUDY

Jessica M. Richards, Doctor of Philosophy, 2014

Directed By: Professor Carl W. Lejuez, Department of Psychology

Nicotine dependence is a prevalent and costly disorder characterized by notoriously high relapse rates. Extant research implicates stress as a key mechanism driving smoking across the stages of addiction, and neurobiological models of stress and addiction emphasize the role of overlapping corticolimbic circuits in both emotion dysregulation and compulsive drug seeking. However, neuroimaging research examining the neural correlates of stress processing in human smokers is limited and lacking in some areas, leaving key questions unanswered. Specifically, it is unclear how neural responses to stress may explain individual differences in nicotine dependence severity and cessation attempt outcomes. Moreover, more recent theoretical and empirical work has highlighted the importance of looking beyond functioning in discreet neural regions and has emphasized the importance of examining how brain functioning at a network level, through the use of resting state

functional connectivity, might explain addictive behavior. However, research examining the relationship between functional connectivity and clinically-relevant smoking measures is also limited. As a first step toward addressing these gaps in the literature, the current study utilized a novel fMRI-compatible psychological stress induction task to examine the relationships between stress-induced neural activation, as well as resting state functional connectivity within stress-related corticolimbic circuits, and clinically-relevant smoking characteristics among a sample of adult cigarette smokers. Analysis of the fMRI data collected during administration of the novel stress induction task revealed significant stress-induced activation in the right insula, a region previously implicated in the interoceptive experience of negative affective states, as well as visceral symptoms of nicotine withdrawal and craving. Contrary to expectations, there were no significant relationships identified between stress-induced neural functioning, or functional connectivity within stress-related circuits, and the clinically-relevant smoking measures that were assessed. Findings are discussed in light of several study limitations and directions for future research are enumerated.

CORTICOLIMBIC FUNCTIONING, NICOTINE DEPENDENCE CHARACTERISTICS, AND SMOKING LAPSE HISTORY: AN FMRI STUDY

By

Jessica M. Richards

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, College Park, in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2014

Advisory Committee:
Professor Carl W. Lejuez, Ph.D., Chair
Associate Professor Stacey B. Daughters
Associate Professor Laura MacPherson
Associate Professor Jens Herberholz
Associate Professor Eric Wish
Dr. Elliot A. Stein

© Copyright by
Jessica M. Richards
2014

Table of Contents

List of Tables

List of Figures

List of Illustrations

Chapter 1: Introduction

1.1. Project Overview

Nicotine dependence is a prevalent and costly disorder characterized by notoriously high relapse rates, thus representing a significant public health concern. Given the intractable nature of the disorder, a strong emphasis has been placed on understanding the processes associated with smoking maintenance and relapse following cessation. Extant research implicates stress as a key mechanism driving substance use across the stages of addiction. Moreover, neurobiological models (e.g., Li & Sinha, 2008) emphasize the role of overlapping corticolimbic circuits in both emotion dysregulation and compulsive drug seeking. However, neuroimaging research examining the neural correlates of stress processing in human smokers is very limited and lacking in some areas, leaving key questions unanswered. Specifically, it is unclear how neural responses to stress may explain individual differences in nicotine dependence severity and cessation outcomes. Moreover, recent theoretical and empirical work has highlighted the importance of looking beyond functioning in discreet neural regions by examining how brain functioning at a network level may explain addictive behavior through the use of resting state functional connectivity. However, work of this kind among human smokers is also limited to date. As such, the current study was designed to address these gaps in the extant literature by examining the relationships between stress-induced neural activation, as well as resting state functional connectivity within corticolimbic circuits, and clinically-relevant smoking-related variables among a sample of adult smokers. The current study sought to set the stage for larger, prospective longitudinal studies that aim

to predict smoking outcomes among treatment seeking smokers based on their stress-related corticolimbic functioning and network level functioning in stress- and addiction-related circuits.

1.2. Smoking as a Public Health Concern

The CDC estimates that approximately 19% of all adults in the United States currently smoke cigarettes, with men exhibiting higher rates of smoking than women (21% vs. 17% respectively) (Schiller, Lucas, Ward, & Peregoy, 2012). As a result, 8.6 million people in the U.S. suffer from smoking-related illnesses, leading to staggering economic costs including over $130 billion per year in direct medical costs, and an additional $150 billion annually in lost productivity (CDC, 2005; USDHHS, 2014). Beyond the high rates of illness and financial costs, cigarette smoking is also the leading cause of preventable death, responsible for approximately 1 in 5 deaths in the U.S. (~480,000) each year (USDHHS, 2014). Despite the negative consequences of smoking, cessation is notoriously difficult. Approximately one third of smokers attempt to quit each year; however, only about 10% of those who attempt to quit will ultimately succeed in maintaining long-term abstinence (CDC, 2005).

Clearly, cigarette smoking is highly prevalent, costly, and intractable, thus presenting a major public health concern. Therefore, researchers have examined various factors associated with cigarette smoking, with a growing body of research focusing specifically on the role of stress and negative affectivity in nicotine use, dependence, and relapse following cessation. Given the large body of evidence supporting the role of stress and negative affectivity as a key factor underlying substance use outcomes across drug classes, the following review begins with a very broad overview of stress and

addiction and a discussion of negative reinforcement theories that emphasize the role of stress in substance use in relapse. We then focus on a review of the literature on stress and cigarette smoking more specifically.

1.3 Stress and Addiction

In examining the potential mechanisms that may underlie substance use and relapse, a long history of evidence implicates stress and negative affectivity as a contributing factor across drug classes (Conger, 1956; Khantzian, 1985; Koob et al., 2014; Koob & Le Moal, 1997, 2001; Leventhal & Cleary, 1980; Marlatt & Gordon, 1985; Russell & Mehrabian, 1975; Sher & Levenson, 1982; Shiffman, 1982; Sinha, 2001; Solomon, 1977; Tomkins, 1966; Wikler, 1948; Wills & Shiffman, 1985). Affective distress includes feelings such as anxiety, stress, and irritability, and is often associated with poor substance use outcomes (Baker, Japuntich, Hogle, McCarthy, & Curtin, 2006). For instance, studies consistently report relapse to drug use in situations involving negative moods such as anxiety, anger, and depression (Brandon, Tiffany, Obremski, & Baker, 1990; ElGeili & Bashir, 2005; Litman, Stapleton, Oppenheim, & Peleg, 1983; Marlatt & Gordon, 1985; Tate, Brown, Unrod, & Ramo, 2004), and the severity of these symptoms has been shown to predict treatment outcome and relapse across drug classes (e.g., Ciraulo, Piechniczek-Buczek, & Iscan, 2003; Mulvaney, Alterman, Boardman, & Kampman, 1999).

In line with evidence supporting the relationship between affective distress and substance use, negative reinforcement theories collectively emphasize that the motivational basis of addictive drug use is the reduction or avoidance of aversive internal states (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Khantzian, 1985; Solomon,

1977; Wikler, 1948). Thus, substance dependent individuals in the initial stages of an abstinence attempt who experience the highest levels of withdrawal-induced or environmentally-induced affective distress (e.g., stress, frustration, irritability), are most likely to relapse to drug use as a means of temporarily alleviating emotional discomfort. Over time, individuals become biased toward engaging in behavioral responses that have most effectively reduced negative affect in the past (i.e., substance use), and at very high levels of negative affect, these behavioral responses may be engaged reflexively (Baker et al., 2004). At the same time, alternative behavioral responses that are less tightly linked with the amelioration of negative affect are devalued, resulting in an overreliance on substance use as a means of regulating negative affect.

1.4 Stress and Cigarette Smoking

Specific to smoking, ample evidence suggests that acute and chronic affective distress is related to smoking across multiple stages of the addiction process. In studies involving self-report of smoking behavior and motivations, smokers have reported that they initiated smoking due to elevated life stress and the belief that smoking would help them relax (Nichter, Nichter, Vuckovic, Quintero, & Ritenbaugh, 1997). Once initiated, smokers consistently report stress relief as a primary motivator for continued smoking (Fidler & West, 2009; McEwen, West, & McRobbie, 2008), as well as a reluctance to quit smoking due to high stress levels in their lives (Lader, 2007). Additionally, retrospective self-report studies have frequently shown significant relationships between exposure to stressful or traumatic events (e.g., surviving Hurricane Katrina, being sexually assaulted, and witnessing the September 11th terrorist attacks in New York City) and increased smoking behavior (e.g., Amstadter, Nugent, et al., 2009; Amstadter,

Resnick, et al., 2009; Nandi, Galea, Ahern, & Vlahov, 2005). However, a similar study of individuals exposed to a fire with mass casualties in the Netherlands did not find evidence of increased smoking among survivors following the event (Reijneveld, Crone, Verhulst, & Verloove-Vanhorick, 2003). Finally, individuals who have recently quit smoking show a positive relationship between negative affect and smoking urges (Doherty, Kinnunen, Militello, & Garvey, 1995) and commonly endorse stress as a key factor to explain relapses to smoking following cessation (Cohen & Lichtenstein, 1990; Falba, Teng, Sindelar, & Gallo, 2005; Heishman, 1999; Hymowitz, Sexton, Ockene, & Grandits, 1991; Matheny & Weatherman, 1998; Siahpush & Carlin, 2006; Wewers, 1988).

Laboratory studies involving exposure to acute stress manipulations with human smokers generally support self-report evidence for a relationship between stress and smoking. Specifically, smokers have reported greater desire to smoke when completing a stressful computer task compared to a control task (Perkins & Grobe, 1992). Moreover, exposure to other stressful stimuli in the laboratory, including loud noises (Cherek, 1985) and a social stress induction (Rose, Ananda, & Jarvik, 1983) leads to increases in actual smoking behavior. Interestingly, data collected on a moment-to-moment basis in real-time using ecological momentary assessment (EMA) have failed to show a relationship between acute negative affect and smoking behavior among active smokers (Shiffman et al., 2002), but these same data do show that rapid acute increases in stress tend to immediately precede smoking lapses among individuals trying to quit smoking (Shiffman & Waters, 2004).

Animal models have also been used to study the role of stress in relapse to smoking. Reinstatement models are generally used to test which factors contribute to a return to self-administration of a drug following extinction. Similar to other drugs of abuse, exposure to stress is associated with a return to nicotine self-administration, even after prolonged extinction (Buczek, Le, Wang, Stewart, & Shaham, 1999; Zislis, Desai, Prado, Shah, & Bruijnzeel, 2007). Furthermore, rats exposed to a restraint stress show reinstatement of nicotine-induced conditioned place preference following extinction procedures (Leao, Cruz, & Planeta, 2009).

Taken together, evidence from human self-report and experimental studies, as well as work with animal models of stress and addiction, support the idea that stress plays a key role in smoking across the stages of addiction. However, not every individual who experiences heightened stress will go on to initiate or relapse to smoking, thus highlighting the need identify mechanisms, including neurobiological mechanisms, driving the stress-smoking relationship among human smokers in order to identify individuals who are most vulnerable to stress-induced smoking and relapse, and inform treatment development.

1.4 Operationalizing Smoking Severity and Outcomes

Importantly, one factor to consider in conducting research examining the processes underlying the stress-addiction relationship in smokers is the selection of specific smoking-related variables to assess. Indeed, across studies of smoking (and addiction more generally), there is wide variability in the way that addiction severity and outcomes have been operationalized (for reviews and recommendations, see Shiffman, Hickcox, et al., 1996; West, Hajek, Stead, & Stapleton, 2005), and studies examining

neural processes underlying addictive behavior have shown that neurobiological measures can differentially predict substance use outcomes, depending on how the outcomes are operationalized (e.g., Sinha & Li, 2007).

One approach that is often used is to assess self-reported dependence severity using standardized psychometric scales designed to assess the various thoughts, feelings, symptoms, and behaviors associated with nicotine dependence. One such measure is the Fagerström Test for Nicotine Dependence (FTND; T. F. Heatherton, L. T. Kozlowski, R. C. Frecker, & K. O. Fagerstrom, 1991). The FTND includes 6 items and produces a score from 0 to 10, with higher scores indicating more severe nicotine dependence. The FTND has been shown to mark genetic liability for nicotine dependence, with heritability rates ranging from 0.72 to 0.75 across studies (Kendler et al., 1999; Vink, Willemsen, & Boomsma, 2005). Over the past two decades, the FTND has emerged as a standard measure of nicotine dependence in the field, and its use in the field of human neuroimaging research in particular continues to grow.

Alternatively, researchers can also assess severity of smoking behaviorally by assessing heaviness of smoking, as indicated by average number of cigarettes smoked per day. Given that the mood enhancing and anxiolytic properties of nicotine have been estimated to last only about 10 minutes following acute cigarette exposure (Parrott, 1995), individuals who are more averse to experiencing negative affect, and thus more vulnerable to the negatively reinforcing properties of cigarettes, may smoke with a shorter latency between cigarettes in order to avoid acute withdrawal symptoms, leading to an overall larger number of cigarettes smoked per day. Number of cigarettes per day is also important to assess as a complement to self-reported nicotine dependence severity as

there is evidence of racial differences in the relationship between number of cigarettes smoked per day and self-reported ratings of dependence, with African American individuals evidencing higher levels of self-reported nicotine dependence than their Caucasian counterparts, even when smoking the same number of cigarettes per day (Luo et al., 2008). There is also evidence that a variety of factors, including psychological factors, race, varying nicotine doses across cigarette brands, and choice of mentholated versus unmentholated cigarettes can all impact the amount of nicotine ingested per cigarette and the rate at which nicotine is metabolized once it is taken in (e.g., Clark, Gautam, & Gerson, 1996; Patterson et al., 2003; Wagenknecht et al., 1990). These findings suggest that number of cigarettes per day does not necessarily reflect total nicotine intake, and may explain why number of cigarettes smoked per day does not directly map onto nicotine dependence severity. As such, number of cigarettes per day is another important outcome to assess given its theoretical relevance to the relationship between stress and smoking, and also due to the variety of factors that modulate the relationship between cigarettes per day and self-reported dependence severity, suggesting that simple reports of number of cigarettes per day may tap different aspects of smoking severity as compared to self-reported nicotine dependence.

Another highly relevant measure to assess is stress-induced craving. There is ample evidence to suggest that psychological stress is associated with increases in self-reported craving among chronic substance users across drug classes (Sinha, 2001, 2008). Further, craving is a reliable predictor of substance use outcomes, with prospective studies consistently showing a relationship between craving and relapse to substance use following cessation, a pattern that also holds across drug classes (Crits-Christoph et al.,

2007; Doherty et al., 1995; Litt, Cooney, & Morse, 2000; O'Connell, Schwartz, Gerkovich, Bott, & Shiffman, 2004; Paliwal, Hyman, & Sinha, 2008). As such, stress-induced craving represents an important clinical construct of interest, and may be an important process to study in examining the mechanisms underlying the relationship between stress and addiction.

Additionally, looking at one's history of smoking behavior can also be highly informative in smoking research. Smoking lapse history, and a history of 'early lapse' (i.e., within 24 hours of attempted cessation) in particular, represents a clinically-relevant behavioral outcome variable when studying stress and nicotine addiction (e.g., R. A. Brown, Lejuez, Kahler, Strong, & Zvolensky, 2005). Here, lapse is defined as an instance of smoking (even a puff of a cigarette) following a smoking cessation attempt. Evidence suggests that uncomfortable withdrawal symptoms and negative affect both are predictive of early lapse among smokers (al'Absi, Hatsukami, Davis, & Wittmers, 2004; Brandon et al., 2003; Kenford et al., 2002; McCarthy, Piasecki, Fiore, & Baker, 2006; Shiffman et al., 1997; Strasser et al., 2005) and that those who ultimately lapse to smoking do so due to a failure to initiate immediate coping in the face of distress (Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996). As such, smoking lapse history represents another important clinical measure of interest, and serves as a theoretically relevant outcome to assess in studying the relationship between stress and addiction.

1.5 Preliminary Summary and Next Steps

Based on the evidence reviewed above, it appears that stress contributes to drug craving and substance use severity and maintenance, as well as relapse risk across drug classes (e.g., Cohen & Lichtenstein, 1990; Shiffman, Paty, et al., 1996; Sinha, 2008;

Wills, Sandy, & Yaeger, 2002). Specific to smoking, stress is predictive of a variety of different clinically-relevant, smoking-related variables, suggesting that stress may contribute to smoking behavior in a variety of ways, including increasing smoking urges or craving, exacerbating smoking heaviness and dependence severity, and contributing to poor cessation outcomes. However, less is known about the specific mechanisms, including neurobiological mechanisms, that may determine who is most vulnerable to stress-induced craving and smoking, and may help to identify novel targets for smoking interventions.

To date, there have been very few neuroimaging studies directly examining emotional stress processing in human participants with substance use disorders. Despite the limited data on the direct relationship between stress and addiction, a large body of work has explored these processes separately, and a smaller body of work is beginning to study the neural correlates of stress and addiction together. Based on this work, there is support for the role of overlapping corticolimbic circuits in both stress processing and regulation, and addiction. As such, the following section reviews the available literature on the neural correlates of stress and addiction. We begin with an overview of the primary method, functional magnetic resonance imaging (fMRI), that is used to examine neural functioning in humans. We then review specific neural regions and circuits that have been implicated in both stress and addiction, and finally, we provide a theoretical model of the neural mechanisms underlying the relationship between these two processes.

1.6 The Neurobiology of Addiction and Stress

1.6.1 fMRI basics

Functional magnetic resonance imaging (fMRI) is a noninvasive neuroimaging technique that has the temporal and spatial resolution necessary to investigate fluctuations in brain functioning over time within millimeters of neural structures of interest (P. Bandettini, 2007; Huettel, Song, & McCarthy, 2009). MRI scanners work by using strong magnetic fields to create images of biological tissue. Specifically, the scanner is calibrated to emit electromagnetic signals that are in tune with the frequency of hydrogen nuclei, which are the most prevalent nuclei in the human body due to their abundance in water molecules. The hydrogen nuclei absorb the energy emitted by the scanner, and later emit their own signals that vary depending on the numbers and types of nuclei present in the tissue being scanned. By measuring variations in the signals emitted by hydrogen nuclei, the MRI scanner can distinguish between different types of tissue, such as gray and white matter in the brain, and a static image can be created, providing an anatomical map of the brain.

By using an MRI scanner to repeatedly measure the signals emitted by hydrogen atoms over time, inferences about neural functioning can be made (Forster et al., 1998). When neural activation occurs, there is an increase in local oxygenated blood flow, which alters the magnetic signal emitted by hydrogen atoms. This altered magnetic signal is known as the blood oxygenated level dependent (BOLD) response. With this knowledge, it became possible to create MRI compatible tasks that were designed to isolate particular processes of interest, and then contrast the magnitude of the BOLD signal in response to varying task conditions in order to localize task-induced neural functioning. Using this

BOLD contrast technique, researchers have been able to localize the neural basis of a wide range of motor, sensory, and cognitive processes, and use of this technique continues to grow (P. Bandettini, 2007). In the current study, a psychological stress induction task was administered and the BOLD contrast between a stressful task phase compared to a non-stressful task phase will be used in an attempt to localize stress-related neural functioning.

Beyond measuring task-induced activation within circumscribed neural regions, fMRI can also be used to infer the strength of network level connections within the human brain. Functional connectivity is defined as, "the temporal dependency of neuronal activation patterns of anatomically separated brain regions" (van den Heuvel & Hulshoff Pol, 2010, p. 520) and the past several years have seen a growing body of research utilizing "resting state" fMRI scans to measure this co-activation across discrete neural regions in order to make inferences about functional connections within the brain. Rather than completing a task in the scanner, participants undergoing resting state scans are asked to relax and think of nothing in particular, either with their eyes closed or while fixating on a minimal stimulus screen, while the scan is completed. Researchers then select a region of interest to serve as a reference region (also called a seed region) and correlate spontaneous fluctuations in BOLD functioning over the course of the resting-state time series in the seed region with the time series of all other brain regions. These analyses result in a functional connectivity map reflecting the functional connections between the predefined seed region and the rest of the brain.

Unfortunately, this method of measuring functional connectivity in the brain does not provide information regarding the causality or directionality of communication

between brain regions (i.e., Is brain region A "speaking to or influencing" the activation of brain region B, or vice versa? Or is a third brain region simultaneously influencing functioning in BOTH region A and B?). However, the strength of functional connectivity in neural circuits across the brain has been linked to cognitive functioning, intelligence, and various neurological and psychiatric disorders (van den Heuvel & Hulshoff Pol, 2010). Given the complex neuroanatomical connectivity between and within networks of the brain, this method of measuring neural functioning has the potential to provide more detailed and nuanced data regarding neural mechanisms associated with a wide range of clinically-relevant behaviors, including addiction and relapse. Thus, this method will be employed in the current study and reviewed in the literature below on the neurobiology of stress and addiction in humans.

1.6.2 Historical overview of neurobiological models of addiction

Several neurobiological models have been proposed to explain the development of substance use disorders, as well as vulnerability to relapse, with a great deal of emphasis placed on the role of neuroadaptive changes that take place in brain reward, stress, and cognitive control circuits over the course of chronic drug use (e.g., Everitt & Robbins, 2005; Goldstein & Volkow, 2002; Koob & Le Moal, 2001, 2008; Li & Sinha, 2008; Robinson & Berridge, 1993, 2001; Sutherland, McHugh, Pariyadath, & Stein, 2012; Wise, 1980, 2002). Although not mutually exclusive, each model is unique in the extent to which particular neural circuits are emphasized as mechanisms driving the progression from initial experimentation to eventual substance dependence. Early models implicated midbrain dopaminergic activation as the critical mechanism driving addictive behavior (e.g., Wise, 1980); however, these models have since been further refined to

emphasize the neuroadaptive changes that occur in these brain regions over the course of chronic substance use that serve to increase the incentive salience of addictive substances over time (Robinson & Berridge, 1993, 2001). Additional models have placed greater emphasis on dysfunctional prefrontal inhibitory control regions, leading to impaired response inhibition and loss of control over addictive behavior (Goldstein & Volkow, 2002), while others have suggested a transition at the neural level from initial prefrontal control over voluntary substance use, to eventual striatal control (as well as a shift within the striatum from ventral to dorsal control) driving habitual compulsive drug seeking (Everitt & Robbins, 2005). More recent models are beginning to place less emphasis on functioning in discreet neural regions, and are focusing more on the role of large scale neural networks in the development of craving during acute drug abstinence (Sutherland et al., 2012). Of greatest relevance to the current study are models emphasizing the neurocircuitry underlying the "dark side of addiction" (Koob & LeMoal, 2008); namely, the relationship between stress and substance use disorders. As such, although each of the models described above have contributed greatly to our understanding of the neural correlates of addiction, the current review will draw heavily from a neurobiological model largely derived from functional magnetic resonance imaging (fMRI) research on *stress* among human substance users (Li & Sinha, 2008) in order to provide a framework for the current study.

