COGNITIVE DISTRESS TOLERANCE AND EMOTION-RELATED NEURAL CORRELATES OF SMOKING CESSATION DURING THE N-BACK TASK

by

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(Under the Direction of Lawrence H. Sweet)

ABSTRACT

Cigarette smoking causes economic and health-related problems, including addiction that is resistant to behavioral and pharmacological intervention. Models of nicotine use disorder consistently suggest that the ability to tolerate the distress associated with craving and withdrawal is a key factor leading to relapse. During stressful tasks, the salience network and frontoparietal attention network activate, while regions associated with emotion and default mode processing deactivate relative to baseline. However, it is unclear whether these systems mediate the likelihood of relapses. The present study used functional neuroimaging to measure brain responses to a stressful cognitive task (the n-Back) and determine whether they are associated with smoking cessation. Results demonstrated that less suppression of bilateral amygdala was associated with successful abstinence, and less suppression of the posterior cingulate cortex was associated with the number of days to relapse. After controlling for known predictors of smoking cessation, dependence severity and right amygdala suppression were shown to uniquely predict abstinence. These findings demonstrate that unsuccessful regulation of task-unrelated cognitive and emotional brain function is associated with poorer cessation.

INDEX WORDS: n-Back, emotion, cognition, deactivation, abstinence, relapse

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CHAPTER 1

INTRODUCTION

Cigarette smoking is extremely costly to the United States, exceeding $170 billion in direct healthcare costs, and over $150 billion from lost productivity (Xu, Bishop, Kennedy, Simpson, & Pechacek, 2014). Thus, it is advantageous from a health perspective, as well as an economic perspective, to reduce cigarette smoking in the US. Reducing the number of active smokers in the United States is complicated by the addictive properties of nicotine. Most smokers would like to quit, but maintaining abstinence is challenging, and the majority (>66%) of those who attempt to quit are unsuccessful (Thompson, Michnich, Friedlander, Gilson, Grothaus, & Storer, 1988; Prochazka, 2000). Cognitive behavioral therapy, nicotine replacement therapy, and other pharmaceutical interventions have been employed to assist in smoking cessation. While these treatments increase cessation by 50-200% versus quitting cold turkey, relapses still occur over 70% of the time (Cahill, Stevens, Perera, & Lancaster, 2013). There is some evidence that these treatments work on different brain systems (Cahill et al., 2013), and that a combination of treatment strategies (Koegelenberg, Noor, Bateman, van Zyl-Smit, Bruning, O'Brien, ... & Irusen, 2014) can provide incremental improvement of smoking cessation. There is a clear need for research investigating the pathophysiological mechanisms of addiction to cigarettes and the neural mechanisms involved in effective smoking cessation. Improving neural models of addiction is likely to enable design of more effective treatment strategies to aid in quitting.

The process of becoming addicted to cigarettes is thought to occur through neuroplastic changes in brain regions associated with reward, emotion, and cognition (Volkow, Koob, & McLellan, 2016). The disruption of these brain systems is thought to be the root cause of altered internal states and behavioral changes that are traditionally associated with nicotine addiction such as craving, withdrawal, and drug-seeking. However, the progression of substance use initiation to addiction is gradual, with changes thought to occur in multiple brain systems at the same time (Volkow et al., 2016). The goal of this study is to shed light on the relative importance of the brain's emotion-related regions in processing and responding to distress. While some suggest that cigarette addiction is primarily a disorder of self-control (McClure & Bickel, 2014), the proposed research is designed to test whether the function of emotion-related brain systems may be used to predict smoking behaviors and outcomes. To achieve this, we examined functional neuroimaging data acquired during a challenging cognitive task (the n-Back) and investigated relationships between activity in emotion-related regions of interest and measures of smoking severity and abstinence.