Considering evidence from human neuroimaging research, there appear to be clear overlaps between the neural circuitry implicated in addiction and the circuitry associated with stress and emotion regulation (Li & Sinha, 2008). Highly interconnected cortical and subcortical networks comprised of brain regions such as the amygdala,

striatum, insula, medial prefrontal, and cingulate cortices are involved in the perception and appraisal of emotional and stressful stimuli, while circuitry including the brain stem (i.e., locus ceruleus and related arousal regions), hypothalamus, thalamus, striatal, and limbic regions are involved in physiological and emotional responses (Sinha, 2008). Together, these regions compose the neural circuitry mediating the experience and regulation of distress. Given the roles of these neural networks in both stress and addiction, the following section will review literature suggesting that the structures comprising these circuits may serve as regions of interest in the relationship between stress and addiction. Although the regions within these specialized circuits will be introduced and initially discussed in isolation, it is important to note that they are functionally interconnected through substantial direct and indirect projections, and the circuits themselves are highly overlapping. As such, the descriptions of individual brain regions will be followed by a discussion of how the degree of functional coupling between these regions is altered over the course of chronic substance use, and may also drive the relationships between stress, craving, and relapse.

1.6.3 The role of limbic regions in stress and addiction

Important markers of emotional processing include limbic regions, such as the amygdala, striatum, and anterior insular cortex (insula). The amygdala has been identified as a key structure involved in emotion processing. Although the amygdala is involved in the processing of both positive and negative emotions, it is uniquely implicated in threat-related processes and serves as a key mediator of avoidance behavior (e.g., LeDoux, 2000). It is reliably activated in response to fearful stimuli (Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003), and affective distress, particularly among individuals with

psychopathology marked by negative affect, including PTSD (Rauch et al., 2000; Shin et al., 1999) and depression (Abercrombie et al., 1998). Further, the amygdala is activated in response to monetary reward and punishment, and activation in the amygdala following monetary loss and reward is significantly correlated with subjective ratings of emotional experience, including changes in frustration (Zalla et al., 2000). Amygdala functioning also appears to mediate autonomic responses to large monetary gains or losses as individuals with bilateral amygdala damage who are exposed to gains and losses fail to show a physiological response (Bechara & Martin, 2004). Thus, activation in the amygdala can be said to signal the immediate emotional salience of environmental stimuli, linking features of the stimulus to its affective/emotional attributes, thereby providing a motivational basis for impulsive responding (e.g., substance use) in the presence of threatening or stress-inducing stimuli (Bechara, 2005).

Additionally, activation of the insula, an important region within the limbic system, has been linked to the representation of bodily responses, interoception (Caria et al., 2007; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004), and perception of subjective emotions (Caria et al., 2007), as well as conscious awareness (Craig, 2009). In particular, activation of the insula is associated with the experience of negative feelings, such as fear, disgust, and anxiety, as well as recall of emotional memories (e.g., Winkielman, Knutson, Paulus, & Trujillo, 2007). Further, the insula is linked with awareness of visceral responses that are heightened in negative emotional states (Critchley et al., 2004), and has been implicated in the experience of cue-induced and abstinence-induced craving (Brody et al., 2002; Z. Wang et al., 2007).

Emerging research suggests that the insula, and its connections with other cortical and subcortical regions involved in affective and motivational processes, may be of particular interest within the field of smoking. Specifically, smokers with insula lesions following brain trauma are more likely to quit smoking soon after the injury, maintain their abstinence, report less desire to smoke, and experience fewer conscious smoking urges as compared to individuals with damage to other regions of the brain (Naqvi, Rudrauf, Damasio, & Bechara, 2007). Importantly, participants with insula lesions who quit smoking did not report any disruption in appetite or pleasure from eating, suggesting that the effects of insula damage were relatively specific to smoking, and did not impact motivational processes more broadly. Stemming from these findings, researchers have posited that during acute abstinence, the insula plays a key role in converting interoceptive withdrawal symptoms (e.g., irritability, anxiety, craving) into conscious drug urges, and in turn interacts with other regions (e.g., the ACC, vmPFC, amygdala, and striatum) that mediate the decision-making processes involved in relapse (Naqvi & Bechara, 2009, 2010). As such, insula reactivity to interoceptive cues (e.g., stress and craving) and connectivity with other regions implicated in affective and motivational functions may contribute to stress-induced relapse among smokers.

Another important neural marker of emotion processing, particularly in times of stress, is activation in the striatum. In times of stress, there is increased dopaminergic transmission in the ventral striatum (VS), with evidence suggesting that dopaminergic neurotransmission in this region is critical for encoding rewarding stimuli, thus serving as a learning signal (Schultz, 2013), and may play a key role in the motivational basis of behavior. Specifically, animal studies have demonstrated a relationship between stress

and dopamine transmission (Piazza, Deminiere, Le Moal, & Simon, 1989; Piazza & Le Moal, 1996), which is argued to explain increases in drug self-administration in response to laboratory stressors (e.g., Piazza & Le Moal, 1998). Similarly, evidence from human fMRI studies demonstrate increases in VS activation in response to and in anticipation of aversive stimuli among healthy individuals (Becerra, Breiter, Wise, Gonzalez, & Borsook, 2001; Jensen et al., 2003; McCullough & Salamone, 1992; Sorg & Kalivas, 1991), and cortisol release in response to psychological stress tasks correlates significantly with dopamine release in the VS (Oswald et al., 2006; Pruessner, Champagne, Meaney, & Dagher, 2004). Moreover, activation in both the ventral and dorsal striatum have been associated with craving among drug users (Li & Sinha, 2008). Thus, activation in the VS may be indicative of more than just reward functioning, but also of a motivational response bias toward substance use while experiencing affective distress.

Given the importance of the limbic system in emotion processing and motivation in response to aversive stimuli, activation and strength of connectivity within and between these structures may significantly relate to individual differences in smoking heaviness and dependence severity, as well as the ability to persist in an abstinence attempt and resist the urge to lapse to substance use. Neurobiological models of addiction and accumulating empirical evidence suggest that these systems are indeed disrupted among drug-dependent individuals. For example, Koob & LeMoal (2008) hypothesize that as dependence and withdrawal develop, brain stress systems including CRF circuits localized in the central nucleus of the amygdala and the bed nucleus of the stria terminalis undergo neuroadaptive changes such that activation in these stress-processing

regions is chronically elevated in an attempt to restore homeostatic function. Consequently, these regions become chronically hyperactive, resulting in an aversive hedonic stress-like state characterized by increased irritability, emotionality, dysphoria, and frustration, thereby leading to stress-induced relapse to drug use (Koob & Le Moal, 2001). This hypothesized relationship is supported by evidence that a hyperactive extended amygdala CRF system mediates the behavioral responses associated with an emotionally stressed state, and in particular, increased drug self-administration and the development of drug dependence (Baldwin, Rassnick, Rivier, Koob, & Britton, 1991; George et al., 2007; Koob & Heinrichs, 1999; Specio et al., 2008; Valdez et al., 2002).

Taken together, neurobiological models and converging evidence from animal and human research suggest that hyperactivation in limbic regions, particularly the amygdala, insula, and VS, in response to affective distress may significantly contribute to smoking, dependence, and poor cessation outcomes. Moreover, the interconnections between these regions likely modulate the relationship between stress and substance use, as it is through these interconnections that stress-induced physiological arousal (mediated by activation in the amygdala and VS) is converted into conscious interoceptive sensations and urges (within the insula) and ultimately translated into motivated behavior (mediated by a combination of limbic regions including the amygdala and VS, as well as their interconnections with cortical regions discussed below).

1.6.4 The role of cortical regions in stress and addiction

Activation in medial prefrontal brain regions, including the ventromedial prefrontal cortex (vmPFC) and anterior cingulate cortex (ACC), is generally associated with regulatory control over cognition, behavior, and emotion. For instance, the ACC is

believed to influence numerous aspects of human cognition and behavior, including behavioral monitoring, planning, and decision making (Damasio, 1994; Dehaene, Posner, & Tucker, 1994; Devinsky, Morrell, & Vogt, 1995; Posner & DiGirolamo, 1998; Stuss & Benson, 1986). A prerequisite to engaging inhibitory control functions and selecting an optimal behavioral response is the ability to monitor behavioral errors when they occur so that subsequent behaviors can be adjusted accordingly (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Rabbitt, 1966), with research frequently implicating the ACC in these error-related functions (J. W. Brown & Braver, 2005; Dehaene et al., 1994; Magno, Foxe, Molholm, Robertson, & Garavan, 2006). Further, the ACC is most activated when participants are asked to both evaluate their options based on performance feedback and use that information to make a behavioral choice (Elliott & Dolan, 1998). The functions supported by the ACC are clearly relevant to the study of stress and substance use as behavioral evidence suggests that in the face of stress, addicted individuals who fail to inhibit their prepotent response toward substance use and immediately initiate alternative non-substance-related coping behaviors are most likely to fail in their abstinence attempt (Shiffman, Paty, et al., 1996). Thus, the ACC may be a region of interest in the study of stress and substance use.

Indeed, consistent evidence points to impaired functioning in prefrontal regions, including the ACC, in chronic substance users (Bechara, 2005; Goldstein & Volkow, 2002; Li & Sinha, 2008; Volkow, Fowler, & Wang, 2004). For example, substance users demonstrate impaired response inhibition and error monitoring compared to non-substance users in fMRI paradigms involving inhibitory control, and these deficits are associated with hypoactivation in medial prefrontal brain regions (Hester & Garavan,

2004; Kaufman, Ross, Stein, & Garavan, 2003). Additionally, impaired medial prefrontal activation in substance users also has been associated with increased emotion dysregulation. Specifically, Li et al. (2008) reported hypoactivation in the rostral ACC (rACC) during a stop signal task in cocaine users compared to controls, independent from behavioral performance on the task, and that task-induced activation in the rACC among substance users was negatively correlated with scores on the self-report impulse control subscale of the Difficulty in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004). The impulse control subscale of the DERS includes self-rated statements such as "When I'm upset, I lose control over my behaviors." Thus, in addition to its role in impulse control, the findings reported by Li et al. (2008) suggest that activation in the ACC might be particularly important for inhibiting behaviors in the face of affective distress.

The vmPFC is another cortical region of interest in understanding the relationship between stress and addiction. The vmPFC is involved in the evaluation of both the immediate and long-term consequences of an action, and selection of the optimal behavior to initiate based on the balance between the two. Individuals with bilateral lesions to the vmPFC display marked impairments in the ability to make decisions that optimize long-term outcomes. That is, when confronted with a decision that involves a conflict between an immediate reward but a long term negative consequence, these patients tend to choose the immediate reward, at the expense of severe negative future consequences, including financial loss, loss of social status, and even loss of family and friends (e.g., Bechara, 2001; Bechara, Tranel, & Damasio, 2000; Damasio, 1994). The same can be said for individuals with substance use disorders who compulsively engage in addictive behavior despite experiencing long-term negative consequences (Verdejo-

Garcia & Bechara, 2009), and this pattern of maladaptive decision making in substance users has been linked to impaired functioning in the vmPFC (e.g., Volkow et al., 2004). Thus individuals with substance use disorders and patients with vmPC lesions share a "myopic" view of the future such that they are insensitive to future punishment (Verdejo-Garcia & Bechara, 2009).

Given the similarities between vmPFC patients and substance users, the somatic marker hypothesis has been applied to both of these patient populations in an effort to explain the neural deficits underlying these patterns of maladaptive decision making (Damasio, 1994; Verdejo-Garcia & Bechara, 2009). The somatic marker hypothesis suggests that optimal decision making is dependent on a balance between functioning in limbic regions that encode for immediate "feeling" states such as stress and drug craving, and prefrontal regulatory regions, including the vmPFC, that is more reflective of the long-term consequences of a behavior (Verdejo-Garcia & Bechara, 2009). Based on this hypothesis, hypoactivation in the vmPFC among drug users may be one mechanism driving compulsive drug seeking, particularly in the face of affective distress when the rewards (i.e., amelioration of negative affect) are immediate, and the negative consequences (i.e., long-term health, financial, and social consequences) are delayed and uncertain.

Taken together, cortical regions, including the ACC and vmPFC are crucial for effective inhibitory control and decision making. Further, these regions appear to be impaired among chronic drug users and these impairments are associated with maladaptive decision-making, particularly in the context of stress. As such, deficient stress-induced activation in these regions may be indicative of a reduced ability to

adaptively regulate one's emotions and recruit inhibitory control functions needed to resist engaging in previously negatively reinforced behaviors (i.e., substance use).

1.6.5 Limbic and prefrontal neural connectivity

Not only do prefrontal and limbic structures play separate roles in emotion regulation and decision making, but the circuitry connecting these regions appears to be important for modulating emotional experience, inhibiting emotionally driven impulses, and determining an appropriate behavioral response (e.g., Li & Sinha, 2008; Ochsner & Gross, 2008; Sutherland et al., 2012). State-related changes in cortico-striatal-limbic circuits following chronic drug use, or during acute withdrawal from an addictive substance, may reduce one's ability to adapt or cope in the face of distress, and lead to impairments in response inhibition and decision making. For instance, failure to activate the vmPFC and ACC is associated with dysregulation of amygdala functioning in humans (Motzin, Philippi, Wolf, Baskaya, & Koenigs, 2014), as well as impairments in distress processing and with maladaptive decision making in the face of distress (Myers-Schulz & Koenigs, 2012), which are both characteristic of drug dependent individuals (for a detailed review see Li & Sinha, 2008).

In addition, imaging studies point to increased prefrontal activation as a mechanism underlying the regulation of emotion (Beauregard, Levesque, & Bourgouin, 2001; Critchley, Melmed, Featherstone, Mathias, & Dolan, 2001; Kober et al., 2010; Lane et al., 1998; Sinha, Lacadie, Skudlarski, & Wexler, 2004), and effortful cognitive regulation of negative emotions and drug craving has been shown to increase activation in frontal regions and decrease amygdala activity over time (e.g., Kober et al., 2010) (for review see Ochsner & Gross, 2008). Thus, increased cortical activation, in combination

with decreased limbic activation, in the context of stress, may indicate an enhanced ability to cope adaptively with affective distress and to inhibit impulses to engage in maladaptive behaviors.

Studies directly examining the strength of functional coupling between the amygdala and midline cortical regions through resting state functional connectivity has revealed that increased amygdala-vmPFC functional connectivity strength is associated with decreased self-reported anxiety levels among non-clinical samples (Kim et al., 2011). Moreover, chronic drug users show weakened amygdala-cortical connections (Gu et al., 2010; W. Wang et al., 2010), providing further support for the role of weakened corticolimbic functional connectivity as the neural substrate by which substance users evidence an impaired ability to adapt to stress and regulate emotions effectively.

In their integrated model of stress regulation, craving, and inhibitory control, Li & Sinha (2008) propose that weak cortico-striatal-limbic circuitry in patients with substance dependence increases susceptibility to drug seeking, particularly while experiencing affective distress (for illustration of the model, see *Illustration 1*). Specifically, during times of high stress and arousal, when prefrontal regions are activated and connections to limbic regions are strong, there is good inhibitory control and low levels of craving. However, reduced activation in the PFC/ACC potentially resulting from a hyperactive limbic system, and/or weak connectivity within the cortico-striatal-limbic circuit, limits inhibitory control and allows for habitual and automatic responses in times of stress.

Notably, the model proposed by Li and Sinha (2008) was developed several years ago based largely on users of illicit stimulants, including amphetamines and cocaine, and was limited by the modest, but burgeoning, body of neuroimaging research on stress and

addiction that was available at the time. Therefore, additional network connectivity that was not explicitly emphasized by Li & Sinha (2008), but has received more attention in recent years, is worth consideration as it may be of relevance to the study of stress and addiction, and perhaps most relevant to the field of stress and smoking in particular.

Specifically, the insula is likely to play a critical role in smoking as smokers deprived of nicotine show elevated activation in the insula, and this abstinence-induced insula activation is associated with stronger self-reported smoking urges (Z. Wang et al., 2007). Moreover, smokers who suffer insula damage are significantly more likely to experience reduced smoking urges and to ultimately terminate smoking (Naqvi 2001). Importantly, recent neuroimaging studies of emotion nearly always report co-activation of the insula and the ACC, a region discussed above for its role in monitoring and inhibiting impulsive behavior. This frequently replicated finding has led some to suggest that it is communication between the insula and ACC that functions to translate interoceptive 'feelings' into a behavioral response (Craig, 2009). Specific to substance use, it has also been posited that during acute withdrawal, the insula mediates the conversion of interoceptive sensations (e.g., emotions, craving) into conscious drug urges, and the interconnections between the insula and regions involved in affect regulation, motivation, and behavior (e.g., striatum, amygdala, vmPFC, ACC) may provide the neural substrates by which psychological processes such as stress and craving can drive relapse to substance use.

Despite the theoretical links between corticolimbic functioning, stress, and substance use that have been reviewed above, very little research exists to date directly examining the neural correlates of stress processing among substance users. Further, the

body of research examining the relationships between stress-induced neural functioning, as well as functional connectivity in stress- and addiction-related corticolimbic circuits, with clinically-relevant substance use outcomes is even smaller. The following section will review the limited literature available along this vein, and discuss the limitations of the extant work, as well as specific directions for future research.

1.7. Extant fMRI Work on the Neural Correlates of Stress and Smoking

1.7.1 fMRI studies of stress and addiction

Currently, there is a small, yet growing, body of functional neuroimaging work that has begun to directly test the functional neural correlates of the relationship between stress and addiction among illicit drug users and smokers. Given the extremely small body of extant neuroimaging work that directly assesses the neural correlates of stress processing among smokers, the following review of fMRI studies of stress processing and addiction will begin with studies involving substance users more broadly, and then narrow the focus of the discussion to fMRI studies of stress among smokers in particular.

1.7.2 fMRI studies of stress among illicit drug users

The theoretical evidence reviewed above on the role of corticolimbic functioning in the relationship between stress and substance use outcomes has been supported in a small body of fMRI studies among illicit drug users. For example, in an fMRI study of cocaine-dependent individuals and healthy controls, participants were exposed to stressful and neutral personalized imagery scripts while lying inside the fMRI machine (Sinha et al., 2005). Although both groups evidenced similar levels of self-reported distress and physiological arousal (i.e., increased heart rate) during stress imagery script

exposure relative to neutral scripts, the healthy controls showed a specific pattern of stress-induced neural activation in the ACC, while the cocaine-dependent sample failed to display this pattern of activation. Instead, cocaine-dependent participants showed increased activation in limbic regions, including the caudate and dorsal striatum during stress exposure, and the magnitude of activation in these regions was positively correlated with self-reported stress-induced cocaine craving (Sinha et al., 2005). Thus, expanding upon previous work indicating hypoactivation in the ACC among cocaine users during inhibitory control and error monitoring tasks (for review, see Garavan & Hester, 2007), these findings suggest that activation in the ACC is also deficient in response to stress among cocaine users. Moreover, this stress-induced hypoactivation in the ACC, along with stress-induced hyperactivation in striatal regions is associated with increased stress-induced craving.

In a follow-up study, Sinha and colleagues (2005, as cited in Sinha & Li, 2007) conducted a follow-up interview with the same cocaine-dependent participants from above at 90 days post-treatment and examined the relationship between stress-induced neural activation and a variety of substance use outcome variables. Findings revealed that greater stress-induced activation in limbic regions, including the insula, was associated with a higher number of days of cocaine use, while increased activation in the posterior cingulate was positively associated with the amount of cocaine used per occasion. The authors suggest that stress-induced hyperactivation in the insula and posterior cingulate may serve as a risk factor for loss of control over cocaine intake and binge episodes respectively. This finding is of particular interest given recent conceptualizations reviewed above regarding the role of coactivation in the insula and cingulate as a neural

mechanism mediating the translation of interoceptive feelings (e.g., emotions, drug craving) into a behavioral response. As such, it appears that hyperactivation in these regions may indicate an inability to override a prepotent behavioral response (i.e., substance use) in the face of aversive interoceptive sensations (i.e., distress and stress-induced cravings).

Despite the advancements that have been made in our understanding of the relationship between stress-related neural functioning and substance use, few studies have utilized neuroimaging techniques to examine stress-induced neural activation among cigarette smokers in particular, and how this activation is associated with smoking-related outcomes. Further, there are clear areas in which more research is needed in order to directly assess the relationship between the neural correlates of stress processing and real-world smoking outcomes. As such, the following sections review the limited available fMRI studies examining stress among smokers, and highlights directions for additional research.

1.7.3 fMRI studies of stress among smokers

Despite strong emphasis within both clinical and neurobiological models of addiction on the role of stress in addictive behavior, few studies have directly examined the neural correlates of stress among smokers. In fact, to our knowledge, there is only one published study to date reporting on stress-induced neural activation among smokers. Over two separate fMRI sessions, Dagher and colleagues (2009) exposed 15 smokers to a psychosocial stressor that involved completion of a challenging mathematical processing task (i.e., the Montreal Imaging Stress Task [MIST]; (Dedovic et al., 2005)) that was designed to incorporate key contributors to psychological stress such as uncontrollability

and social-evaluative threat, and a non-stressful control task that included similar mathematical problems, but without time constraint (i.e., reduced uncontrollability) or social evaluation. Following exposure to each of the experimental conditions, participants were shown smoking cues involving video clips of smokers in order to examine the effects of psychosocial stress on cue-induced neural activation.

Exposure to the stress task was associated with significantly decreased neural activation in cortical regions, including the subgenual ACC, vmPFC, and ventrolateral PFC relative to the control task. Somewhat paradoxically, stress task exposure was also associated with significant deactivation in limbic and paralimbic regions, including but not limited to the amygdala, posterior insula, and nucleus accumbens as compared to the control task. In terms of smoking cue reactivity, exposure to the psychological stressor was associated with significantly increased cue-induced neural activation in regions involved in visual attention and assigning incentive values to cues, including the medial prefrontal cortex, posterior cingulate cortex, and caudate nucleus, among others. Additionally, the researchers examined the relationship between stress-induced neural activation and cue-induced neural activation and found that the magnitude of stress-induced deactivation in limbic regions predicted increased neural reactivity to smoking cues in wide ranging cortical and limbic circuits. (Dagher et al., 2009).

The authors suggest that these findings provide support for the idea that stress increases the incentive salience of addictive substances, which in turn increases the risk of relapse in the context of stress. However, the finding of widespread deactivation across paralimbic regions is somewhat surprising given that previous animal and human studies of stress implicate activation in limbic regions as indicative of stress; yet, these findings

are consistent with previous work utilizing the same task among healthy non-smokers (Pruessner et al., 2008). The authors argue that stress-induced *deactivation* in limbic regions, including the amygdala and nucleus accumbens (as opposed to increased activation as might be expected) may be due to the fact that the task employed was a psychosocial stressor, as opposed to a fear-inducing task like those that have been used in past research, and that for this particular task, the magnitude of deactivation serves as the primary indicator of stress reactivity. The study did not include a comparison control group of non-smokers, so it is not clear how the magnitude of stress-induced limbic deactivation exhibited among smokers would compare to non-smokers. Nonetheless, this study provides initial support for the role of stress-induced corticolimbic functioning in enhanced smoking cue reactivity, thus adding to the empirical literature on the relationship between stress and smoking. However, the contradictory findings in terms of the role of decreased rather than increased limbic activation in cue-induced reactivity underscores the need for more research to understand the unique neurobiological substrates of stress and cigarette smoking. More research is clearly needed in this area to replicate existing findings, and to examine the direct effects of stress-induced neural activation on clinically-relevant real-world smoking outcomes.

1.7.4 Functional connectivity studies of corticolimbic circuits in smokers

As emphasized in Li and Sinha (2008)'s integrated neurobiological model of stress and addiction, as well as more recent network level models of addiction based on resting state functional connectivity research, it is not just functioning in circumscribed cortical and limbic regions that is important for addiction liability, but the strength of connectivity between cortical and limbic regions also influences the extent to which

individuals can adaptively monitor both interoceptive and external stimuli, allocate attentional resources accordingly, regulate their emotions, and abstain from addictive behaviors. As such, researchers have also examined corticolimbic functional connectivity among smokers. For example, Hong and colleagues (2009) examined the relationship between nicotine addiction severity, as measured by total scores on the Fagerstrom Test of Nicotine Dependence, and cingulate resting-state functional connectivity among a sample of healthy smokers. Results indicated that greater severity of nicotine dependence was associated with the weaker functional connectivity within the dorsal anterior cingulate cortex (dACC)–striatal circuits, and this relationship remained consistent both when participants wore nicotine patches during the resting scan, as well as when they wore a placebo patch. As such, the authors suggest that functional connectivity in the dACC-striatal circuit may reflect a circuitry level endophenotypic marker of nicotine dependence. The findings reported by Hong and colleagues (2009) are consistent with the model proposed by Li & Sinha (2008), which posits that stronger functional connectivity between prefrontal regulatory regions (i.e., the dACC) and limbic regions associated with emotion processing and drug motivation (i.e., the striatum) should enhance top-down regulatory control of prefrontal regions over limbic functioning, thus reducing compulsive drug seeking.

Researchers have also tested the relationship between cue induced neural activation and resting state functional connectivity among smokers (Zhang et al., 2011). When exposed to smoking cues relative to neutral cues, smokers evidenced exaggerated cue-induced activation in several cortical regions including the dorsal lateral prefrontal cortex (dlPFC), dorsal medial prefrontal cortex (dmPFC), dorsal anterior cingulate

cortex/cingulate cortex, rostral anterior cingulate cortex (rACC), occipital cortex, and insula relative to non-smokers. These regions were then used as seed regions in secondary resting state functional connectivity analyses to examine how they functioned at a network level to predict neural reactivity to smoking cues. Results indicated significant relationships between the strength of connectivity between these regions and the magnitude of neural reactivity to smoking cues, such that connectivity between the rACC and dlPFC was positively related to cue reactivity in the dlPFC, connectivity between the dlPFC and dmPFC was positively related to cue reactivity in the dmPFC, and connectivity between the dmPFC and insula was inversely related to cue reactivity within both of these regions. As such, these findings suggest that the strength of connectivity between these cortical circuits can influence the magnitude of neural response to smoking cues. However, it is unclear how these factors directly translate into clinically-relevant smoking dependence characteristics or behavior.

To our knowledge, one study to date has examined resting state corticolimbic functional connectivity a prospective predictor of real-world smoking outcomes (Janes et al., 2010). Specifically, a sample of healthy smokers completed an fMRI scan prior to a smoking quit attempt, during which they were shown a series of smoking-related and neutral images. Researchers conducted functional connectivity analyses on the fMRI data that was collected during the smoking-cue reactivity task and examined the relationship between insula-frontocingulate functional connectivity and 'slips' (operationalized as smoking a cigarette following at least 24 hours of complete abstinence) following cessation. Smokers who went on to 'slip' during their smoking cessation attempt displayed weaker functional connectivity between the dACC and the insula in the context

of smoking-related images (Janes et al., 2010). Thus, these findings provide additional support for the role of functional connectivity between corticolimbic regions, including the ACC and insula in particular, in the regulation and inhibition of addictive behavior among smokers.

Most recently, Lerman and colleagaues (2014) made novel use of resting state functional connectivity data to test a newer network level model of nicotine dependence proposed by Sutherland and colleagues (2012). The model proposes that a salience network (SN) comprised of the insula and ACC monitors incoming information, and depending on the most subjectively relevant stimuli available, serves as a "toggle" switch, allocating attentional resources differentially between the default mode network (DMN, a network of midline regions involved in internal reflective thinking) and the executive control network (ECN, including lateral cortical regions involved in sustained attention to external stimuli and goal-oriented behavior). The model suggests that in the context of acute nicotine abstinence, the SN would allocate more resources to monitor internal withdrawal-related symptoms, thus biasing functioning toward the DMN and away from the ECN. Lerman compared the relative strength of connections between the SN-DMN and SN-ECN among smokers in the context of nicotine-satiated versus nicotine-deprived states. Findings supported the idea that the SN biases functioning toward the DMN during nicotine deprivation (SN-DMN connectivity was weaker during nicotine deprivation, indicating reduced inhibition of the DMN by the SN), and the magnitude of this relative bias toward the DMN while nicotine-deprived relative to nicotine-satiated predicted greater urges to smoke, as well as reduced suppression of the DMN during a working memory task. These findings suggest that not only chronic

smoking, but also acute smoking status (i.e., nicotine deprivation versus satiation) can significantly alter network dynamics and that these alterations may underlie withdrawal-induced cognitive impairments and enhanced craving among smokers.

1.8. Remaining Questions

Despite what is known about the neural correlates of addiction and stress in smokers, there are clear gaps in the literature and key questions remain unanswered. First, there are no published studies to our knowledge that have examined the relationship between stress-induced corticolimbic functioning and real-world, clinically-relevant smoking outcomes, such as stress-induced craving, nicotine dependence severity, number of cigarettes per day, or smoking cessation outcome history. However, one unpublished study of this kind was presented at the 2009 Joint Conference of the Society for Research on Nicotine & Tobacco (SRNT) and SRNT-Europe, and has been cited in a text book chapter written by David and colleagues (2011). Specifically, Finnerty (2009, as cited in David et al., 2011) presented nine abstinent smokers with neutral, negative, and positive affective images during an fMRI session. Neural activation in response to the negative affective images was examined as a predictor of smoking severity, as measured by cigarettes smoked per day. The researchers found positive correlations between number of cigarettes per day and neural reactivity to the negative emotional images in regions including a large cortical frontoparietal attentional network, as well as subcortical regions including the caudate and thalamus. However, this study remains unpublished to date leaving many questions unanswered about the exact nature of the findings, thus highlighting the clear need for more neuroimaging work examining the relationship between neural reactivity to stress and smoking outcomes.

Noting the dearth of research on the neural underpinnings of the relationship between stress and addiction among humans, researchers in the field are calling for more studies to address this gap in the literature. For example, Schutz (2008) emphasized that existing research into the brain mechanisms underlying relapse and reinstatement of addictive behavior predominantly rely on animal studies, thus pointing to the need for more novel human fMRI-based paradigms designed to study key triggers, including psychological stress, that have been implicated in substance use and relapse. The author went on to argue that additional research of this kind could lead to the development of targeted interventions to prevent relapse. Similarly, Sinha (2008) noted that although evidence suggests that stress-induced neural activation, particularly in stress and reward circuits of the brain, may serve as a mechanism underlying the known relationship between stress and addiction, human research directly linking stress-induced changes in neural activity and real-world addictive behavior is needed in order to more definitively establish the association between stress, neural activation, and addiction risk, as well as treatment outcomes. As such, additional fMRI-based research is clearly needed to directly test the relationship between stress-induced neural activation and clinically-relevant smoking variables, such as stress-induced craving, number of cigarettes per day, dependence severity, and smoking cessation outcome history.

As emphasized by neurobiological models of addiction (Li & Sinha, 2008; Sutherland et al., 2012), it is also important that research examining the neural mechanisms driving addictive behavior look beyond the role of neural functioning in discrete brain regions, and focus more on how neural circuits function at a network level to gain a deeper understanding of neuropsychiatric disorders. Although neuroimaging

research that utilizes cognitive subtraction task paradigms (e.g., comparing neural functioning in response to no stress versus stress to isolate stress-induced functioning) can provide information about stress reactivity within specific brain regions, resting state functional connectivity analyses can provide complementary insight into how interactions between regions might drive state-dependent neural reactivity, and predict clinically-relevant outcomes. The body of resting state functional connectivity research among smokers is growing, but there are currently no studies to our knowledge that use this approach to specifically examine how functional connectivity between brain regions activated by stress might function to predict clinically-relevant outcomes such as smoking dependence characteristics, craving, and smoking lapse history.

1.9. Summary and Significance

Nicotine dependence is a prevalent and costly disorder characterized by notoriously high relapse rates, thus representing a significant public health concern. Given the intractable nature of the disorder, a strong emphasis has been placed on understanding the processes associated with smoking and relapse following cessation. Self-report and experimental studies have provided support for the role of affective distress as a mechanism driving substance use across the stages of addiction, and neurobiological models (e.g., Li & Sinha, 2008) have been developed emphasizing the role of corticolimbic functioning in emotion dysregulation and compulsive drug seeking. Neuroimaging studies among smokers in particular have largely supported the model proposed by Li & Sinha (2008); however, research within human smokers is very limited and lacking in some areas, leaving key questions unanswered. Specifically, can stress-

induced corticolimbic activation, and functional connectivity within stress-related corticolimbic circuits, predict clinically-relevant real-world smoking outcomes?

1.10 Current Study

The current study addresses clear gaps in the existing literature on the neural correlates of stress and smoking by examining the relationship between corticolimbic functioning (i.e., stress-induced activation and functional connectivity within stress-related corticolimbic circuitry) and clinically-relevant smoking-related outcome variables, including self-reported stress-induced craving, number of cigarettes smoked per day, retrospective smoking lapse history (i.e., number of past quit attempts lasting longer than 12 hours, and duration of longest past abstinence attempt), and nicotine dependence severity as measured by the Fagerstrom Test for Nicotine Dependence (FTND; T. F. Heatherton et al., 1991).

As noted by Sinha (2008) and Schutz (2008), research that directly addresses stress-related neurobiological processes and their association with behavioral outcomes within addiction is sorely needed. By examining the specific relationships between stress-related corticolimbic functioning and smoking-related outcomes, the current study aimed to set the stage for larger, prospective longitudinal studies to predict smoking outcomes among treatment seeking smokers based on their neural reactivity to affective distress, as well as the strength of functional connectivity in stress-related corticolimbic circuits.

1.11 Specific Aims

1.11.1 Primary Aim

To examine the relationship between stress-induced neural activation and clinically-relevant smoking measures.

Hypothesis: Reduced reactivity to stress in cortical regions including the ACC and vmPFC, as well as increased reactivity to stress in limbic regions including the amygdala, insula, and striatum during a stressful fMRI task will be significantly related to higher levels of stress-induced craving as measured by a Likert-type craving scale administered pre- and post-stress task, poorer self-reported smoking lapse history, greater number of cigarettes per day, and higher scores on an established self-report measure of nicotine dependence (i.e., the FTND).

1.11.2 Secondary Aim

Corticolimbic regions that show significant stress-induced activation were then used as seed regions for secondary analyses that aimed to examine the relationship between resting state functional connectivity in stress-related corticolimbic circuits and clinically relevant smoking measures.

Hypothesis: Weaker functional connectivity between components of the addiction-relevant limbic circuits that are activated by stress, including the striatum, amygdala, and insula, and cortical circuits (particularly the vmPFC and ACC) will be significantly related to higher levels of stress-induced craving as measured by a Likert-type craving scale administered pre- and post-stress task, poorer self-reported smoking lapse history, greater number of cigarettes per day, and higher scores on an established self-report measure of nicotine dependence (i.e., the FTND).

Chapter 2: Research Design

2.1. Recruitment

A total of 35 current cigarette smokers (17 female) were recruited as part of a larger study examining the neural correlates of distress tolerance among healthy smokers and non-smoking controls at the National Institute on Drug Abuse Intramural Research Program (NIDA IRP) in Baltimore, Maryland. Individuals were recruited for this study through IRB-approved advertisements and outreach initiatives, by referral from healthcare workers or facilities, or by referral from other study participants. Interested participants completed an initial telephone screening, and if they passed this initial screening, presented to NIDA IRP for a complete in-person assessment in line with NIDA IRP's standard procedures for assessing participant medical and mental health history to determine eligibility for NIDA fMRI studies. Participants meeting the inclusion/exclusion criteria for the current study were contacted by study staff to schedule their participation.

Of the 35 current smokers who were recruited to participate in the current study, a total of 15 participants were excluded from study analyses (see *Illustration 2* for a complete illustration of how participants were selected for inclusion in study analyses). Reasons for participant exclusion from analyses included, (a) technical problems (i.e., problems with joystick calibration) (n = 2) that precluded participants from completing the stress task in the fMRI, (b) participant decision to terminate scan before completing the entire protocol (n = 1), (c) excessive head motion during resting state scan (n = 4), and (d) excessive head motion during stress task scan (n = 8). Head motion was

determined to be “excessive” if, greater than 25% of the fMRI data had to be censored out due to head motion (data points were censored out if there was more than 0.3mm of motion between successive TRs). Thus, the data analysis for the current study is based on the remaining sample of 20 participants (10 female) (see *Section 3.1.1.1* for tests of potential group differences in demographic and other relevant characteristics between participants who were included in analyses, versus those who were excluded).

2.2 Inclusion/Exclusion Criteria

To qualify for the current study, participants must have been (1) between the ages of 18 and 50, (2) in good health (see exclusion criteria below for specific markers of poor health that excluded participants from the study), (3) right-handed, and (4) current smoker of 10 cigarettes a day or more.

Participants were excluded from the current study if they (1) were pregnant; (2) had implanted metallic devices (cardiac pacemaker or neurostimulator, some artificial joints, metal pins, surgical clips or other implanted metal parts) or claustrophobia rendering them unable to undergo fMRI scanning; (3) had major medical illnesses to include, but not limited to, hypertension, cardiovascular disease, asthma, diabetes, peripheral vascular diseases, coagulopathies, syncope, history of superficial or deep vein thrombosis, HIV, or other clinically significant infectious diseases; (4) had current major psychiatric disorders including, but not limited to, mood, anxiety, borderline personality disorder, psychotic disorders, or substance-induced psychiatric disorders; (5) had neurological illnesses including, but not limited to, seizure disorders, migraine, multiple sclerosis, movement disorders, or history of head trauma, CVA, CNS tumor; (6) met DSM-IV criteria for any past or current dependence besides nicotine or use of illicit

substances in the last 30 days; (7) reported regular use of any prescription, over-the-counter, or herbal medication that may alter CNS function, cardiovascular function or neuronal-vascular coupling; (8) had cognitive impairment as assessed by screening WASI vocabulary subtest below 48, corresponding to full IQ of below 85 (in that case in screening, a full WASI was administered to verify IQ of 85 or above); (9) showed acute drug intoxication or positive urine drug screen upon arrival for fMRI scan; and (10) tested positive on a urine pregnancy test.

2.4 Procedure

2.4.1 Pre-scan procedures

The entire visit lasted approximately 5-6 hours (See *Illustration 3* for a complete timeline of all procedures carried out during the study visit). Participants were asked to arrive 1.5 hours before the scheduled scan, and were told that they could smoke cigarettes as normal prior to their arrival for the study visit. Upon arrival, participants first completed the informed consent procedures. Once consent was provided, participants were escorted to nursing to complete a brief physical exam, including measurement of vital signs, brief assessment of any changes in health status since their last NIDA visit, a breathalyzer test for alcohol use, a urine drug-use assessment (Triage®), a urine pregnancy test (females only), and an MRI safety checklist that reviewed any health or medical conditions that would interfere with completion of an fMRI scan.

Next, participants were given instructions on how to complete all tasks that were to be administered in the fMRI, and completed training modules of each of the four tasks (see *Section 2.4.2* for more details about the tasks). For the stress task reported in the current study (i.e., the PASAT-M, described in detail in *Section 2.4.4*), participants

practiced the easy phase of the task on a desk-top computer until they got five consecutive number presentations correct, at which time it was clear that they understood the instructions and could perform the task. Following task training, participants were asked to smoke one last cigarette immediately before being escorted to the scanner for physiological and MRI setup.

2.4.2 Scan Set-up and Scan Procedures

Physiological and MRI setup occurred next. A trained Magnetic Resonance Technician (MR Tech) ran all scanning procedures, and a trained graduate or post-bachelor level research assistant communicated with participants throughout all sessions. Upon entering the scanner, a quadrature birdcage RF volume coil was placed around participants' heads and their heads were held in place by a head restraint that consisted of hardened polyurethane foam (expanding packing foam) placed inside double plastic bags. Four adhesive-coated electrocardiogram (EKG) electrodes were attached to participants' chests to monitor heart rhythms throughout the scan. All scanning took place in a Siemens 3Tesla Allegra MRI at the NIDA IRP.

The entire scanning procedure lasted approximately two hours (see part (B) within *Illustration 3* for a pictorial representation of scan procedures). The scan began with a T1-weighted anatomical scan. Next, participants completed a working memory task (the N-Back; for review, see Owen, McMillan, Laird, & Bullmore, 2005) and a sustained attention task (the Go/No-Go; e.g., Garavan, Ross, Murphy, Roche, & Stein, 2002), both of which were analyzed as part of the larger study on the neural correlates of distress tolerance, but the results of which are not reported here. The order of these two tasks was counter-balanced across participants. Participants were then told to close their

eyes and relax while the resting state functional connectivity scan was completed, lasting approximately eight minutes.

Finally, participants completed two novel stress tasks modified for use in the fMRI, including the Mirror Tracing Persistence Test for fMRI (MTPT-M; modified, using an event-related design, from the computerized version of the MTPT described in Strong et al., 2003) and the Paced Auditory Serial Addition Test for fMRI (PASAT-M; described in detail in Section 2.4.4), with the order of these two tasks also counter-balanced across participants. We chose to use the functional data from the PASAT-M as our measure of stress-induced neural functioning for the current study as the event-related design utilized in the current study's version of the MTPT-M was found to be less powerful at detecting stress-related neural functioning. The MTPT-M has since been redesigned using a block design format, similar to the PASAT-M, for use in subsequent studies. Participants' individual ratings of emotional distress were assessed frequently, including before, during (i.e., between task scans), and after the scan. A safety protocol, which was described to participants prior to the scan, was in place should any participants experience elevated distress following scan completion; however, no participants necessitated any special safety measures.

Given that some participants completed two tasks prior to the PASAT-M, while others completed three, and that the order of task completion varied across participants, we tested for the effects of task order on participants' subjective mood ratings that were provided during the PASAT-M, as well as the effects of task order on stress-induced neural functioning in response to the PASAT-M. No significant effects of task order, on

either subjective responses or neural responses to stress, during the PASAT-M were identified.

2.4.3 Post-Scan Procedures

After the scan, participants completed self-report measures, including smoking measures (described in *Section 2.5.3*). At the end of the testing session, participants were compensated according to the following payment schedule: $20/hour for study visit, $50 flat rate for time in the scanner, $15 for travel, and an additional $25 bonus based upon participant compliance during all study procedures. Participants were told that the $25 bonus was based on their performance on the task in order to further increase affective distress during task completion. Participants were fully debriefed at study completion.

2.4.4 Stress task: The Paced Auditory Serial Attention Task for fMRI (PASAT-M)

2.4.4.1 Overview of PASAT-M

All participants completed the Paced Auditory Serial Attention Task for fMRI (PASAT-M) during the second half of the fMRI scan. The original PASAT-C, developed as a behavioral measures of distress tolerance (Lejuez, Kahler, & Brown, 2003), was used as the template for the development of an fMRI compatible version used in the current study. The PASAT-M was created as a block design task, with an "easy phase" designed to control for cognitive and motor functioning, and a "hard phase" designed to elicit affective distress. We first present the task rules that were consistent across all task phases, followed by greater detail regarding how the task phases varied from one another as the task progressed.

Similar to the PASAT-C, a series of numbers flashed on the screen one at a time and the participants were asked to add the current number on the screen to the previously

presented number, and then use an MRI compatible joystick to indicate the correct answer before the subsequent number appeared. For instance, if a '3' appeared, followed by a '6', the participant must have chosen '9' before the next number appeared. There were four options to choose from for the response and the participants were instructed to move the joystick in the direction of the correct response. Correct responses resulted in a pleasant bell sound and an increase in the participants' score, while incorrect and slow responses resulted in an explosion noise and a decrease in points. The volume level of the task was determined based on pilot testing prior to the current study. For all study participants, the volume was set at a constant level that was determined during pilot testing to be sufficiently loud to allow for participants to hear the task noises over the noise of the MRI machine. A meter on the screen reflected the participants' overall score. As participants earned points, the meter went up and turned green, and as they lost points, the meter went down and turned red.

Participants were told during both informed consent and task training that their payment at the end of the session would be determined by their total performance on the task. This was also stated in the instructions on the computer screen while they were in the scanner. A monetary reward/loss paradigm was chosen because evidence suggests money represents a common currency for other basic rewards (i.e., food, sex; Montague & Berns, 2002), and would therefore elicit similar responses to loss across participants. To assess changes in distress during each of the task phases, participants used a joystick to complete mood ratings (e.g., "Irritability", "Stress", "Frustration", "Anxiety", and "Craving") before and after each phase on 100-point Likert scales displayed on the screen.