Functional Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) uses a strong magnetic field and radiofrequency pulses to align and then perturb the magnetic spins of protons (Wager & Lindquist, 2015). This technique can be used to visualize any object that has water in it, since water is comprised of hydrogen atoms (protons) and oxygen. Protons are small spherical bits of mass, which rotate about their own axis and have a small magnetic field. When protons are placed in the static magnetic field generated by the MRI magnet, their small magnetic field interacts with the strong static magnetic gradient, causing the protons to align with the magnetic field. These protons, once aligned, will absorb the energy of applied radiofrequency pulses, which causes them to

temporarily break free from alignment with the magnetic field. This perturbation causes energized protons to release an electromagnetic wave, which contains spatiotemporal characteristics that can be measured with receiver coil antennae (Hashemi, Bradley & Lisanti, 2012). In MRI, these data are used to contrast different tissue types and construct accurate three-dimensional spatial maps.

Functional MRI (FMRI) is an extension of MRI principles used to quantify neural function in the brain. The human brain is comprised of neurons, which have a great amount of structural diversity, but the most important components of all neurons are cell bodies and axons. Neuronal cell bodies receive signals from other neurons and will transmit a signal to other neurons through axonal projections if their threshold of activation is met. This process, the 'firing' of neurons, is the underlying mechanism that allows human brains to process information. This biological process requires energy and metabolites, which are supplied via oxygenated blood. FMRI measures the presence of oxygenated blood, which has been shown to be a valid approximation of the activity of the signal generated by large groups of neurons in the brain (Logothetis, 2003). Blood-oxygen-level dependent (BOLD) FMRI signal is generated by comparing changes in the concentration of oxyhemoglobin to deoxyhemoglobin in the brain's blood supply over time (Hare, Smith, Forster, MacKay, Whittall, Kiehl, K. A., & Liddle, 1998). Whenever a brain region's neurons become involved in performing a task, they will fire more frequently and require more metabolic resources. This process can be observed in the brain as a very brief immediate decrease in blood oxygenation, followed by a large inflow of excess oxygenated blood that peaks after approximately 5-10 seconds, and then a slow decrease toward baseline after about 20 seconds (Hashemi et al., 2012). This has been termed the 'hemodynamic response', and it is the primary data being modeled in studies that use task-related BOLD FMRI.

FMRI can be used to examine brain regions that exhibit relative increases or decreases in BOLD signal during active tasks. Advanced techniques use FMRI signal to examine collaborative brain networks (Beckmann, DeLuca, Devlin, & Smith, 2005) and infer causal influence between associated brain regions (Bressler & Seth, 2011). Well-established tasks have been adapted for use in the scanning environment to minimize movement-related artifacts (Lazeron, Rombouts, De Sonneville, Barkhof & Scheltens, 2003). For instance, visual stimuli are typically presented through goggles or a projection screen and auditory information via headphones. Responses are collected using a keypress box in lieu of spoken responses to avoid head movement and because MRI acquisition generates loud noise. Neural response to these experimental tasks, which have been observed to relatively increase or decrease baseline activity in specific neurocognitive systems, are compared to a control condition, such as viewing a fixation cross or a simplified visuomotor control version of the experimental task. These control for the baseline function, and a general linear model (Chatfield & Collins, 1981) is used to identify variance in BOLD signal that is specific to performance of the experimental task rather than noise (Friston, Holmes, Poline, Grasby, Williams, Frackowiak, & Turner, 1995). The development of FMRI methodology has allowed researchers to identify brain regions that are associated with a wide variety of cognitive, behavioral, and emotional constructs.