2.4.4.2 PASAT-M individual task phases (*Illustration 4*)

The task began with the first set of mood ratings, followed by the first phase of the task. The first phase was an easy phase that was expected to activate the motor and working memory components of the task while keeping the amount of affective distress experienced by participants to a minimum. For the easy phase, only two answer options were available (instead of four), with the other two response locations replaced with an 'X'. In addition, the subsequent number was not presented on the screen until the participant makes each response; therefore, there was no time pressure involved, as the participants could proceed at their own pace. There was a total of eight 45-second activity blocks, beginning, ending and alternating with 30-second rest blocks (during which a cross hair is presented in a central fixation point on the screen in a typical block-design fashion), for a total of 10.5 minutes.

Following the easy phase and a second mood rating period, a five-minute latency test phase began in order to determine each participant's individual skill level. The difficulty level increased substantially on this phase, in that there were now four response options to choose from instead of two, and each time a participant got a response correct, the subsequent number appeared 500 milliseconds faster than it did the previous time. Conversely, each time a participant was too slow or chose an incorrect response, the subsequent number appeared 250 milliseconds slower. This is the phase that participants began to 'lose' frequently, which was accompanied by a decreasing point meter and a loud explosion sound after each 'incorrect' or 'too slow' response. Ability level was calculated as the mean latency during this phase of the task.

The third phase of the task was the hard phase. This phase was designed in the same manner as the easy phase (eight 45-second activity blocks, beginning, ending and alternating with 30-second rest for a total of 10.5 minutes), but difficulty was significantly increased, such that each activity block in the hard phase had four response options to choose from instead of two, and the response time allotted for each number presentation was 2.5x faster than their ability level as determined during the latency phase. Further, participants were told that their performance during this phase would influence how much money they would receive at the end of the testing session. The task parameters and procedures that were utilized in the hard phase were developed in order to maximize the chance that participants would perform poorly on this round and experience repeated forced failure and aversive negative performance feedback (i.e., constant explosion noises signaling failure, as well as a decreasing point meter), thereby increasing affective distress.

The final phase was the distress tolerance (DT) phase, and was designed to measure one's ability to persist in goal directed behavior while experiencing affective distress. The rate of number presentation in this phase was identical to the hard phase and the DT phase lasted for a maximum of ten minutes. Participants were told that in this round they had a chance to earn back points they may have lost in the hard phase, but they would no longer lose points for 'incorrect' or 'too slow' responses. Participants no longer lost points and had the opportunity to win back points to ensure that participants (1) were engaging in goal directed activity, and (2) did not choose to quit the task because it was an adaptive response to prevent further loss. However, the explosion noises and negative feedback for incorrect responses remained. Participants were again

told that their performance would determine how much money they received at the end of the session, but that they were told that they could press a button on the joystick at any time to end the task, and the statement "Press the Button to Quit at any Time" was displayed on the screen throughout this phase.

Although there were a total of four phases of the PASAT-M, the final phase (i.e., the DT phase) was intended as a behavioral measure of distress tolerance, measured as time in seconds to task termination. Given that the duration of the DT phase varied across participants depending on how long they each chose to persist, the functional neuroimaging data from the DT phase was not included in analyses. To examine stress-induced neural function, data from the easy and hard phases were used. Specifically, the PASAT-M easy and hard phases were analyzed as a block-design task, primarily looking at the contrast activation map of [hard-rest] – [easy-rest] to isolate stress-induced neural activation.

2.5. Measures

2.5.1 Diagnostic and screening measures

All of the following measures were administered during the standard NIDA IRP screening procedures to determine eligibility for NIDA fMRI studies:

(a) Demographics Questionnaire: A self-report questionnaire that was used to assess basic information including age, gender, race/ethnicity, education level, occupation, home occupants, and socioeconomic status.

(b) Contact Information Form: This form requests multiple methods of contact for a participant, as well as the preferred contact method, preferred contact time, and emergency contact information.

(c) Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1995): A structured diagnostic interview that was used to assess lifetime prevalence of Axis I diagnoses to determine eligibility for the current study.

(d) Wechsler Abbreviated Scale of Intelligence (WASI): This is an abbreviated version of the Wechsler Adult Intelligence Scales – Third Edition that provides IQ measures of suitable reliability for estimating intelligence. For screening purposes, only the vocabulary portion of the WASI was administered. However, if a participant received a borderline score on the vocabulary subtest (i.e., less than the minimum score of 48 that was required for eligibility), the full WASI was then administered to determine eligibility for the current study. Those with full WASI scores of 85 or more were eligible to participate.

(f) Edinburgh Handedness Inventory (Oldfield, 1971): A self-administered 10-item questionnaire that was used during screening to assess if participants are right handed.

(g) Participant Safety – MRI Screening Form (Standard, NIDA-IRP): A brief self-administered questionnaire that aids in determining whether a participant can safely and effectively receive an MRI.

(h) Standard History and Physical (H&P) Exam: A standard exam including blood pressure, heart rate, and EKG, as well as the participant's current physical and psychological health, history of medical problems, family medical history, urine drug screen, breathalyzer to test for current alcohol intoxication, and first day of last menstrual cycle, as well as urine pregnancy test (for women). A comprehensive H&P was conducted during initial screening for eligibility to participate in NIDA fMRI studies, and abbreviated H&Ps (i.e., participants were only asked about changes in medical status

since their last study visit) were conducted with each participant during the study testing session.

2.5.2 Affective measures

(a) Mood Ratings: A total of five Likert-type scales were presented to participants repeatedly before, during (i.e., in between task scans), and after the entire 2-hour fMRI scan. During the PASAT-M scan in particular, the mood scales were presented five separate times (i.e., pre-easy phase, pre-latency phase, pre-hard phase, post-hard phase, and post-DT phase), assessing subjective feelings of "Irritability", "Stress", "Frustration", and "Anxiety" on a scale of 0-100. Each time the mood ratings were administered, the scales appeared one at a time on the screen. To complete the mood ratings, participants are told to use their joystick to move the cursor to the point on the line which best reflected how they were feeling right at that moment.

2.5.3 Smoking measures

(a) Fagerstrom Test for Nicotine Dependence (FTND; T.F. Heatherton, L.T. Kozlowski, R.C. Frecker, & K.O. Fagerstrom, 1991): The FTND is a 6-item self-report measure that was used during screening as a continuous measure of nicotine dependence. The FTND has shown good internal consistency, a single dimension factor structure, and positive relationships with degree of nicotine intake as assessed by saliva cotinine (T. F. Heatherton et al., 1991). The FTND is considered to be the standard instrument in the field for measuring nicotine dependence. Possible scores on the FTND range from 0-10.

(b) Smoking History Scale (SHQ): A brief self-report questionnaire that was used to assess different aspects of past smoking experience, including number of cigarettes per day and lapse history: two key smoking outcome variables in the current study.

Specifically, the SHQ includes items such as the number of cigarettes smoked per day, age of smoking initiation, smoking status (e.g., daily smoker, occasional smoker, etc.), number of quit attempts, longest time abstinent, and other smokers in the household. The items asking about the number of cigarettes currently smoked per day, number of quit attempts, and duration of longest abstinence attempt were the ones most relevant to the current study as they were used to assess current smoking severity and smoking lapse history.

(c) Stress-induced Craving: Stress-induced craving was assessed using a single-item Likert-type scale that was presented to participants along with the mood ratings at five time points over the course of PASAT-M administration (i.e., pre-easy phase, pre-latency phase, pre-hard phase, post-hard phase, and post-DT phase). Each time, the word "Craving" appeared on the screen and participants were instructed to use their joystick to move the cursor to the point along the line which best reflected how they were feeling right at that moment. Scores range from 0 to 100. Craving scores from post-easy phase and post-hard phase were used to create a difference score ([post-easy craving] – [post-hard craving]) reflecting stress-induced craving, and all analyses examining stress-induced craving controlled for baseline (i.e., post-easy) craving.

2.5.4. Physiological measures

(a) Heart Rate (HR): Increased HR generally accompanies emotional arousal states (Hagemann, Waldstein, & Thayer, 2003; Min, Chung, & Min, 2005); therefore, HR was also measured as a manipulation check to insure that the PASAT-M induced a state of physiological arousal. See *Section 2.6.2* below for details on method of HR measurement and data collection.

2.6. Data Acquisition

2.6.1 fMRI

Data acquisition occurred on a Siemens Allegra 3T scanner (Siemens, Erlangen, Germany). For the functional scans (both the resting functional connectivity scan and the PASAT-M scan), single-shot gradient-echo EPI images were obtained over the whole brain using an oblique axial acquisition plane (approximately 30° axial-to-coronal from AC-PC) that has been shown to minimize signal loss due to field inhomogenaity effects (Deichmann, Gottfried, Hutton, & Turner, 2003). The other imaging parameters are: TR=2s, TE=27ms, FOV=220x220mm^2, 64x64 matrix, slice thickness=4mm, FA=78°, BW=4112Hz/pixel. In each scanning session, a whole-brain T1-weighted structural image (MPRAGE) was acquired for anatomical reference (1mm^3 isotropic voxels, FOV=256x256mm^2, TR=2.5s, TE=4.38ms, TI=1s, FA=8°, BW=130Hz/pixel).

2.6.2 Physiological data

Amplified HR was recorded on a BIOPAC data acquisition system (BIOPAC Systems, Inc., Goleta CA). The recorded data was stored on a PC at a sampling rate of 1 kHz/channel. EKG data was recorded using four Ag-AgCl electrodes placed in the chest area. Beat-to-beat interval as well as HR data was automatically determined and submitted to semiautomatic artifact correction. EKG (HR) data were recorded continuously and were analyzed as average values over the entire length of each phase in order to assess task-related changes in physiological arousal.

2.7. Data Analysis Plan

2.7.1. Aims

The *primary aim* of the data analysis was to specify the relationship between stress-induced neural activation and real-world, clinically-relevant smoking variables, including stress-induced craving as measured by a Likert-type craving scale pre- and post-fMRI stress task, self-reported smoking lapse history (i.e., number of past quit attempts lasting 12 hours or more, and duration of longest past quit attempt), number of cigarettes per day, and scores on an established self-report measure of nicotine dependence (i.e., the FTND). The *secondary aim* of the data analysis was to specify the relationship between the strength of functional connectivity between corticolimbic regions showing significant stress-induced activation and clinically-relevant smoking outcomes (i.e., same variables as listed in primary aim).

2.7.2 Preliminary Analyses

Prior to conducting the main study analyses, the self-reported smoking-related data were examined for significant violations of normality (e.g., skewness greater than 1.0), multicollinearity, and missing values. Methods were employed, as needed, to impute missing data and transform data to approximate normality (i.e., log transformations for positive skewness). Analyses were also conducted to test for systematic differences between individuals who were included in analyses, versus those who were excluded. To assess the effectiveness of the PASAT-M as a distress-induction method, analyses were conducted as a manipulation check to test for significant differences in self-reported negative affect and craving from immediately post-easy phase to immediately post-hard

phase, as well as significant increases in physiological arousal (i.e., heart rate) from the easy phase to the hard phase.

2.7.3 Imaging Analyses

2.7.3.1. Preprocessing PASAT-M scan

The imaging data were analyzed with AFNI (Analysis of Functional NeuroImages, http://afni.nimh.nih.gov/afni/, (Cox, 1996)). First, preprocessing occurred on the single-subject data. This includes motion correction, correction of slice-timing differences, and censoring out time points exhibiting head motion greater than 0.3mm in 3 planes between successive TRs from individual subject data sets. Data sets exhibiting greater than 25% of data loss due to head motion were removed from further analyses.

Next, all functional images were directly registered upon their MPRAGE anatomical scan, translated into 3D stereotaxic coordinates (Talairach & Tournoux, 1988) and blurred to a FWHM of 8mm. First-level functional images from activation-induced MRI signal changes were determined using multiple regression analysis (P. A. Bandettini, Jesmanowicz, Wong, & Hyde, 1993; Worsley & Friston, 1995) using a restricted maximum likelihood approach and including a ARMA(1,1) term to account for autocorrelation of the residuals. Regressors for the PASAT-M were boxcars for [easy-rest] and [hard-rest] contrasts convolved with a model of the hemodynamic response function (HRF). Extra regressors were included to account for baseline, baseline drift, and residual motion. The activation map for the contrast [hard-rest] – [easy-rest] was used to identify significant clusters of stress-induced activation within corticolimbic ROIs. Small-volume corrections were applied to the a priori hypothesized ROIs (i.e., amygdala, striatum, insula, vmPFC and ACC, all defined based on their locations in the

Talairach Daemon atlas (Lancaster, Woldorff, Parsons et al., 2000) in AFNI; see *Table 1* for list of Talairach coordinates for the center of mass of each ROI). Data were then corrected for multiple comparisons to omnibus $p<0.05$ using a combination of voxel-wise threshold and minimum cluster size (Forman et al., 1995). Specifically, using 3dClustSim in AFNI following small volume correction, it was determined that at a voxelwise threshold of $p<0.001$, a minimum cluster size of 8 voxels was required to maintain an omnibus threshold of $p<0.05$.

2.7.3.2. Preprocessing Resting State Functional Connectivity Scan

Functional connectivity analyses were conducted in AFNI (Cox, 1996), SPM5 (Friston et al., 1995) and MATLAB (The MathWorks, Inc., Natick, MA). Preprocessing included slice-timing correction, motion correction, and censoring out time points exhibiting head motion greater than 0.3mm in 3 planes between successive TRs from individual subject data sets. Data sets exhibiting greater than 25% of data loss due to head motion were removed from further analyses. Preprocessing continued with linear detrending and low-pass temporal filtering with a cutoff frequency of 0.1 Hz to retain the low frequency fluctuation components that contribute to functional connectivity (Biswal, Yetkin, Haughton, & Hyde, 1995; Lowe, Mock, & Sorenson, 1998).

To facilitate group analysis, data was spatially normalized to the standard Talairach space with a resampled resolution of $3\times3\times3$ mm^3. Spatial smoothing with a 6-mm Gaussian kernel was performed to increase spatial signal to noise ratio (SNR). To further align the resting-state functional data across subjects, an unbiased group-wise nonlinear registration method was used to deform each spatially smoothed image to an implicit group reference image based on a small deformation elastic model (Geng, 2007).

Seed regions were defined based on functional clusters of significant stress-induced activation on the PASAT-M (i.e., during the [hard-rest] – [easy-rest] contrast) in a-priori hypothesized corticolimbic regions that have previously been shown to play a role in both stress and addiction. One such cluster in the right insular cortex was identified (reported in full detail in Results section below). For the significant cluster of stress-induced neural activation that was identified, the entire cluster was extracted as a mask that served as the seed region for functional connectivity analyses. A reference time course from the seed region was generated by averaging the time courses of all voxels within the cluster. Subsequently, a cross-correlation coefficient (CC) map for the seed region was obtained by correlating each voxel's time course with the corresponding reference time course. Global fluctuations, originating presumably from systemic effects, such as respiration and cardiac function were corrected by extracting the top three principal component time-courses each from voxels in white matter and ventricular CSF. These masks were generated by segmenting the high resolution structural images in SPM5 and down-gridding them to the same resolution as the functional data. Correction for global fluctuations were then performed by regressing these time courses during calculation of CCs. Before proceeding to group-level analysis, the CC maps were converted to z-score maps that have the same tail probability as CC maps using AFNI's built-in function to improve the normality.

2.7.3.3. Primary Aim

The primary aim was to examine the unique relationships between stress-induced neural activation and each of the five clinically-relevant smoking outcome variables outlined above (i.e., stress-induced craving, FTND score, cpd, longest past quit attempt,

and number of past quit attempts lasting longer than 12 hours). Second-level (i.e. group) analyses consisted of voxel-wise multiple linear regression analyses on the beta-weight maps resulting from the first-level analysis of the PASAT-M task data described above (namely, the activation map from the contrast [hard-rest] – [easy-rest]), using the 3dRegAna program (Ward, 1998) within AFNI. This program allows users to enter the quantitative level that applies for each of the independent variables, and specify which variables are to appear in the full linear regression model as well as a simpler reduced model (Ward, 1998). Regressors for each analysis included any demographic variables showing a significant relationship with the smoking outcome data, followed by the smoking outcome variable of interest. Bonferroni corrections (Bland & Altman, 1995) were applied to correct for family wise error rate related to the five separate regression analyses. Specifically, to maintain an omnibus threshold of $p<0.05$, the threshold for each individual regression analysis was adjusted to $p<0.01$ (i.e., $\alpha/k = 0.05/5 = 0.01$).

For the activation maps resulting from each regression analysis, small-volume corrections were applied to the a priori hypothesized ROIs (i.e., amygdala, striatum, insula, vmPFC and ACC, all defined based on their locations in the Talairach Daemon atlas (Lancaster, Woldorff, Parsons et al., 2000) in AFNI; see *Table 1*). Data were then corrected for multiple comparisons to omnibus $p<0.01$ using a combination of voxel-wise thresholding and minimum cluster size (Forman et al., 1995). Specifically, using 3dClustSim in AFNI following small volume correction, it was determined that at a voxelwise threshold of $p<0.001$, a minimum cluster size of 12 voxels was required to maintain an omnibus threshold of $p<0.01$.

2.7.3.4. Secondary Aim

The secondary aim was to examine the unique relationships between resting state functional connectivity in a priori hypothesized corticolimbic circuits and each of the clinically-relevant smoking-related variables. The z-score map for the functionally defined seed region was included in separate multiple linear regression analyses using 3dRegAna in AFNI. Regressors for each analysis included any demographic variables showing a significant relationship with the smoking outcome data, followed by the smoking outcome variable of interest. Bonferroni corrections (Bland & Altman, 1995) were applied to correct for family wise error rate related to the five separate regression analyses. Specifically, to maintain an omnibus threshold of $p<0.05$, the threshold for each individual regression analysis was adjusted to $p<0.01$ (i.e., $\alpha/k = 0.05/5 = 0.01$).

For the maps resulting from each regression analysis, small-volume corrections were applied to the a priori hypothesized ROIs (i.e., amygdala, striatum, insula, vmPFC and ACC, all defined based on their locations in the Talairach Daemon atlas (Lancaster, Woldorff, Parsons et al., 2000) in AFNI). Data were then corrected for multiple comparisons to omnibus $p<0.01$ using a combination of voxel-wise thresholding and minimum cluster size (Forman et al., 1995). Specifically, using 3dClustSim in AFNI following small volume correction, it was determined that at a voxelwise threshold of $p<0.001$, a minimum cluster size of 8 voxels was required to maintain an omnibus threshold of $p<0.01$.

Chapter 3: Results

3.1 Preliminary Analyses

3.1.1 Descriptives

3.1.1.1Sample Characteristics

A total of 20 participants were included in study analyses (see *Illustration 1* for flow chart illustrating how participants were selected for inclusion in analyses). Participants ranged in age from 21 to 48 (M = 29.8, SD = 8.5). With regard to racial/ethnic background, 65% identified as White/Caucasian (n = 13), 30% identified as Black/African American (n = 6), and 5% were Asian or Southeast Asian (n = 1). In terms of highest education level, 20% (n = 4) reported less than a high school education, 25% (n = 5) reported completing high school or obtaining a GED, and 55% (n = 11) reported at least some college or technical school or a college degree. About one-third of the sample reported current unemployment (35%, n = 7), and the majority of the sample reported an average household income of less than $40,000 a year (80%, n = 16). The duration of participants' smoking history ranged from 3-34 years (M = 12.5 years; SD = 8.5) and smoked an average of 15.28 (SD = 4.62) cigarettes per day (cpd) in the last week (reports ranged from 10cpd to 25cpd).

Given the substantial number of participants that had to be excluded from analyses due to head motion and other factors, we tested for significant demographic, smoking, and intelligence differences between individuals who were included versus those excluded from analyses, in order to elucidate any potential systematic differences

between these two groups. There were no significant group differences in age, gender, ethnicity, income, education, employment status, intelligence (as measured by the WASI-vocab score obtained during screening), self-reported number of cigarettes smoked per day, or duration of participants' self-reported smoking history in years.

3.1.1.2 Descriptive statistics: Smoking measures

Descriptive statistics for each smoking-related measure are provided in *Table 2*. Based on responses to items in the SHQ, smokers reported smoking an average 15.28 (*SD* = 4.62) cigarettes per day (cpd) in the last week (reports ranged from 10cpd to 25cpd). In terms of their history of quit attempts, the number of past quit attempts lasting longer than 12 hours reported by participants ranged from 0 to 20 times (*Mean* = 3.60; *SD* = 4.30) and the duration of longest past quit attempts ranged from 1 to 730 days (*Mean* = 244.48; *SD* = 270.70). The distribution of responses to the item about the number of past quit attempts lasting longer than 12 hours was positively skewed, thus a log10 transformation was applied and the transformed values were used in all subsequent analyses that included number of past quit attempts as a regressor. Skewness values both prior to and following the log10 transformation are included in *Table 2.*

Regarding measurement of nicotine dependence severity, participants completed the FTND with scores ranging from 2 to 8 (*Mean* = 5.25; *SD* = 1.80), which is in line with previous neuroimaging studies utilizing this measure among cigarette smokers (e.g., Hong et al., 2010). Finally, descriptive statistics are provided for our measure of stress-induced craving. Immediately following the easy phase of the PASAT-M (i.e., before the "stressful" elements of the task were introduced), participants reported an average craving of 37.31 (*SD* = 39.12) on a scale of 0-100. Following the hard phase of the task,

average craving increased to 43.72 (*SD* = 37.73). The average change score reflecting stress-induced craving (i.e., (post-hard phase craving) – (post-easy phase craving)) was 6.41 (*SD* = 16.58). A repeated measures ANOVA revealed no significant difference in craving from post-easy to post-hard phase of the task, reflecting the wide range of variability across participants in terms of the effect of the task on individual craving scores. The distribution of stress-induced craving was positively skewed; therefore, a log10 transformation was applied and transformed values were used in all analyses in which stress-induced craving was included as a regressor.

Of all smoking-related measures that are included in subsequent analyses (i.e., number of quit attempts lasting longer than 12 hours, duration of longest quit attempt, cigarettes per day, FTND score, and stress-induced craving), none of them evidenced significant correlations with the other measures (all p's > 0.07) suggesting that they are each tapping into unique smoking-related constructs. A correlation matrix including correlations among all smoking measures is provided in *Table 3*.

3.1.2 Examination of potential covariates

First, bivariate correlation analyses were conducted to examine the relationship between age and the various smoking outcome variables. There was a significant correlation between age and duration of longest past quit attempt (r = .83; p < .001). None of the other smoking variables were significantly related to age (all p's > 0.10). Thus, all subsequent analyses that include the variable for duration of longest past quit attempt control for age.[1]

Regarding gender, independent samples t-tests revealed a significant relationship with only one smoking-related variable: number of quit attempts lasting longer than 12

hours ($t(18) = -2.36$; $p = .03$). Specifically, women reported a history of 1.80 ($SD = 1.48$) past quit attempts lasting more than 12 hours, while men reported 5.44 ($SD = 1.72$) past quit attempts of 12 hours or longer. Therefore, subsequent analyses examining number of past quit attempts controlled for gender. There were no significant gender effects on any of the remaining smoking-related variables. Additionally, there were no other significant effects of demographic variables (including race, highest education, and income), or intelligence (as measured by WASI vocab scores obtained during study screening) on smoking-related variables.

3.1.3 Overview of behavioral and self-report responses to the PASAT-M

In terms of task performance, repeated measures ANOVAs revealed a significant decrease in correct responses from the easy phase to the hard phase ($F(1, 19) = 28.54$; $p < .001$), as well as a significant increase in incorrect responses ($F(1, 19) = 33.87$; $p < .001$), indicating that the hard phase was indeed significantly more difficult to perform successfully than the easy phase. Regarding task effects on mood ratings and arousal (as measured by HR), repeated measures ANOVAs revealed significant increases from post-easy phase to post-hard phase in ratings of Anxiety ($F(1, 19) = 6.28$; $p = .02$), Irritability ($F(1, 19) = 9.50$; $p = .01$), Frustration ($F(1, 19) = 17.41$; $p < .001$), and Stress ($F(1, 19) = 4.33$; $p = .05$) (*Figure 1*). Changes in HR over the course of the task were also examined. Of the 20 participants included in study analyses, HR data was missing for 7 of them due to technical difficulties or undetectable HR levels upon analyzing the HR data. Among the 13 participants that did have complete HR data, a repeated measures ANOVA showed a non-significant increase in HR from the easy phase (Mean easy HR = 81.16; SD = 19.44) to the hard phase (Mean hard HR = 83.95; SD = 20.37) ($F(1, 12) = 1.97$; $p = .19$).

Despite the fact that there was no significant change in HR from the easy phase to the hard phase, task-related changes in mood ratings suggest that the PASAT-M was an effective method for inducing an increased subjective experience of affective distress.

3.2 PASAT-M task effects: Stress-induced neural activation

Next, analyses were conducted to determine the stress-related effects of the PASAT-M on neural activation. Specifically, the activation map for the contrast of interest, [hard-rest] – [easy-rest], was examined, with small volume corrections applied to the *a priori* hypothesized regions of interest (i.e., the ACC, vmPFC, insula, amygdala, and striatum). A combination of voxelwise thresholding and clusterizing was used to control for multiple comparisons. Specifically, setting a voxelwise threshold of $p<.001$ required a minimum of 8 voxels to maintain an omnibus threshold of $p<.05$. As expected, analyses revealed a significant 14-voxel cluster of stress-induced activation in the posterior portion of the right insula (Brodman Area 13; Talairach coordinates: [57, -33, 18]; Peak T-statistic = 5.08; *Figure 2*). None of the other hypothesized regions showed any significant stress-related effects in response to the PASAT-M. The significant cluster of stress-induced neural activation in the right insula was used as the seed region for subsequent resting state functional connectivity analyses that were conducted to address the secondary aim of the current study.

3.3. Primary Aim: Relationship between Stress-Induced Neural Activation and Smoking Measures

To examine the relationship between smoking-related variables and stress-induced neural activation in response to the PASAT-M, separate regression analyses were

conducted for each smoking variable of interest in AFNI using 3dRegAna, specifically examining the relationship between each smoking variable and neural activation during the contrast [hard-rest] – [easy-rest] on the PASAT-M, with small volume corrections applied to the a priori hypothesized regions of interest. Analyses revealed no significant relationships between stress-induced neural activation and any of the smoking-related variables, including stress-induced craving, cigarettes per day, duration of longest past quit attempt, number of past quit attempts lasting twelve hours or more, or FTND scores.

3.4. Secondary Aim: Resting State Functional Connectivity and Smoking Outcomes

To examine the relationship between smoking-related variables and functional connectivity within corticolimbic circuits, separate regression analyses were conducted for each smoking variable of interest in AFNI using 3dRegAna, specifically examining the relationship between the strength of functional connectivity with the significant cluster of stress-induced neural activation in the right insula, and the various smoking variables of interest. Analyses revealed no significant relationships between functional connectivity with the right insula and any of the smoking-related variables, including stress-induced craving, cigarettes per day, duration of longest past quit attempt, number of past quit attempts lasting twelve hours or more, or FTND scores.

Chapter 4: Discussion

4.1. Summary of Main Findings

The current study utilized an fMRI-compatible psychological stress-induction task to examine the relationships among stress-induced neural activation, as well as resting state functional connectivity within stress-related corticolimbic circuits, and clinically-relevant smoking-related variables among a sample of current adult cigarette smokers. Based on existing neurobiological models of addiction that emphasize the role of overlapping corticolimbic circuits in both emotion dysregulation and compulsive drug seeking (e.g., Li & Sinha, 2008), it was hypothesized that decreased reactivity to stress in cortical regions including the ACC and vmPFC; increased reactivity to stress in limbic regions including the amygdala, insula, and striatum; and weaker functional connectivity between these circuits at rest, would be significantly related to higher levels of stress-induced craving, poorer self-reported smoking lapse history, greater number of cigarettes per day, and higher scores on an established self-report measure of nicotine dependence (i.e., the FTND). Analyses revealed a significant cluster of stress-induced activation in the right insula in response to the stress task; however, there were no significant relationships between stress-induced neural activation, or functional connectivity in stress-related corticolimbic circuits, and the smoking related variables. The findings are discussed below in light of study limitations.

4.1.1. Task effects: Stress-induced neural functioning

Consistent with previous research, fMRI data from the PASAT-M revealed significant stress-induced activation in the right insula. Extant research suggests a key role for the insula in the experience of negative feelings, such as fear, disgust, and anxiety (e.g., Phan, Wager, Taylor, & Liberzon, 2002; Winkielman et al., 2007), as well as interoceptive awareness of visceral responses that are heightened in negative emotional states (Critchley et al., 2004). Thus, activation in the right insula in response to a stressful task was expected given the significant self-reported increases in negative affective experiences that were reported by participants.

The fact that we saw stress-induced activation in the posterior portion of the right insula in particular was somewhat unexpected. In general, activation in the posterior portion of the insula has been associated with perception of primary sensory stimuli (e.g., pain, temperature changes, itch), while activation in the anterior portion of the insula has more frequently been implicated in more subjective interpretations of interoceptive and homeostatic responses to stimuli, including the experience of emotional feelings and self-awareness more broadly (Craig, 2011). Thus, we would have expected more task-induced activation in the anterior insula as opposed to the posterior insula given participants' reports of significantly increased ratings of negative mood states in the hard phase relative to the easy phase. However, a recent study found that activation in the posterior insula in response to a gambling task predicted risky behavior on the task (Xue, Lu, Levin, & Bechara, 2010). The authors posited that the posterior insula might play a role in the experience of homeostatic responses associated risk, which influences subsequent risky decisions. Therefore, it is possible that participants' performance on the task in the

current study was interpreted as a form of risk insofar as participants were told that their opportunity for maximum reward (i.e., financial compensation) was contingent on their performance on the task. They also may have been thinking ahead about their decision to either persist or quit the task during the final round of the PASAT-M. More research is needed to parse out the influences of stress vs. risk on task-induced activation within the anterior and posterior portions of the insula, and how this activation relates to subsequent behavior. Given interest in understanding the role of functional connectivity between corticolimbic regions previously implicated in both emotion dysregulation and compulsive drug seeking, the significant cluster of activation in the right insula was later utilized as a functionally defined seed region to better understand how it interacts with other corticolimbic regions at a network level to predict smoking characteristics.

No additional significant effects of stress during the PASAT-M were identified in the other hypothesized corticolimbic regions of interest, including the ACC, vmPFC, amygdala, or the striatum. In considering why the stress-induced neural effects during the PASAT-M were relatively limited, it is necessary to consider the possibility that the task simply was not an effective method for reliably and robustly increasing stress across participants. On average, subjective ratings of stress, frustration, anxiety, and irritability did increase significantly from the easy phase to the hard phase; however, it is possible that these self-reported increases in negative affect ratings could have been influenced by demand characteristics (i.e., participants may have reported increased distress if they believed that they were expected to be stressed by the task). Notably, every effort was made during testing sessions to avoid referring to the PASAT-M as 'stressful' in front of participants. Rather, task instructions referred to the PASAT-M as a 'challenging'

mathematical processing task in order to reduce the possibility of biasing participant ratings. Nonetheless, a more effective approach to assessing stress reactivity to the task would be to collect objective physiological measures of stress and arousal. Unfortunately, the only objective measure of physiological arousal that was available in the current study, heart rate (HR), showed no significant change from the easy to the hard phase. This does not necessarily mean that the task was not stressful. Although emotionally aroused states are generally accompanied by increased HR (Hagemann et al., 2003; Min et al., 2005), exceptions to this rule have been reported, particularly in response to attentional tasks (e.g., Berntson, Cacioppo, & Quigley, 1993). Moreover, participants in the current study could have experienced an anticipatory increase in HR at the end of each rest block as they prepared to begin the task again, which may have dampened any significant change in average HR between rest and task blocks in the hard phase. Additionally, signal from the scanner may have interfered with HR readings, and the sample size was relatively small to detect significant effects. Future studies may benefit from including additional measures of autonomic arousal, such as pulse readings in the extremities, or changes in blood pressure or respiration in order to determine if the stress manipulation does indeed increase arousal as it was expected to.

There are a number of potential reasons why the PASAT-M might not have been as stressful as was anticipated. First, the task may not have been aversive enough to elicit a reliable and robust stress response across participants. Extensive pilot testing was conducted during the development of the PASAT-M to determine effective parameters for maximizing the aversiveness of the task, such as the volume necessary for participants to hear the explosions that went off with each incorrect response during the hard phase of

the task. A volume level was chosen based on the results of piloting and was held constant across participants during data collection for the current study. It is possible, however, that some participants in the current study could not adequately hear the explosions over the constant noise of the scanner, or that they were not bothered by the explosion sounds.

Second, laboratory stress paradigms have been found to be most effective at activating physiological stress responses when they include elements of both uncontrollability and social evaluative threat (Dickerson & Kemeny, 2004). While the PASAT-M was indeed designed to be 'uncontrollable' as the speed of the hard phase is deliberately set beyond each individual participant's ability level, leading to constant forced failure, the version of the PASAT-M that was utilized in the current study did not include any overt social evaluative threat. Since data collection was completed for the current study, the PASAT-M has been modified for use in subsequent studies to include overt negative evaluations of participants' performance during task administration in order to enhance the robustness of the PASAT-M as a psychological stress induction. Specifically, during the newly modified PASAT-M, research assistants now speak to each participant immediately following completion of the latency phase (i.e., right before they begin the hard phase of the task) to tell them that they are not performing as well as other participants normally do, and that they need to try harder.

Finally, it is notable that the scanner itself may also serve as a stressor (Muehlhan, Lueken, Wittchen, & Kirschbaum, 2011). This is an important consideration when using cognitive subtraction methods to detect neural responses to stress. If participants are already experiencing elevated stress at the beginning of the task (i.e., during the easy

phase of the PASAT-M) simply as a byproduct of being in the scanner, the effect that this unintended stress has on neural functioning is subtracted out when the contrast of interest is applied (i.e., [hard-rest] – [easy-rest]) in an attempt to isolate the effects of stress on neural functioning. Efforts were made to limit this possibility by always administering the PASAT-M during the second half of the scan session, after participants had time to acclimate to the scan environment, but it remains possible that the scanner itself may have elevated participant stress levels, thus limiting our ability to detect stress-related neural functioning that would be attributable to the task.

4.1.2. Relationship between stress-induced neural functioning and smoking-related variables

Next, analyses were conducted to examine the relationships between stress-induced neural functioning and our smoking-related variables (i.e., stress-induced craving, cigarettes per day, smoking lapse history, and FTND scores); however, no significant relationships were identified. There are a number of possible explanations for our null findings. First, as discussed above, it is possible that the PASAT-M did not serve as an adequately robust method for inducing psychological stress. As such, the fMRI data collected during the PASAT-M might not serve as a valid measure of stress-induced neural responding, and thus, would not be related to smoking characteristics in the manner that was hypothesized. Alternatively, the lack of findings could be due to the fact that participants were not deprived of nicotine prior to the scan, but instead, all participants were asked to smoke a cigarette immediately before entering the scanner, which was approximately 1-1.5 hours prior to PASAT-M administration. This approach is consistent with the method used by Dagher and colleagues (2009) who reported that participants smoked their last cigarette about one hour prior to beginning the fMRI stress

task in their study. Nonetheless, it is possible that there may have been more robust findings if participants in the current study had completed the stress task in a nicotine-deprived state.

It is also possible that the neural model that was used as the basis of the hypotheses for the current study may have been too narrow. Namely, the current study relied largely on the neural model of emotion dysregulation and compulsive drug seeking proposed by Li & Sinha (2008) which emphasized specific corticolimbic regions and their interconnections, including the vmPFC, ACC, amygdala, and striatum. Additionally, the insula was added into the current model given a recent emphasis in the field on the role of the insula in interoception (Craig, 2002; Craig, 2009), especially as it relates to the experience of the physical and affective symptoms associated with withdrawal among substance users, including smokers in particular (Naqvi & Bechara, 2010). By using small volume corrections to isolate the study analyses to these discrete regions of interest, we may have missed significant effects of stress-induced functioning in other regions of the brain in predicting smoking characteristics.

4.1.3. Relationship between resting state functional connectivity and smoking-related variables

Next, analyses were conducted to better understanding the relationship between network level functioning in corticolimbic circuits that were activated by stress and smoking-related variables. As such, using the one a priori hypothesized corticolimbic region, the right insula, which showed significant stress-induced neural activation in response to the PASAT-M as a seed region, analyses were conducted to examine the relationship between the strength of functional connectivity with the right insula and

smoking-related outcomes. No significant relationships were identified between network level connectivity with the right insula and smoking measures.

Again, it is possible that the inability to detect a significant effect of functional coupling with the right insula may have been due to the nicotine satiated state of participants during the current study. Recent conceptualizations of insula functioning at a network level, particularly as it relates to nicotine dependence, have emphasized alterations in insula coupling within large-scale neural networks among smokers which vary as a function of acute nicotine exposure (i.e., when smokers are nicotine deprived vs. satiated). For example, Naqvi and Bechara (2010) have offered a theoretical model that parses out the role of the insula in interoception at varying stages of addictive behavior, including drug-taking, withdrawal, and craving states. When nicotine deprived, Naqvi and Bechara (2010) suggest that the insula tracks internal visceral symptoms of nicotine withdrawal, and interacts with other regions involved in affective and motivational processing, such as the vmPFC, amygdala, and striatum, which in turn alter subjective affective and behavioral responses to smoking cues and urges.

More recently, Sutherland and colleagues (2012) have gone even further to delineate the role of the insula and its interconnections in the modulation of attentional allocation during nicotine-satiated versus deprived states. The authors propose that the insula and the ACC together acting as a salience network (SN) tracks moment-to-moment stimuli coming in from both internal and external sources, identifies the most subjectively relevant stimuli at a given moment, and then influences information processing in real-time by serving as a "toggle" switch to modulate activity between two additional networks known as the default mode network (DMN) and the executive control network

(ECN). The DMN is composed of midline structures including the dmPFC, vmPFC, and posterior cingulate cortex (PCC), is consistently activated during passive states, and is believed to underlie internal cognitive operations, such as interospective functions (Raichle et al., 2001; Sestieri et al., 2011). Meanwhile, the ECN is composed of prefrontal and parietal structures, and is routinely activated during cognitively demanding tasks, supporting attentional allocation and processing of exogenous stimuli (Corbetta & Shulman, 2002; Seeley et al., 2007). Based on the model defined by Sutherland and colleagues (2012), when smokers are acutely deprived of nicotine, the SN allocates greater attentional resources toward the processing of internal withdrawal-related symptoms, thus biasing neural functioning toward the DMN and away from the ECN. This attentional bias toward interoceptive withdrawal-related symptoms and away from external stimuli may provide the neural basis for cognitive and attentional deficits that are consistently seen in nicotine-deprived smokers, and may also serve as a driver of nicotine craving.

Indeed, Lerman and colleagues (2014) recently utilized a novel approach to examine the effects of nicotine deprivation on the relative resources that the SN allocates to the ECN versus the DMN among cigarette smokers. Findings revealed that nicotine deprivation was associated with a weaker connection between the SN and DMN at rest, suggesting an impaired ability of the SN to suppress DMN functioning. Moreover, the magnitude of change in functional connectivity from smoking to a deprived state predicted withdrawal-induced smoking urges, as well as impaired suppression of DMN functioning during a working memory task.

The theoretical and empirical work reviewed above highlights the significant effects that acute nicotine exposure (or deprivation) can have on network level functioning and more specifically, the strength of insula connectivity with other brain regions involved in the allocation of attention to internal versus external stimuli, thus having an impact on affective, motivational, and cognitive functions. Given that the current study only measured resting state functional connectivity with the insula during a nicotine satiated state, the study analyses may have missed effects of insula connectivity on smoking-related characteristics that might have been more pronounced in a nicotine deprived state.

4.2. Limitations and Future Directions

4.2.1. Limitations

The current findings must be interpreted in the context of several study limitations. First, analyses reported here do not include direct comparisons of neural functioning data collected from smokers with matched data acquired from non-smoking control participants. As such, no conclusive statements can be made about the extent to which the self-reported affective responses and patterns of neural functioning evidenced in response to the PASAT-M are uniquely attributable to smoking status, whether or not our sample of smokers evidenced impaired or abnormal stress-induced neural responses to the task relative to non-smokers, or if other variables that tend to co-vary with smoking status or dependence severity may better account for our findings. A matched control group would allow for experimental control over potential confounds, and would also provide further support for the utility of the PASAT-M as an effective stress induction method for the general population. A control group of non-smokers was indeed recruited

for the larger study from which the current study was proposed and analyses directly comparing neural activation in response to the PASAT-M among smokers vs. non-smokers are underway.

A second limitation is that the current study is cross-sectional in design, thus precluding any possibility of drawing conclusions about the causal nature of significant relationships between neural functioning and smoking characteristics, had we seen any. That is, if either stress-induced neural functioning or resting state functional connectivity had predicted smoking-related variables, we would not be able to say whether individual differences in nicotine dependence severity or smoking lapse history caused variations in corticolimbic, and specifically, stress-related neural functioning, or if individual differences in neural functioning causally influenced smoking characteristics.

Third, there were inherent limitations in the specific measures that were used to measure smoking characteristics and neural function. The smoking-related measures were all collected via self-report; therefore, these measures are only valid to the extent that participants had sufficient insight into their emotions and smoking-related behaviors, and in the case of smoking lapse history measures, accurate memories of their past smoking cessation attempts. It is also notable that our measure of neural functioning (i.e., changes in blood oxygen level dependent (BOLD) signal) does not provide any information about the specific neurochemical events that are responsible for the change in BOLD functioning in the right insula that was identified in response to the PASAT-M. The use of alternative technologies, such as positron emission tomography (PET) scans would allow for researchers to measure the release of specific neurotransmitters in the brain that may underlie stress-related neural responses.

Finally, the current study is limited in the extent to which findings can be generalized to the larger population of smokers. Specifically, the current study excluded individuals with current Axis I or II psychopathology, individuals who used any illicit substances within the past 30 days, individuals on certain medications, and individuals with major medical conditions in an attempt to isolate effects that could be uniquely attributed to smoking. Notably, cigarette smokers are at an increased risk of meeting criteria for psychiatric disorders including depression, anxiety, and substance use disorders (Black, Zimmerman, & Coryell, 1999), and smokers with co-occurring psychiatric illnesses tend to report more severe nicotine dependence symptoms and smoke more cigarettes per day relative to smokers who do not meet criteria for psychiatric disorders (Grant, Hasin, Chou, Stinson, & Dawson, 2004). As such, the recruitment efforts for the current study precluded our ability to assess the relationships between corticolimbic functioning and smoking-related variables in a substantial portion of the smoking population, and may have missed individuals at the most severe end of the nicotine dependence spectrum who could have been excluded based on co-occurring mental illness or use of prescription medication for the treatment of psychiatric or medical illnesses. Moreover, these exclusion criteria yielded a relatively small sample of smokers over the course of over two years of study recruitment, reflecting the limited number of cigarette smokers in the larger NIDA research participant pool who met all study criteria. As this was a first attempt to characterize neural response to the PASAT-M and the relationships between corticolimbic functioning and smoking-related variables, recruitment criteria were selected in an effort to maximize internal validity. However,

more research with larger, and more representative, samples is clearly needed to enhance generalizability.

4.2.2. Future Directions

Many questions remain regarding the role of corticolimbic functioning in the relationship between stress and nicotine dependence, smoking maintenance, and relapse. First, the fMRI-compatible version of the PASAT (the PASAT-M) is a novel task for examining stress-induced neural functioning; therefore there is a need to further clarify the reliability and validity of the task as a stress-induction method that is powerful enough to impact neural function. To this end, future studies that utilize the PASAT-M to examine stress-related neural function should include additional objective measures of physiological arousal and stress responding, such as galvanic skin conductance and hypothalamic-pituitary-adrenal (HPA) axis functioning (e.g., via salivary cortisol samples).

Additionally, research with larger samples, that also include healthy control groups, will be invaluable to support the utility and generalizability of this task as a reliable psychological stress induction method that can robustly activate stress-related neurocircuitry. The current study found only one cluster of significant stress-induced neural activation in response to the task; however, it is unclear if this limited neural response to the PASAT-M may be indicative of maladaptive neural responding to stress among smokers. A direct comparison with healthy non-smokers would allow us to say more about the utility of the PASAT-M's utility more generally, and would enhance our understanding of the unique effects of cigarette smoking on stress-induced neural functioning. Larger and more diverse samples could also facilitate the further

development of larger models that include individual difference factors, such as specific genetic polymorphisms, early and chronic stress exposure, gender, and personality factors that may influence corticolimbic functioning and reactivity to stress.