Models of addiction and relapse

Early models of addiction approached the topic from a behaviorist perspective. These models primarily sought to determine the incentives and disincentives for smoking, in order to design treatments that would aid in quit attempts. Researchers proposed positive reinforcement and negative reinforcement as potential mechanisms for both the development and maintenance of addiction (Epstein, Grunberg, Lichtenstein, & Evans, 1989). The positive reinforcement

reported by smokers includes the taste, sensations, and positively perceived social consequences of smoking. Conversely, cigarette addiction leads to craving and withdrawal symptoms, which can be alleviated by smoking cigarettes, and this negative reinforcement is thought to be a primary contributor to the maintenance of addiction. These behaviorist theories motivated clinicians to design tailored treatment plans that could specifically counteract these motivations. For instance, an early study demonstrated that aversion therapy is effective for those who are motivated to smoke by positive reinforcement, while nicotine replacement therapy (NRT) is more effective for those who smoke more for negative reinforcement (Zelman, Brandon, Jorenby, & Baker, 1992). Furthermore, Zelman (1992) found that smokers who were high in baseline negative affect experienced greater benefits from support counseling, which highlights emotion as an additional factor that may play a critical role in cigarette addiction.

While early research into the effectiveness of treatment strategies provides insight into underlying cognitive factors motivating smoking behavior, new insights were gained from examining how the motivation to smoke was related to beliefs about affective and social consequences. An aim of this research was to determine whether conscious beliefs about smoking were associated with smoking cessation, and test whether cognitive-oriented therapy could be used to treat smoking addiction. The Smoking Consequences Questionnaire (SCQ; Brandon & Baker, 1991), was designed to assesses smokers' perceptions of the positive and negative consequences of smoking. Using the SCQ, expected outcomes of smoking are measured (e.g., 'When I smoke the taste is pleasant") and participants' answers on this survey can be directly linked to smoking use. For instance, confirmatory factor analysis of items on the SCQ shows that that negative reinforcement expectancies are related to successful abstinence, while positive reinforcement expectancies are not (Wetter, Smith, Kenford, Jorenby, Fiore, Hurt,

... & Baker, 1994). Additionally, negative reinforcement expectancy is related to baseline negative affect and perceived stress. The SCQ has been used more recently to demonstrate that negative reinforcement expectancies are also associated with higher levels of negative affectivity, emotional dysregulation, and anxiety sensitivity (Johnson, Morgan-Lopez, Breslau, Hatsukami, & Bierut, 2008). This study specifically showed that smokers who believe cigarette smoking can alleviate negative moods tend to have negative emotional vulnerability. Researchers have also examined smokers' expectations regarding social consequences of smoking, finding similar results. One study demonstrated that negative social consequences of smoking, such as peer rejection (i.e. being told that you smell like smoke), is associated with a greater likelihood of cessation, while positive social consequences do not seem to predict cessation (Kahler, Daughters, Leventhal, Gwaltney, & Palfai, 2007). In sum, early studies identified positive and negative reinforcement, particularly as related to negative emotionality as crucial motivators in acquisition and maintenance of cigarette addiction.

Over time, theoretical models of addiction have become more elaborate. One model (Robinson & Berridge, 1993) proposed that addictive substances cause reward-related brain regions to be sensitized toward drug salience. In this model, the modification of incentive salience in dopaminergic reward-related brain systems, thought to represent the 'wanting' of the drug, were proposed as the mediator of cravings. This is distinguished from the 'liking' of the pleasurable effects of drugs, which was described as the hedonic, pleasurable sensation of the drug. The liking of drugs in this model was proposed to be mediated by the opioid neurotransmitter systems of the brain. The 'wanting' system was proposed as the fundamental system mediating the development of addiction and leading to relapse (Robinson & Berridge, 2003). Others have proposed alternate underlying brain systems that may mediate smoking