Future research may also benefit from more nuanced measures of nicotine dependence severity that capture unique, theoretically-based, facets that contribute to nicotine use motivations and dependence. For example, the Wisconsin Inventory of Smoking Dependence Motives (WISDM-68; Piper et al., 2004) is a multidimensional 68-item self-report measure developed to assess thirteen different theoretically relevant motivational factors driving nicotine dependence. A second example, the Nicotine Dependence Syndrome Scale (NDSS; Shiffman, Waters, & Hickcox, 2004) is a multidimensional self-report measure of nicotine dependence severity that was developed under the assumption that nicotine dependence itself is a multi-faceted construct (Shadel, Shiffman, Niaura, Nichter, & Abrams, 2000). The measure allows for the measurement of five factor analytically-derived facets of the nicotine dependence syndrome. Multidimensional measures of nicotine dependence, such as the WISDM-68 and the NDSS, may be particularly useful for examining neural mechanisms underlying stress and addiction, as these more nuanced scales would enable researchers to identify specific aspects of nicotine dependence, such as negative reinforcement motives (WISDM-68) and craving (NDSS), which may be uniquely associated with stress-related neural functioning among smokers.

Additionally, there is a need for longitudinal research designs to determine the utility of stress-related neural functioning to prospectively predict smoking outcomes, and to identify the extent to which smoking cessation may alter neural responses to stress.

Moreover, inclusion of a nicotine manipulation (i.e., within-subject comparisons of neural reactivity to stress and resting state functional connectivity when participants are nicotine deprived vs. nicotine satiated) would also substantially enhance our understanding of the potentially nicotine-dependent effects of stress on neural function. A nicotine manipulation could elucidate the relative utility of stress-related corticolimbic functioning during nicotine-deprived versus nicotine-satiated states to predict smoking-related outcomes. That is, the brain may respond to stress quite differently in a nicotine satiated state as compared to a state of acute nicotine withdrawal or long-term abstinence from smoking, and these differences may vary in their ability to predict clinically-relevant outcomes.

Finally, continued research identifying the neural correlates of stress reactivity among smokers and the relationship between stress-induced neural activation and clinically-relevant smoking outcomes may provide biological targets for future interventions designed to treat smokers with heightened stress reactivity and stress-related relapse vulnerability. Already, smoking interventions drawing from stress management strategies such as acceptance-based approaches (R. A. Brown et al., 2008) and mindfulness-based meditation (Brewer et al., 2011) have shown promising results among smokers, including those with a history of early lapse. By modeling the neural correlates of stress-related relapse vulnerability, more efficient targeted intervention strategies may be employed to identify and isolate those at greatest risk, treat the specific vulnerability that they present, and (as speculated by some researchers) perhaps even elucidate biomarkers to track treatment efficacy (e.g., Hong et al., 2009).

Research examining the neural basis of stress processing in individuals suffering from addiction could also contribute to the development of novel applications of real-time fMRI itself for the treatment of substance use disorders. Indeed, the combination of real-time fMRI and biofeedback represents a nascent, yet promising, avenue for the treatment of a variety of psychiatric illnesses, including substance use disorders. To date, most real-time fMRI studies have focused on participant-driven modulation of BOLD signal in cortical regions, including the somatomotor cortex (deCharms et al., 2005), auditory cortex (Yoo et al., 2007), insular cortex (Caria et al., 2007), medial frontal cortex (Phan et al., 2004), and ACC (deCharms et al., 2004; deCharms et al., 2005), and have largely included healthy participants between the ages of 18-45 years old. A smaller body of research has focused on subcortical structures, including the amygdala (Posse et al., 2003).

Moreover, preliminary studies are emerging in support of real-time fMRI and participant-driven signal modulation as potential treatments for clinical disorders, including epilepsy (Fernandez et al., 2001; Kesavadas et al., 2007) and chronic pain (deCharms, 2007; deCharms et al., 2005). More recently, investigators have begun piloting procedures that provide real-time feedback to aid smokers in the modulation of neural functioning in the ACC and medial prefrontal cortex in order to reduce cigarette craving (Hartwell et al., 2013). This work is in extremely early stages and the researchers themselves acknowledge that this is only a first step toward using real-time fMRI feedback as a noninvasive approach to treat nicotine dependence. Much more work is needed in this area.

Taken together, the current study is a first step toward identifying neural mechanisms driving the relationship between stress and smoking dependence severity. Given the dearth of significant findings in the current study, there is clearly a need for researchers to continue developing and testing neural models of stress and substance use, using multi-method approaches to measuring stress and nicotine dependence severity, in order to gain a greater understanding of the role of stress in smoking initiation, maintenance, and relapse. Continued work in this vein could potentially provide additional targets for the development of more effective smoking cessation interventions.

Illustration 1: Integrated model emphasizing the role of corticolimbic dysfunction in compulsive drug seeking, stress responsivity, and self-control (modified from Li & Sinha, 2008).

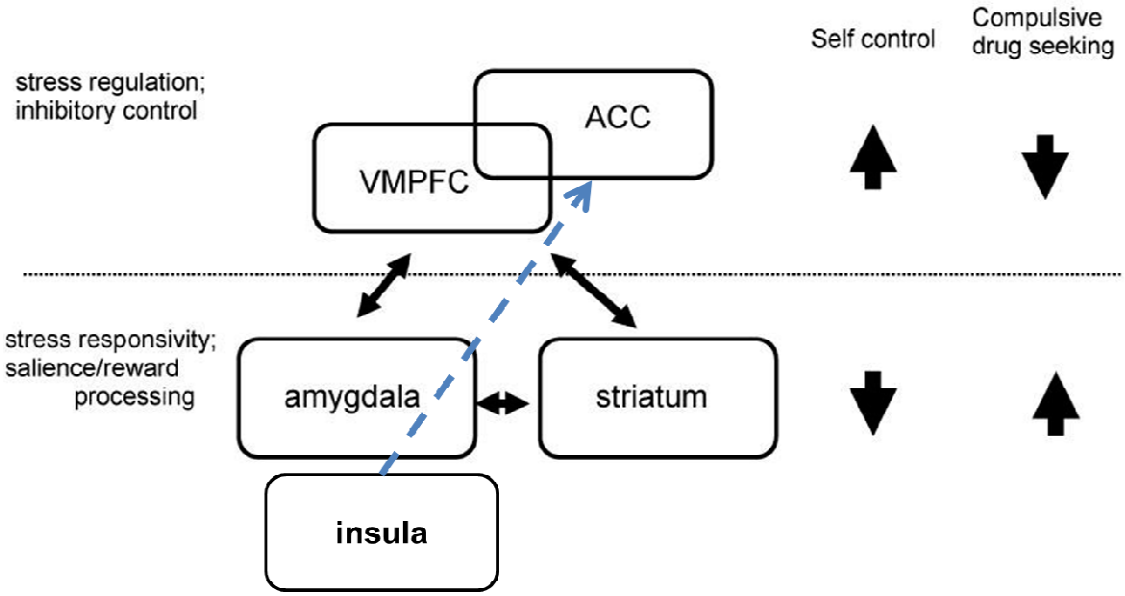

Illustration 2: Flow chart illustrating the selection of participants for final data analyses

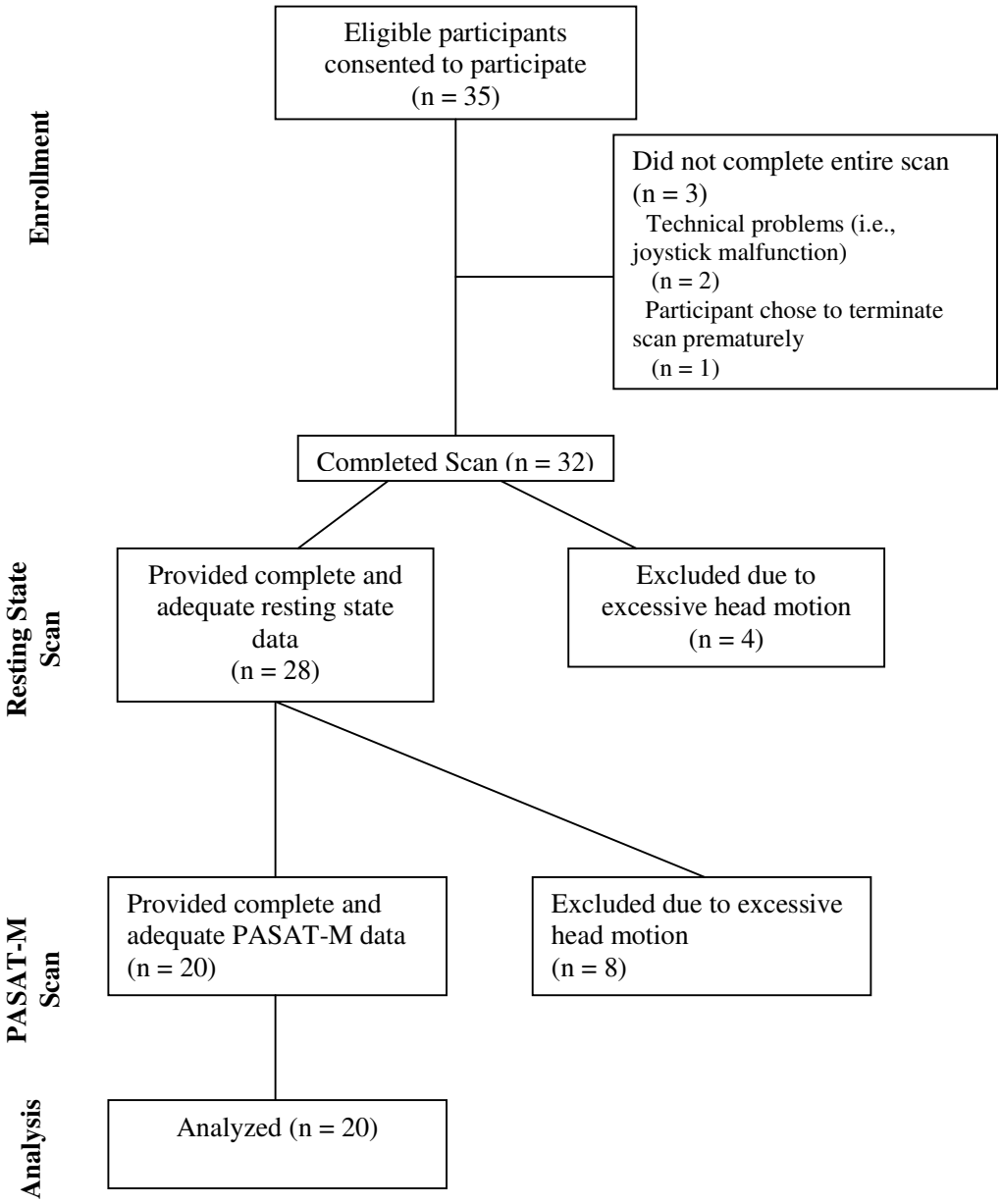

Illustration 3: Testing session Timeline: (A) The top portion of the illustration outlines all procedures that took place over the course of the entire testing session, lasting approximately five hours total. The numbers immediately below the figure reflect the time points that procedures began relative to the start of all scanning procedures. Specifically, participants arrived 1.5 hours before scanning was scheduled to begin. Participants provided informed consent, underwent a brief history and physical exam, and completed task training. About ten minutes prior to the start of the scan, participants were escorted outside to smoke a cigarette. Participants then completed all scan procedures, lasting no more than 2 hours. Finally, participants were administered a packet of self-report questionnaires, were compensated for their time, and escorted to security for release. (B) The bottom portion of the illustration provides a more detailed account of all scan procedures.

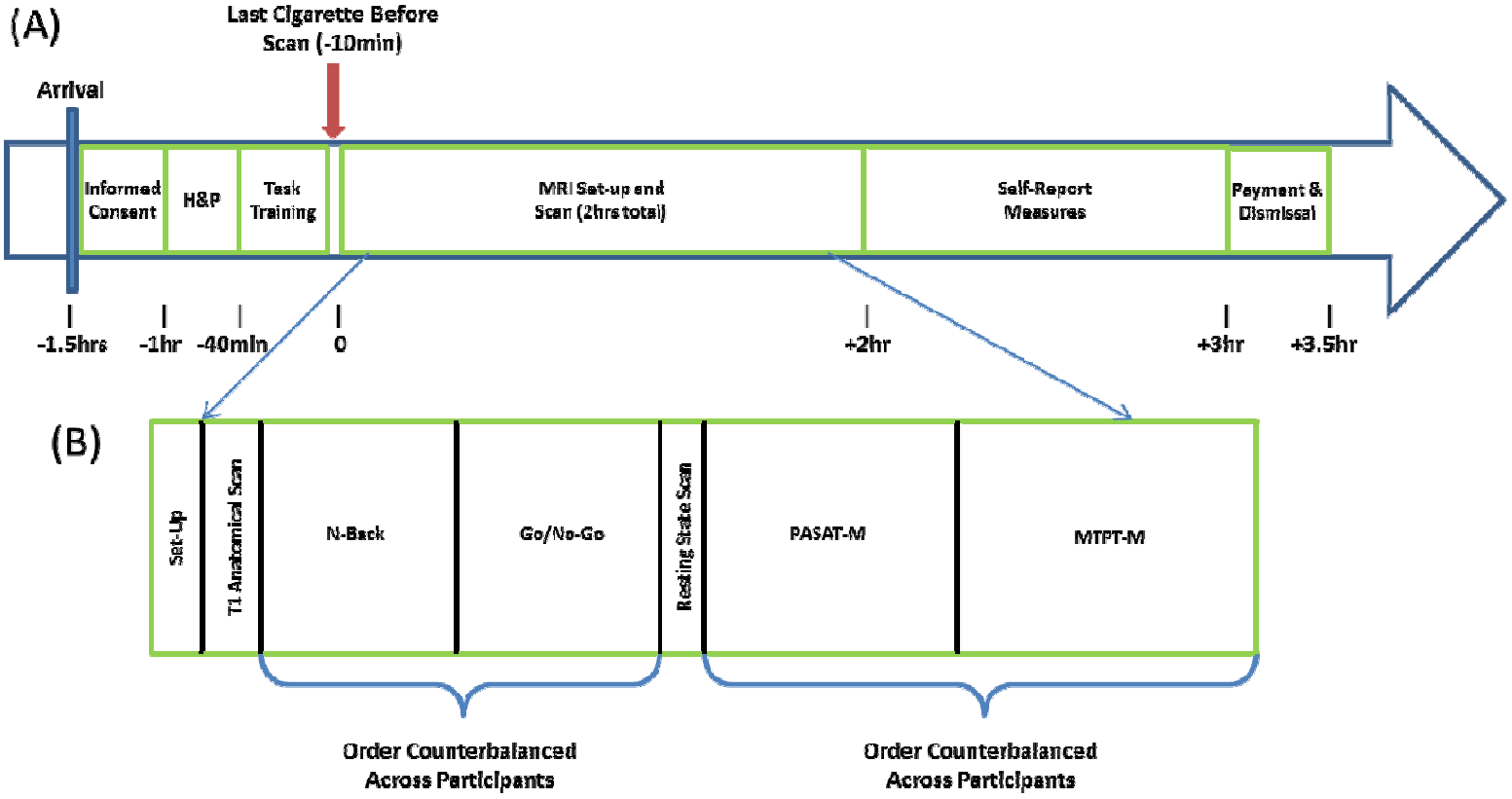

Illustration 4: PASAT-M Timeline

Figure 1. Negative mood ratings over the course of the PASAT-M scan. Error bars reflect standard error of the mean rating value at each time point (i.e., rating post-easy phase and rating post-hard phase). All four negative mood ratings increased significantly (p<.05) from post-easy to post-hard phase.

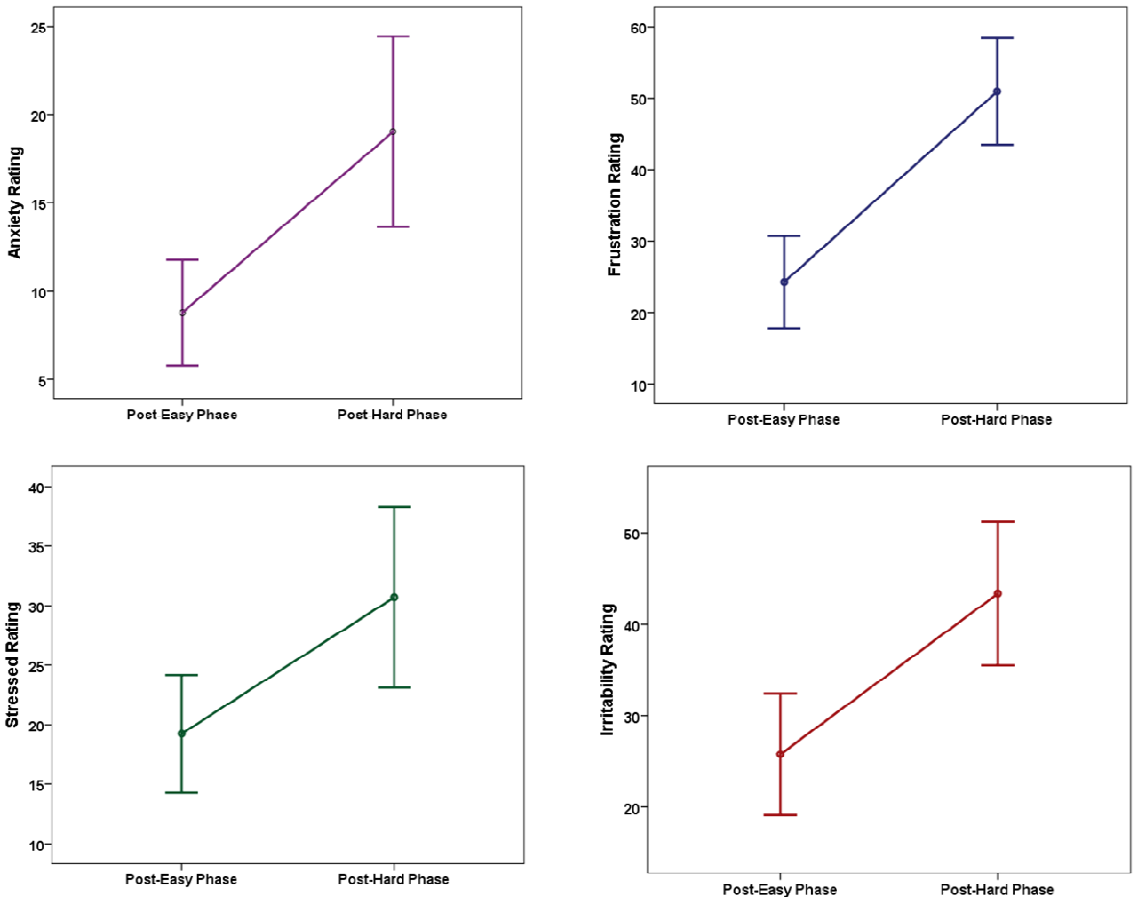

Figure 2. Significant stress-related activation in the posterior portion of the right insula (Brodman Area 13; Talairach coordinates: [57, -33, 18]. Color scale reflects value of T-statistics for the contrast [hard-rest] – [easy-rest] in each voxel of the significant activation cluster.

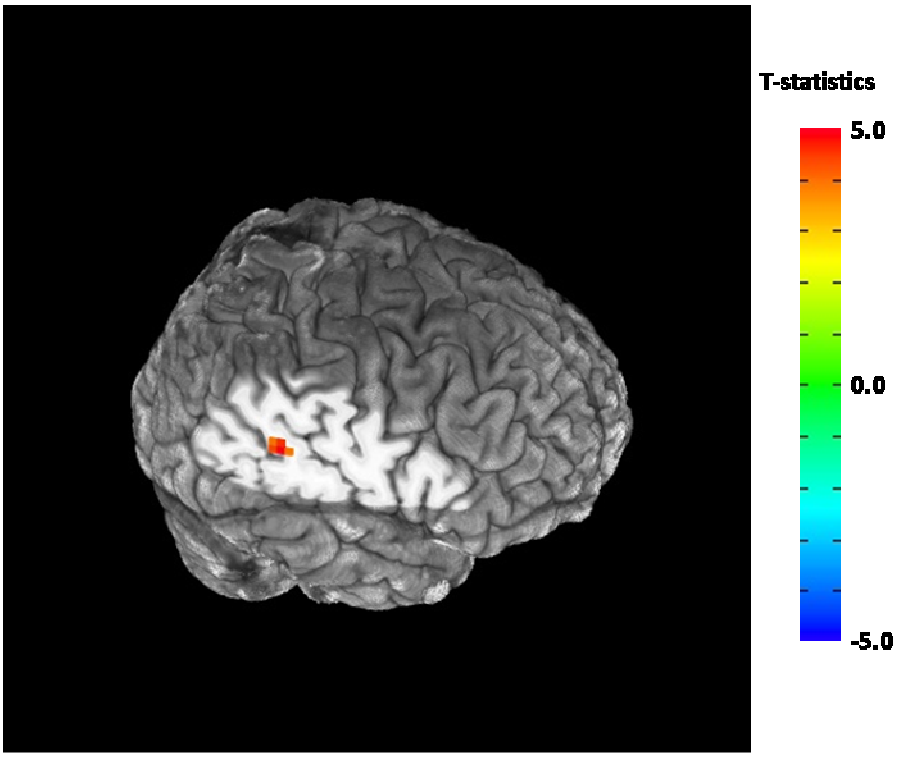

Table 1. Complete list of a priori hypothesized ROIs to which small volume corrections were applied in group level analyses. Regions were defined based on their locations in the Talairach Daemon atlas in AFNI. The total number of voxels (i.e., cluster size) and Talairach coordinates for the center of mass of each ROI are provided below.

Region	Cluster Size	*x*	*y*	*z*
L./R. ACC	485/536	-8/8	32	7
L./R. vmPFC (BA10)	571/578	-24/24	56	6
L./R. Insula	581/556	-39/39	-7	9
L./R. Amygdala	43/47	-23/23	-5	-15
*L./R. Striatum	399/406			
L./ R. Caudate		-11/11	7	9
L./ R. Putamen		-24/24	0	3

*The bilateral ROIs for the striatum are composed of both the bilateral caudate and putamen as defined by the Talairach Daemon atlas in AFNI.

Table 2. Descriptive statistics for smoking variables

Measure	Mean	SD	Min	Max	Skewness
SHQ					
Cigs/day	15.28	4.62	10	25	0.403
# quit attempts	3.60	4.30	0	20	3.13
# quit attempts-log10	0.54	0.32	0	1.32	0.97
Longest quit	244.48	270.70	0	730	0.86
FTND	5.25	1.80	2	8	0.00
Stress-induced craving	6.41	16.58	-10	50.50	1.49
Str-induced craving-log10	1.03	0.50	0	1.79	-.69

Table 3. Correlation matrix of smoking-related variables. Log10 transformed values were used for # quit attempts and stress-induced craving

Smoking Measures	1	2	3	4	5
1. cpd	-	-	-	-	-
2. # quit attempts	-.375	-	-	-	-
3. Longest quit	.20	.04	-	-	-
4. FTND	.41	.10	.06	-	-
5. Stress-induced craving	.14	-.12	.30	-.13	-

Bibliography

Abercrombie, H. C., Schaefer, S. M., Larson, C. L., Oakes, T. R., Lindgren, K. A., Holden, J. E., . . . Davidson, R. J. (1998). Metabolic rate in the right amygdala predicts negative affect in depressed patients. *Neuroreport, 9*(14), 3301-3307.

al'Absi, M., Hatsukami, D., Davis, G. L., & Wittmers, L. E. (2004). Prospective examination of effects of smoking abstinence on cortisol and withdrawal symptoms as predictors of early smoking relapse. *Drug Alcohol Depend, 73*(3), 267-278.

Amstadter, A. B., Nugent, N. R., Koenen, K. C., Ruggiero, K. J., Acierno, R., Galea, S., . . . Gelernter, J. (2009). Association between COMT, PTSD, and increased smoking following hurricane exposure in an epidemiologic sample. *Psychiatry, 72*(4), 360-369. doi: 10.1521/psyc.2009.72.4.360

Amstadter, A. B., Resnick, H. S., Nugent, N. R., Acierno, R., Rheingold, A. A., Minhinnett, R., & Kilpatrick, D. G. (2009). Longitudinal trajectories of cigarette smoking following rape. *J Trauma Stress, 22*(2), 113-121. doi: 10.1002/jts.20398

Baker, T. B., Japuntich, S. J., Hogle, J. M., McCarthy, D. E., & Curtin, J. J. (2006). Pharmacologic and behavioral withdrawal from addictive drugs. *Current Directions in Psychological Science, 15*(5), 232-236.

Baker, T. B., Piper, M. E., McCarthy, D. E., Majeskie, M. R., & Fiore, M. C. (2004). Addiction motivation reformulated: an affective processing model of negative reinforcement. *Psychol Rev, 111*(1), 33-51. doi: 10.1037/0033-295X.111.1.33 2004-10332-002 [pii]

Baldwin, H. A., Rassnick, S., Rivier, J., Koob, G. F., & Britton, K. T. (1991). CRF antagonist reverses the "anxiogenic" response to ethanol withdrawal in the rat. *Psychopharmacology (Berl), 103*(2), 227-232.

Bandettini, P. (2007). Functional MRI today. *Int J Psychophysiol, 63*(2), 138-145. doi: 10.1016/j.ijpsycho.2006.03.016

Bandettini, P. A., Jesmanowicz, A., Wong, E. C., & Hyde, J. S. (1993). Processing strategies for time-course data sets in functional MRI of the human brain. *Magn Reson Med, 30*(2), 161-173.

Beauregard, M., Levesque, J., & Bourgouin, P. (2001). Neural correlates of conscious self-regulation of emotion. *J Neurosci, 21*(18), RC165. doi: 20015619 [pii]

Becerra, L., Breiter, H. C., Wise, R., Gonzalez, R. G., & Borsook, D. (2001). Reward circuitry activation by noxious thermal stimuli. *Neuron, 32*(5), 927-946. doi: S0896-6273(01)00533-5 [pii]

Bechara, A. (2001). Neurobiology of decision-making: risk and reward. *Semin Clin Neuropsychiatry, 6*(3), 205-216. doi: S1084361201000247 [pii]

Bechara, A. (2005). Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nat Neurosci, 8*(11), 1458-1463. doi: nn1584 [pii] 10.1038/nn1584

Bechara, A., & Martin, E. M. (2004). Impaired decision making related to working memory deficits in individuals with substance addictions. *Neuropsychology, 18*(1), 152-162. doi: 10.1037/0894-4105.18.1.152 2004-10255-016 [pii]

Bechara, A., Tranel, D., & Damasio, H. (2000). Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain, 123 (Pt 11)*, 2189-2202.

Berntson, G. G., Cacioppo, J. T., & Quigley, K. S. (1993). Cardiac psychophysiology and autonomic space in humans: empirical perspectives and conceptual implications. *Psychol Bull, 114*(2), 296-322.

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med, 34*(4), 537-541.

Black, D. W., Zimmerman, M., & Coryell, W. H. (1999). Cigarette smoking and psychiatric disorder in a community sample. *Ann Clin Psychiatry, 11*(3), 129-136.

Bland, J. M., & Altman, D. G. (1995). Multiple significance tests: the Bonferroni method. *BMJ, 310*(6973), 170.

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychol Rev, 108*(3), 624-652.

Brandon, T. H., Herzog, T. A., Juliano, L. M., Irvin, J. E., Lazev, A. B., & Simmons, V. N. (2003). Pretreatment task persistence predicts smoking cessation outcome. *J Abnorm Psychol, 112*(3), 448-456.

Brandon, T. H., Tiffany, S. T., Obremski, K. M., & Baker, T. B. (1990). Postcessation cigarette use: the process of relapse. *Addict Behav, 15*(2), 105-114. doi: 0306-4603(90)90013-N [pii]

Brewer, J. A., Mallik, S., Babuscio, T. A., Nich, C., Johnson, H. E., Deleone, C. M., . . . Rounsaville, B. J. (2011). Mindfulness training for smoking cessation: Results from a randomized controlled trial. *Drug Alcohol Depend*. doi: S0376-8716(11)00253-5 [pii] 10.1016/j.drugalcdep.2011.05.027

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]

Brown, J. W., & Braver, T. S. (2005). Learned predictions of error likelihood in the anterior cingulate cortex. *Science, 307*(5712), 1118-1121. doi: 307/5712/1118 [pii] 10.1126/science.1105783

Brown, R. A., Lejuez, C. W., Kahler, C. W., Strong, D. R., & Zvolensky, M. J. (2005). Distress tolerance and early smoking lapse. *Clin Psychol Rev, 25*(6), 713-733. doi: S0272-7358(05)00055-3 [pii] 10.1016/j.cpr.2005.05.003

Brown, R. A., Palm, K. M., Strong, D. R., Lejuez, C. W., Kahler, C. W., Zvolensky, M. J., . . . Gifford, E. V. (2008). Distress tolerance treatment for early-lapse smokers: rationale, program description, and preliminary findings. *Behav Modif, 32*(3), 302-332. doi: 32/3/302 [pii] 10.1177/0145445507309024

Buczek, Y., Le, A. D., Wang, A., Stewart, J., & Shaham, Y. (1999). Stress reinstates nicotine seeking but not sucrose solution seeking in rats. *Psychopharmacology (Berl), 144*(2), 183-188.

Caria, A., Veit, R., Sitaram, R., Lotze, M., Weiskopf, N., Grodd, W., & Birbaumer, N. (2007). Regulation of anterior insular cortex activity using real-time fMRI. *NeuroImage, 35*(3), 1238-1246. doi: S1053-8119(07)00038-9 [pii] 10.1016/j.neuroimage.2007.01.018

CDC. (2005). Annual smoking-attributable mortality, years of potential life lost, and productivity losses, United States, 1997-2001. *MMWR Morbidity and Mortality Weekly Report, 54*, 625-628.

Cherek, D. R. (1985). Effects of acute exposure to increased levels of background industrial noise on cigarette smoking behavior. *Int Arch Occup Environ Health, 56*(1), 23-30.

Ciraulo, D. A., Piechniczek-Buczek, J., & Iscan, E. N. (2003). Outcome predictors in substance use disorders. *Psychiatr Clin North Am, 26*(2), 381-409.

Clark, P. I., Gautam, S., & Gerson, L. W. (1996). Effect of menthol cigarettes on biochemical markers of smoke exposure among black and white smokers. *Chest, 110*(5), 1194-1198.

Cohen, S., & Lichtenstein, E. (1990). Perceived stress, quitting smoking, and smoking relapse. *Health Psychol, 9*(4), 466-478.

Conger, J. J. (1956). Alcoholism: theory, problem and challenge. II. Reinforcement theory and the dynamics of alcoholism. *Q J Stud Alcohol, 17*(2), 296-305.

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res, 29*(3), 162-173. doi: S0010480996900142 [pii]

Craig, A. D. (2009). How do you feel--now? The anterior insula and human awareness. *Nat Rev Neurosci, 10*(1), 59-70. doi: nrn2555 [pii] 10.1038/nrn2555

Critchley, H. D., Melmed, R. N., Featherstone, E., Mathias, C. J., & Dolan, R. J. (2001). Brain activity during biofeedback relaxation: a functional neuroimaging investigation. *Brain, 124*(Pt 5), 1003-1012.

Critchley, H. D., Wiens, S., Rotshtein, P., Ohman, A., & Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nat Neurosci, 7*(2), 189-195. doi: 10.1038/nn1176 nn1176 [pii]

Crits-Christoph, P., Gibbons, M. B. C., Barber, J. P., Hu, B., Hearon, B., Worley, M., & Gallop, R. (2007). Predictors of sustained abstinence during psychosocial treatments for cocaine dependence. *Psychotherapy Research, 17*(2), 240-252.

Dagher, A., Tannenbaum, B., Hayashi, T., Pruessner, J. C., & McBride, D. (2009). An acute psychosocial stress enhances the neural response to smoking cues. *Brain Res, 1293*, 40-48. doi: S0006-8993(09)01433-4 [pii] 10.1016/j.brainres.2009.07.048

Damasio, A. R. (1994). *Descartes' error: Emotion, reason, and the human brain.* New York, NY: Avon Books.

David, S. P., Sweet, L. H., Cohen, R. A., MacKillop, J., Mulligan, R. C., & Niaura, R. (2011). Application of functional neuroimaging to examination of nicotine dependence. In R. A. Cohen & L. H. Sweet (Eds.), *Brain imaging in behavioral medicine and clinical neuroscience*. New York: Springer.

deCharms, R. C. (2007). Reading and controlling human brain activation using real-time functional magnetic resonance imaging. *Trends Cogn Sci, 11*(11), 473-481. doi: S1364-6613(07)00247-1 [pii]10.1016/j.tics.2007.08.014

deCharms, R. C., Christoff, K., Glover, G. H., Pauly, J. M., Whitfield, S., & Gabrieli, J. D. (2004). Learned regulation of spatially localized brain activation using real-time fMRI. *NeuroImage, 21*(1), 436-443. doi: S1053811903005500 [pii]

deCharms, R. C., Maeda, F., Glover, G. H., Ludlow, D., Pauly, J. M., Soneji, D., . . . Mackey, S. C. (2005). Control over brain activation and pain learned by using real-time functional MRI. *Proc Natl Acad Sci U S A, 102*(51), 18626-18631. doi: 0505210102 [pii]10.1073/pnas.0505210102

Dedovic, K., Renwick, R., Mahani, N. K., Engert, V., Lupien, S. J., & Pruessner, J. C. (2005). The Montreal Imaging Stress Task: using functional imaging to

investigate the effects of perceiving and processing psychosocial stress in the human brain. *J Psychiatry Neurosci, 30*(5), 319-325.

Dehaene, S., Posner, M. I., & Tucker, D. M. (1994). Localization of a neural system for error detection and compensation. *Psychological Science, 5*, 303-305.

Deichmann, R., Gottfried, J. A., Hutton, C., & Turner, R. (2003). Optimized EPI for fMRI studies of the orbitofrontal cortex. *NeuroImage, 19*(2 Pt 1), 430-441. doi: S1053811903000739 [pii]

Devinsky, O., Morrell, M. J., & Vogt, B. A. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain, 118 (Pt 1)*, 279-306.

Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychol Bull, 130*(3), 355-391. doi: 10.1037/0033-2909.130.3.355

Doherty, K., Kinnunen, T., Militello, F. S., & Garvey, A. J. (1995). Urges to smoke during the first month of abstinence: relationship to relapse and predictors. *Psychopharmacology (Berl), 119*(2), 171-178.

ElGeili, E. S., & Bashir, T. (2005). Precipitants of relapse among heroin addicts. *Addictive Disorders & Their Treatment, 4*(1), 29-38.

Elliott, R., & Dolan, R. J. (1998). Activation of different anterior cingulate foci in association with hypothesis testing and response selection. *NeuroImage, 8*(1), 17-29. doi: S1053-8119(98)90344-5 [pii]10.1006/nimg.1998.0344

Everitt, B. J., & Robbins, T. W. (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci, 8*(11), 1481-1489. doi: nn1579 [pii]10.1038/nn1579

Falba, T., Teng, H. M., Sindelar, J. L., & Gallo, W. T. (2005). The effect of involuntary job loss on smoking intensity and relapse. *Addiction, 100*(9), 1330-1339.

Fernandez, G., de Greiff, A., von Oertzen, J., Reuber, M., Lun, S., Klaver, P., . . . Elger, C. E. (2001). Language mapping in less than 15 minutes: real-time functional MRI during routine clinical investigation. *NeuroImage, 14*(3), 585-594. doi: 10.1006/nimg.2001.0854S1053-8119(01)90854-7 [pii]

Fidler, J. A., & West, R. (2009). Self-perceived smoking motives and their correlates in a general population sample. *Nicotine Tob Res, 11*(10), 1182-1188. doi: 10.1093/ntr/ntp120

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1995). *Structured Clinical Interview for DSM-IV Axis I Disorders*. New York: New York State Psychiatric Institute.

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., & Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn Reson Med, 33*(5), 636-647.

Forster, B. B., MacKay, A. L., Whittall, K. P., Kiehl, K. A., Smith, A. M., Hare, R. D., & Liddle, P. F. (1998). Functional magnetic resonance imaging: the basics of blood-oxygen-level dependent (BOLD) imaging. *Can Assoc Radiol J, 49*(5), 320-329.

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. *NeuroImage, 2*(1), 45-53. doi: S1053-8119(85)71007-5 [pii]10.1006/nimg.1995.1007

Garavan, H., Ross, T. J., Murphy, K., Roche, R. A., & Stein, E. A. (2002). Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. *NeuroImage, 17*(4), 1820-1829.

Geng, X. (2007). *Transitive inverse-consistent image of registration and evaluation*. Department of electrical and computer engineering, The University of Iowa.

George, O., Ghozland, S., Azar, M. R., Cottone, P., Zorrilla, E. P., Parsons, L. H., . . . Koob, G. F. (2007). CRF-CRF1 system activation mediates withdrawal-induced increases in nicotine self-administration in nicotine-dependent rats. *Proc Natl Acad Sci U S A, 104*(43), 17198-17203. doi: 0707585104 [pii]10.1073/pnas.0707585104

Goldstein, R. Z., & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry, 159*(10), 1642-1652.

Grant, B. F., Hasin, D. S., Chou, S. P., Stinson, F. S., & Dawson, D. A. (2004). Nicotine dependence and psychiatric disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry, 61*(11), 1107-1115. doi: 10.1001/archpsyc.61.11.1107

Gratz, K. L., & Roemer, L. (2004). Multidimensional assessment of emotion regulation and dysregulation: Development, factor structure, and initial validation of the difficulties in emotion regulation scale. *Journal of Psychopathology and Behavioral Assessment, 26*, 41-54.

Gu, H., Salmeron, B. J., Ross, T. J., Geng, X., Zhan, W., Stein, E. A., & Yang, Y. (2010). Mesocorticolimbic circuits are impaired in chronic cocaine users as demonstrated by resting-state functional connectivity. *NeuroImage, 53*(2), 593-601. doi: 10.1016/j.neuroimage.2010.06.066

Hagemann, D., Waldstein, S. R., & Thayer, J. F. (2003). Central and autonomic nervous system integration in emotion. *Brain Cogn, 52*(1), 79-87. doi: S0278262603000113 [pii]

Hariri, A. R., Mattay, V. S., Tessitore, A., Fera, F., & Weinberger, D. R. (2003). Neocortical modulation of the amygdala response to fearful stimuli. *Biol Psychiatry, 53*(6), 494-501. doi: S0006322302017869 [pii]

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.

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. *British Journal of Addiction, 86*, 1119-1127.

Heishman, S. J. (1999). Behavioral and cognitive effects of smoking: relationship to nicotine addiction. *Nicotine Tob Res, 1 Suppl 2*, S143-147; discussion S165-146.

Hester, R., & Garavan, H. (2004). Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. *J Neurosci, 24*(49), 11017-11022. doi: 24/49/11017 [pii]10.1523/JNEUROSCI.3321-04.2004

Hong, L. E., Gu, H., Yang, Y., Ross, T. J., Salmeron, B. J., Buchholz, B., . . . Stein, E. A. (2009). Association of nicotine addiction and nicotine's actions with separate cingulate cortex functional circuits. *Arch Gen Psychiatry, 66*(4), 431-441. doi: 66/4/431 [pii]10.1001/archgenpsychiatry.2009.2

Huettel, S. A., Song, A. W., & McCarthy, G. (2009). *Functional Magnetic Resonance Imaging, Second Edition*. Sunderland, Massachusetts U.S.A.: Sinauer Associates, Inc.

Hymowitz, N., Sexton, M., Ockene, J., & Grandits, G. (1991). Baseline factors associated with smoking cessation and relapse. MRFIT Research Group. *Prev Med, 20*(5), 590-601.

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

Jensen, J., McIntosh, A. R., Crawley, A. P., Mikulis, D. J., Remington, G., & Kapur, S. (2003). Direct activation of the ventral striatum in anticipation of aversive stimuli. *Neuron, 40*(6), 1251-1257. doi: S0896627303007244 [pii]

Kaufman, J. N., Ross, T. J., Stein, E. A., & Garavan, H. (2003). Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. *J Neurosci, 23*(21), 7839-7843. doi: 23/21/7839 [pii]

Kendler, K. S., Neale, M. C., Sullivan, P., Corey, L. A., Gardner, C. O., & Prescott, C. A. (1999). A population-based twin study in women of smoking initiation and nicotine dependence. *Psychol Med, 29*(2), 299-308.

Kenford, S. L., Smith, S. S., Wetter, D. W., Jorenby, D. E., Fiore, M. C., & Baker, T. B. (2002). Predicting relapse back to smoking: contrasting affective and physical models of dependence. *J Consult Clin Psychol, 70*(1), 216-227.

Kesavadas, C., Thomas, B., Sujesh, S., Ashalata, R., Abraham, M., Gupta, A. K., & Radhakrishnan, K. (2007). Real-time functional MR imaging (fMRI) for presurgical evaluation of paediatric epilepsy. *Pediatr Radiol, 37*(10), 964-974. doi: 10.1007/s00247-007-0556-4

Khantzian, E. J. (1985). The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *Am J Psychiatry, 142*(11), 1259-1264.

Kim, M. J., Loucks, R. A., Palmer, A. L., Brown, A. C., Solomon, K. M., Marchante, A. N., & Whalen, P. J. (2011). The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. *Behav Brain Res, 223*(2), 403-410. doi: 10.1016/j.bbr.2011.04.025

Kober, H., Mende-Siedlecki, P., Kross, E. F., Weber, J., Mischel, W., Hart, C. L., & Ochsner, K. N. (2010). Prefrontal-striatal pathway underlies cognitive regulation of craving. *Proc Natl Acad Sci U S A, 107*(33), 14811-14816. doi: 1007779107 [pii]10.1073/pnas.1007779107

Koob, G. F., Buck, C. L., Cohen, A., Edwards, S., Park, P. E., Schlosburg, J. E., . . . George, O. (2014). Addiction as a stress surfeit disorder. *Neuropharmacology, 76 Pt B*, 370-382. doi: 10.1016/j.neuropharm.2013.05.024

Koob, G. F., & Heinrichs, S. C. (1999). A role for corticotropin releasing factor and urocortin in behavioral responses to stressors. *Brain Res, 848*(1-2), 141-152. doi: S0006-8993(99)01991-5 [pii]

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. (2008). Addiction and the brain antireward system. *Annu Rev Psychol, 59*, 29-53. doi: 10.1146/annurev.psych.59.103006.093548

Lader, D. (2007). *Smoking-related Behaviour and Attitudes, 2007*. London.

Lane, R. D., Reiman, E. M., Axelrod, B., Yun, L. S., Holmes, A., & Schwartz, G. E. (1998). Neural correlates of levels of emotional awareness. Evidence of an

interaction between emotion and attention in the anterior cingulate cortex. *J Cogn Neurosci, 10*(4), 525-535.

Leao, R. M., Cruz, F. C., & Planeta, C. S. (2009). Exposure to acute restraint stress reinstates nicotine-induced place preference in rats. *Behav Pharmacol, 20*(1), 109-113. doi: 10.1097/FBP.0b013e3283242f41

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

Lejuez, C. W., Kahler, C. W., & Brown, R. A. (2003). A modified computer version of the Paced Auditory Serial Addition Task (PASAT) as a laboratory-based stressor. *The Behavior Therapist, 26*(4), 290-293.

Leventhal, H., & Cleary, P. D. (1980). The smoking problem: a review of the research and theory in behavioral risk modification. *Psychol Bull, 88*(2), 370-405.

Li, C. S., Huang, C., Yan, P., Bhagwagar, Z., Milivojevic, V., & Sinha, R. (2008). Neural correlates of impulse control during stop signal inhibition in cocaine-dependent men. *Neuropsychopharmacology, 33*(8), 1798-1806. doi: 1301568 [pii]10.1038/sj.npp.1301568

Li, C. S., & Sinha, R. (2008). Inhibitory control and emotional stress regulation: neuroimaging evidence for frontal-limbic dysfunction in psycho-stimulant addiction. *Neurosci Biobehav Rev, 32*(3), 581-597. doi: S0149-7634(07)00137-6 [pii]10.1016/j.neubiorev.2007.10.003

Litman, G. K., Stapleton, J., Oppenheim, A. N., & Peleg, M. (1983). An instrument for measuring coping behaviours in hospitalized alcoholics: implications for relapse prevention treatment. *Br J Addict, 78*(3), 269-276.

Litt, M. D., Cooney, N. L., & Morse, P. (2000). Reactivity to alcohol-related stimuli in the laboratory and in the field: predictors of craving in treated alcoholics. *Addiction, 95*(6), 889-900.

Lowe, M. J., Mock, B. J., & Sorenson, J. A. (1998). Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. *NeuroImage, 7*(2), 119-132. doi: S1053-8119(97)90315-3 [pii]10.1006/nimg.1997.0315

Luo, Z., Alvarado, G. F., Hatsukami, D. K., Johnson, E. O., Bierut, L. J., & Breslau, N. (2008). Race differences in nicotine dependence in the Collaborative Genetic study of Nicotine Dependence (COGEND). *Nicotine Tob Res, 10*(7), 1223-1230. doi: 794985769 [pii]10.1080/14622200802163266

Magno, E., Foxe, J. J., Molholm, S., Robertson, I. H., & Garavan, H. (2006). The anterior cingulate and error avoidance. *J Neurosci, 26*(18), 4769-4773. doi: 26/18/4769 [pii]10.1523/JNEUROSCI.0369-06.2006

Marlatt, G. A., & Gordon, J. R. (Eds.). (1985). *Relapse prevention: Maintenance strategies in the treatment of addictive behaviors*. New York: Guilford Press.

Matheny, K. B., & Weatherman, K. E. (1998). Predictors of smoking cessation and maintenance. *J Clin Psychol, 54*(2), 223-235.

McCarthy, D. E., Piasecki, T. M., Fiore, M. C., & Baker, T. B. (2006). Life before and after quitting smoking: an electronic diary study. *J Abnorm Psychol, 115*(3), 454-466. doi: 2006-09167-007 [pii]10.1037/0021-843X.115.3.454

McCullough, L. D., & Salamone, J. D. (1992). Anxiogenic drugs beta-CCE and FG 7142 increase extracellular dopamine levels in nucleus accumbens. *Psychopharmacology (Berl), 109*(3), 379-382.

McEwen, A., West, R., & McRobbie, H. (2008). Motives for smoking and their correlates in clients attending Stop Smoking treatment services. *Nicotine Tob Res, 10*(5), 843-850.

Min, Y. K., Chung, S. C., & Min, B. C. (2005). Physiological evaluation on emotional change induced by imagination. *Appl Psychophysiol Biofeedback, 30*(2), 137-150.

Montague, P. R., & Berns, G. S. (2002). Neural economics and the biological substrates of valuation. *Neuron, 36*(2), 265-284. doi: S0896627302009741 [pii]

Motzin, J. C., Philippi, C. L., Wolf, R. C., Baskaya, M. K., & Koenigs, M. (2014). Ventromedial prefrontal cortex is critical for the regulation of amygdala activity in humans. *Biological Psychiatry*. doi: http://dx.doi.org/10.1016/j.biopsych.2014.02.014

Muehlhan, M., Lueken, U., Wittchen, H. U., & Kirschbaum, C. (2011). The scanner as a stressor: evidence from subjective and neuroendocrine stress parameters in the time course of a functional magnetic resonance imaging session. *Int J Psychophysiol, 79*(2), 118-126. doi: 10.1016/j.ijpsycho.2010.09.009

Mulvaney, F. D., Alterman, A. I., Boardman, C. R., & Kampman, K. (1999). Cocaine abstinence symptomatology and treatment attrition. *J Subst Abuse Treat, 16*(2), 129-135. doi: S0740-5472(98)00017-8 [pii]

Myers-Schulz, B., & Koenigs, M. (2012). Functional anatomy of ventromedial prefrontal cortex: implications for mood and anxiety disorders. *Mol Psychiatry, 17*(2), 132-141. doi: 10.1038/mp.2011.88

Nandi, A., Galea, S., Ahern, J., & Vlahov, D. (2005). Probable cigarette dependence, PTSD, and depression after an urban disaster: results from a population survey of New York City residents 4 months after September 11, 2001. *Psychiatry, 68*(4), 299-310.

Naqvi, N. H., & Bechara, A. (2009). The hidden island of addiction: the insula. *Trends Neurosci, 32*(1), 56-67. doi: S0166-2236(08)00246-4 [pii]10.1016/j.tins.2008.09.009

Naqvi, N. H., & Bechara, A. (2010). The insula and drug addiction: an interoceptive view of pleasure, urges, and decision-making. *Brain Struct Funct, 214*(5-6), 435-450. doi: 10.1007/s00429-010-0268-7

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

Nichter, M., Nichter, M., Vuckovic, N., Quintero, G., & Ritenbaugh, C. (1997). Smoking experimentation and initiation among adolescent girls: qualitative and quantitative findings. *Tob Control, 6*(4), 285-295.

O'Connell, K., Schwartz, J., Gerkovich, M., Bott, M., & Shiffman, S. (2004). Playful and rebellious states vs. negative affect in explaining the occurrence of temptations and lapses during smoking cessation. *Nicotine Tob Res, 6*(4), 661-674. doi: 10.1080/14622200410001734049VPHN211KANCF3RCW [pii]

Ochsner, K. N., & Gross, J. J. (2008). Cognitive emotion regulation: Insights from social cognitive and affective neuroscience. *Current Directions in Psychological Science, 17*(2), 153-158.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.

Oswald, L. M., Zandi, P., Nestadt, G., Potash, J. B., Kalaydjian, A. E., & Wand, G. S. (2006). Relationship between cortisol responses to stress and personality. *Neuropsychopharmacology, 31*(7), 1583-1591. doi: 1301012 [pii]10.1038/sj.npp.1301012

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp, 25*(1), 46-59. doi: 10.1002/hbm.20131

Paliwal, P., Hyman, S. M., & Sinha, R. (2008). Craving predicts time to cocaine relapse: further validation of the Now and Brief versions of the cocaine craving questionnaire. *Drug Alcohol Depend, 93*(3), 252-259. doi: S0376-8716(07)00405-X [pii]10.1016/j.drugalcdep.2007.10.002

Parrott, A. C. (1995). Smoking cessation leads to reduced stress, but why? *Int J Addict, 30*(11), 1509-1516.

Patterson, F., Benowitz, N., Shields, P., Kaufmann, V., Jepson, C., Wileyto, P., . . . Lerman, C. (2003). Individual differences in nicotine intake per cigarette. *Cancer Epidemiol Biomarkers Prev, 12*(5), 468-471.

Perkins, K. A., & Grobe, J. E. (1992). Increased desire to smoke during acute stress. *Br J Addict, 87*(7), 1037-1040.

Phan, K. L., Fitzgerald, D. A., Gao, K., Moore, G. J., Tancer, M. E., & Posse, S. (2004). Real-time fMRI of cortico-limbic brain activity during emotional processing. *Neuroreport, 15*(3), 527-532. doi: 00001756-200403010-00029 [pii]

Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *NeuroImage, 16*(2), 331-348. doi: 10.1006/nimg.2002.1087

Piazza, P. V., Deminiere, J. M., Le Moal, M., & Simon, H. (1989). Factors that predict individual vulnerability to amphetamine self-administration. *Science, 245*(4925), 1511-1513.

Piazza, P. V., & Le Moal, M. (1998). The role of stress in drug self-administration. *Trends Pharmacol Sci, 19*(2), 67-74. doi: S0165-6147(97)01115-2 [pii]

Piazza, P. V., & Le Moal, M. L. (1996). Pathophysiological basis of vulnerability to drug abuse: role of an interaction between stress, glucocorticoids, and dopaminergic neurons. *Annu Rev Pharmacol Toxicol, 36*, 359-378.

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). *J Consult Clin Psychol, 72*(2), 139-154. doi: 10.1037/0022-006X.72.2.1392004-12113-001 [pii]

Posner, M. I., & DiGirolamo, G. J. (1998). Executive attention: Conflict, target detection, and cognitive control. In R. Parasuraman (Ed.), *The attentive brain* (pp. 401-423). Cambridge, MA: MIT Press.

Posse, S., Fitzgerald, D., Gao, K., Habel, U., Rosenberg, D., Moore, G. J., & Schneider, F. (2003). Real-time fMRI of temporolimbic regions detects amygdala activation during single-trial self-induced sadness. *NeuroImage, 18*(3), 760-768. doi: S1053811903000041 [pii]

Pruessner, J. C., Champagne, F., Meaney, M. J., & Dagher, A. (2004). Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using [11C]raclopride. *J Neurosci, 24*(11), 2825-2831. doi: 10.1523/JNEUROSCI.3422-03.200424/11/2825 [pii]

Pruessner, J. C., Dedovic, K., Khalili-Mahani, N., Engert, V., Pruessner, M., Buss, C., . . . Lupien, S. (2008). Deactivation of the limbic system during acute psychosocial stress: evidence from positron emission tomography and functional magnetic resonance imaging studies. *Biol Psychiatry, 63*(2), 234-240. doi: S0006-3223(07)00435-0 [pii]10.1016/j.biopsych.2007.04.041

Rabbitt, P. M. (1966). Errors and error correction in choice-response tasks. *Journal of Experimental Psychology, 71*, 264-272.

Rauch, S. L., Whalen, P. J., Shin, L. M., McInerney, S. C., Macklin, M. L., Lasko, N. B., . . . Pitman, R. K. (2000). Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biol Psychiatry, 47*(9), 769-776. doi: S0006-3223(00)00828-3 [pii]

Reijneveld, S. A., Crone, M. R., Verhulst, F. C., & Verloove-Vanhorick, S. P. (2003). The effect of a severe disaster on the mental health of adolescents: a controlled study. *Lancet, 362*(9385), 691-696. doi: 10.1016/S0140-6736(03)14231-6

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. (2001). Incentive-sensitization and addiction. *Addiction, 96*(1), 103-114. doi: 10.1080/09652140020016996

Rose, J. E., Ananda, S., & Jarvik, M. E. (1983). Cigarette smoking during anxiety-provoking and monotonous tasks. *Addict Behav, 8*(4), 353-359.

Russell, J. A., & Mehrabian, A. (1975). The mediating role of emotions in alchol use. *Journal of Studies on Alcohol, 36*, 1508-1536.

Schiller, J. S., Lucas, J. W., Ward, B. W., & Peregoy, J. A. (2012). Summary health statistics for U.S. adults: National Health Interview Survey, 2010. *Vital Health Stat 10*(252), 1-207.

Schultz, W. (2013). Updating dopamine reward signals. *Curr Opin Neurobiol, 23*(2), 229-238. doi: 10.1016/j.conb.2012.11.012

Schutz, C. G. (2008). Using neuroimaging to predict relapse to smoking: role of possible moderators and mediators. *Int J Methods Psychiatr Res, 17 Suppl 1*, S78-82. doi: 10.1002/mpr.247

Shadel, W. G., Shiffman, S., Niaura, R., Nichter, M., & Abrams, D. B. (2000). Current models of nicotine dependence: what is known and what is needed to advance understanding of tobacco etiology among youth. *Drug Alcohol Depend, 59 Suppl 1*, S9-22. doi: S0376871699001623 [pii]

Sher, K. J., & Levenson, R. W. (1982). Risk for alcoholism and individual differences in the stress-response-dampening effect of alcohol. *J Abnorm Psychol, 91*(5), 350-367.

Shiffman, S. (1982). Relapse following smoking cessation: a situational analysis. *J Consult Clin Psychol, 50*(1), 71-86.

Shiffman, S., Gwaltney, C. J., Balabanis, M. H., Liu, K. S., Paty, J. A., Kassel, J. D., . . . Gnys, M. (2002). Immediate antecedents of cigarette smoking: an analysis from ecological momentary assessment. *J Abnorm Psychol, 111*(4), 531-545.

Shiffman, S., Hickcox, M., Paty, J. A., Gnys, M., Kassel, J. D., & Richards, T. J. (1996). Progression from a smoking lapse to relapse: prediction from abstinence violation effects, nicotine dependence, and lapse characteristics. *J Consult Clin Psychol, 64*(5), 993-1002.

Shiffman, S., Hickcox, M., Paty, J. A., Gnys, M., Richards, T., & Kassel, J. D. (1997). Individual differences in the context of smoking lapse episodes. *Addict Behav, 22*(6), 797-811. doi: S0306-4603(97)00063-4 [pii]

Shiffman, S., Paty, J. A., Gnys, M., Kassel, J. A., & Hickcox, M. (1996). First lapses to smoking: within-subjects analysis of real-time reports. *J Consult Clin Psychol, 64*(2), 366-379.

Shiffman, S., Waters, A., & Hickcox, M. (2004). The nicotine dependence syndrome scale: a multidimensional measure of nicotine dependence. *Nicotine Tob Res, 6*(2), 327-348. doi: 10.1080/14622200420002024 81VBH32VQ8399VPHFL [pii]

Shiffman, S., & Waters, A. J. (2004). Negative affect and smoking lapses: a prospective analysis. *J Consult Clin Psychol, 72*(2), 192-201. doi: 10.1037/0022-006X.72.2.192

Shin, L. M., McNally, R. J., Kosslyn, S. M., Thompson, W. L., Rauch, S. L., Alpert, N. M., . . . Pitman, R. K. (1999). Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: A PET investigation. *Am J Psychiatry, 156*(4), 575-584.

Siahpush, M., & Carlin, J. B. (2006). Financial stress, smoking cessation and relapse: results from a prospective study of an Australian national sample. *Addiction, 101*(1), 121-127.

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

Sinha, R. (2008). Chronic stress, drug use, and vulnerability to addiction. *Ann N Y Acad Sci, 1141*, 105-130. doi: NYAS1141030 [pii]10.1196/annals.1441.030

Sinha, R., Lacadie, C., Skudlarski, P., Fulbright, R. K., Rounsaville, B. J., Kosten, T. R., & Wexler, B. E. (2005). Neural activity associated with stress-induced cocaine craving: a functional magnetic resonance imaging study. *Psychopharmacology (Berl), 183*(2), 171-180. doi: 10.1007/s00213-005-0147-8

Sinha, R., Lacadie, C., Skudlarski, P., & Wexler, B. E. (2004). Neural circuits underlying emotional distress in humans. *Ann N Y Acad Sci, 1032*, 254-257. doi: 1032/1/254 [pii]10.1196/annals.1314.032

Sinha, R., & Li, C. S. (2007). Imaging stress- and cue-induced drug and alcohol craving: association with relapse and clinical implications. *Drug Alcohol Rev, 26*(1), 25-31. doi: 769824468 [pii]10.1080/09595230601036960

Solomon, R. L. (1977). Addiction: An opponent-process theory of acquired motivation: The affective dynamics of addiction. In J. D. Maser & M. E. P. Seligman (Eds.), *Psychopathology: Experimental Models* (pp. 66-103). New York: W H Freeman/Times Books/Henry Holt & Co.

Sorg, B. A., & Kalivas, P. W. (1991). Effects of cocaine and footshock stress on extracellular dopamine levels in the ventral striatum. *Brain Res, 559*(1), 29-36. doi: 0006-8993(91)90283-2 [pii]

Specio, S. E., Wee, S., O'Dell, L. E., Boutrel, B., Zorrilla, E. P., & Koob, G. F. (2008). CRF(1) receptor antagonists attenuate escalated cocaine self-administration in rats. *Psychopharmacology (Berl), 196*(3), 473-482. doi: 10.1007/s00213-007-0983-9

Strasser, A. A., Kaufmann, V., Jepson, C., Perkins, K. A., Pickworth, W. B., Wileyto, E. P., . . . Lerman, C. (2005). Effects of different nicotine replacement therapies on postcessation psychological responses. *Addict Behav, 30*(1), 9-17. doi: S0306460304001406 [pii]10.1016/j.addbeh.2004.04.005

Strong, D. R., Lejuez, C. W., Daughters, S., Marinello, M., Kahler, C. W., & Brown, R. A. (2003). The computerized mirror tracing task, version 1. *Unpublished Manual*.

Stuss, D. T., & Benson, D. F. (1986). *The frontal lobes*. New York, NY: Raven Press.

Sutherland, M. T., McHugh, M. J., Pariyadath, V., & Stein, E. A. (2012). Resting state functional connectivity in addiction: Lessons learned and a road ahead. *NeuroImage, 62*(4), 2281-2295. doi: 10.1016/j.neuroimage.2012.01.117

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain*. New York: Thieme.

Tate, S. R., Brown, S. A., Unrod, M., & Ramo, D. E. (2004). Context of relapse for substance-dependent adults with and without comorbid psychiatric disorders. *Addict Behav, 29*(9), 1707-1724. doi: S030646030400084X [pii]10.1016/j.addbeh.2004.03.037

Tomkins, S. S. (1966). Psychological model for smoking behavior. *Am J Public Health Nations Health, 56*(12), Suppl 56:17-20.

USDHHS. (2014). *The health consequences of smoking - 50 years of progress: A report of the surgeon general*. Atlanta, GA.

Valdez, G. R., Roberts, A. J., Chan, K., Davis, H., Brennan, M., Zorrilla, E. P., & Koob, G. F. (2002). Increased ethanol self-administration and anxiety-like behavior

during acute ethanol withdrawal and protracted abstinence: regulation by corticotropin-releasing factor. *Alcohol Clin Exp Res, 26*(10), 1494-1501. doi: 10.1097/01.ALC.0000033120.51856.F0

van den Heuvel, M. P., & Hulshoff Pol, H. E. (2010). Exploring the brain network: a review on resting-state fMRI functional connectivity. *Eur Neuropsychopharmacol, 20*(8), 519-534. doi: 10.1016/j.euroneuro.2010.03.008

Verdejo-Garcia, A., & Bechara, A. (2009). A somatic marker theory of addiction. *Neuropharmacology, 56 Suppl 1*, 48-62. doi: S0028-3908(08)00319-5 [pii]10.1016/j.neuropharm.2008.07.035

Vink, J. M., Willemsen, G., & Boomsma, D. I. (2005). Heritability of smoking initiation and nicotine dependence. *Behav Genet, 35*(4), 397-406. doi: 10.1007/s10519-004-1327-8

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. doi: S0028390804002163 [pii]10.1016/j.neuropharm.2004.07.019

Wagenknecht, L. E., Cutter, G. R., Haley, N. J., Sidney, S., Manolio, T. A., Hughes, G. H., & Jacobs, D. R. (1990). Racial differences in serum cotinine levels among smokers in the Coronary Artery Risk Development in (Young) Adults study. *Am J Public Health, 80*(9), 1053-1056.

Wang, W., Wang, Y. R., Qin, W., Yuan, K., Tian, J., Li, Q., . . . Guo, Y. M. (2010). Changes in functional connectivity of ventral anterior cingulate cortex in heroin abusers. *Chin Med J (Engl), 123*(12), 1582-1588.

Wang, Z., Faith, M., Patterson, F., Tang, K., Kerrin, K., Wileyto, E. P., . . . Lerman, C. (2007). Neural substrates of abstinence-induced cigarette cravings in chronic smokers. *J Neurosci, 27*(51), 14035-14040. doi: 27/51/14035 [pii]10.1523/JNEUROSCI.2966-07.2007

Ward, B. D. (1998). Multiple linear regression analysis across fMRI 3d datasets. http://afni.nimh.nih.gov/sscc/gangc/3dRegAna.pdf

West, R., Hajek, P., Stead, L., & Stapleton, J. (2005). Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction, 100*(3), 299-303. doi: ADD995 [pii]10.1111/j.1360-0443.2004.00995.x

Wewers, M. E. (1988). The role of postcessation factors in tobacco abstinence: stressful events and coping responses. *Addict Behav, 13*(3), 297-302.

Wikler, A. (1948). Recent progress in research on the neurophysiologic basis of morphine addiction. *Am J Psychiatry, 105*(5), 329-338.

Wills, T. A., Sandy, J. M., & Yaeger, A. M. (2002). Stress and smoking in adolescence: a test of directional hypotheses. *Health Psychol, 21*(2), 122-130.

Wills, T. A., & Shiffman, S. (1985). Coping and substance abuse: A conceptual framework. In S. Shiffman & T. A. Wills (Eds.), *Coping and substance use* (pp. 3-24). Orlando: Academic Press.

Winkielman, P., Knutson, B., Paulus, M. P., & Trujillo, J. L. (2007). Affective influence on judgments and decisions: Moving towards core mechanisms. *Review of General Psychology, 11*(2), 179-192.

Wise, R. A. (1980). Action of drugs of abuse on brain reward systems. *Pharmacol Biochem Behav, 13 Suppl 1*, 213-223.

Wise, R. A. (2002). Brain reward circuitry: insights from unsensed incentives. *Neuron, 36*(2), 229-240. doi: S0896627302009650 [pii]

Worsley, K. J., & Friston, K. J. (1995). Analysis of fMRI time-series revisited--again. *NeuroImage, 2*(3), 173-181. doi: S1053-8119(85)71023-3 [pii]10.1006/nimg.1995.1023

Xue, G., Lu, Z., Levin, I. P., & Bechara, A. (2010). The impact of prior risk experiences on subsequent risky decision-making: the role of the insula. *NeuroImage, 50*(2), 709-716. doi: 10.1016/j.neuroimage.2009.12.097

Yoo, S. S., Lee, J. H., O'Leary, H., Lee, V., Choo, S. E., & Jolesz, F. A. (2007). Functional magnetic resonance imaging-mediated learning of increased activity in auditory areas. *Neuroreport, 18*(18), 1915-1920. doi: 10.1097/WNR.0b013e3282f202ac00001756-200712030-00008 [pii]

Zalla, T., Koechlin, E., Pietrini, P., Basso, G., Aquino, P., Sirigu, A., & Grafman, J. (2000). Differential amygdala responses to winning and losing: a functional magnetic resonance imaging study in humans. *Eur J Neurosci, 12*(5), 1764-1770. doi: ejn064 [pii]

Zislis, G., Desai, T. V., Prado, M., Shah, H. P., & Bruijnzeel, A. W. (2007). Effects of the CRF receptor antagonist D-Phe CRF(12-41) and the alpha2-adrenergic receptor agonist clonidine on stress-induced reinstatement of nicotine-seeking behavior in rats. *Neuropharmacology, 53*(8), 958-966. doi: S0028-3908(07)00293-6 [pii]10.1016/j.neuropharm.2007.09.007

Footnotes

[1] Longest past quit attempt was also significantly correlated with duration of smoking history (i.e., number of years participants reported being daily smokers) ($r = .74$; $p < .001$). However, duration of smoking history was highly collinear with age ($r = .89$; $p < .001$). Therefore, all analyses that included the variable for duration of longest past quit attempt were run with both age and smoking duration included as covariates, and also re-run with each covariate included alone. Results did not differ regardless of if both covariates were included, or if either one was included individually.