behaviors and the addiction process. In a model by Volkow Koob, & McLellan (2016), three main phases are proposed as the cornerstones of addiction: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. The binge and intoxication phase of addiction is thought to involve conditioned learning reflected in motivational and reward-related brain regions that sensitizes one to smoking cues. This leads to enhanced reward sensation in response to environmental stimuli that are associated with the drug. After time, drug use can lead to the development of withdrawal, negative affect and anhedonia when not under the influence of the drug. These are hallmarks of addiction, and they form the second phase of the addiction cycle, according to this model. Furthermore, extended drug use is thought to induce systematic changes in neuronal signaling in the brain's reward and motivational systems so that non-drug stimuli are less rewarding, and that discontinuing use of the drug is followed by severe withdrawal symptoms. This new baseline causes a shift in behavior in substance abusers – when previously they had taken drugs for their rewarding effects, they begin to require drugs to cope with the negative symptoms of withdrawal. This negative reinforcement learning can be thought of as altered function of two brain systems: emotion (elevated baseline negative affect) and learning (incentive salience of the drug is higher). The third phase of addiction is centered around cognitive brain regions that are responsible for self-regulation, executive decision-making, and inhibitory control. Prefrontal brain circuits, which are thought to mediate this function, become progressively more impaired over time. Some theorize that this is the central disorder of addiction (McClure, & Bickel, 2014), and many types of treatments attempt to bolster self-control in patients. However, each of the three phases of addiction has been linked to cessation success through the examination of brain activation or behavioral measures, suggesting that successful treatment of addiction would benefit from a multifaceted approach.

The utility of a multifaceted approach suggested by the Volkow et al. (2016) model is supported by an extensive number of studies showing that self-regulation (Wilson, Sayette, & Fiez, 2013), affective factors (Kenford, Smith, Wetter, Jorenby, Fiore, & Baker, 2002; Abrantes, Strong, Lejuez, Kahler, Carpenter, Price, ... & Brown, 2008), and the ability to tolerate distress (Brown, Lejuez, Kahler, Strong, 2002; Brown, Lejuez, Kahler, Strong, Zvolensky, 2005) may play a role in motivating smokers to quit. Interactions among cognitive and emotion-related brain systems are likely to mediate these processes, and thereby impact the development of addiction and, conversely, mediate successful cessation. Many emotional constructs in particular have been identified that are associated with early lapses in smokers. This includes the constructs of behavioral distress tolerance (Brown et al, 2002; Brown et al., 2005), smoking cue reactivity (Niaura, Abrams, Demuth, Pinto, Monti, 1989), stress (Sinha, 2001), task persistence (Brandon, Herzog, Juliano, Irvin, Lazev, & Simmons, 2003; Steinberg, Williams, Gandhi, Foulds, Epstein, & Brandon, 2012), and anxiety sensitivity (Brown, Kahler, Zvolensky, Lejuez , & Ramsey, 2001). These are all different forms of negative affect – each with their own measures and robust literatures. In recent years the tolerance of distress has emerged at the forefront of research examining cigarette addiction as a parsimonious explanatory factor that is linked to successful smoking cessation.

Negative affect during withdrawal and craving

Craving and withdrawal are pervasive, long-lasting elements of addiction, and play a significant part in smoking cessation. Craving is the conscious desire to use a drug, which occurs in greater strength as the individual becomes more addicted, and withdrawal includes escalating symptoms of irritability, depression, restlessness, insomnia, anxiety, hunger, and poor concentration (West, & Hajek, 2004). Both craving and withdrawal are linked to negative affect

and thought to hamper the success of individuals in quitting smoking. Recent investigations have focused on the utility of examining the timecourse of urges and negative affect for weeks after a quit attempt in addition to single point measurements (Baker, Japuntich, Hogle, McCarthy, & Curtin, 2006). For instance, they have found that the rise time of craving, duration of intense craving, and duration of intense negative affect are related to cessation. In part, these timecourse findings inform our view that enhanced emotional reactivity per-se is not the primary factor causing smokers to lapse, although enhanced responses to smoking cues has been considered a proximal factor leading to relapse (Niaura, Rohsenow, Binkoff, Monti, Pedraza, & Abrams, 1988). Instead, we have proposed that changes in mood that are often reported as symptoms of withdrawal (e.g. irritability, depression, and anhedonia) may be stronger factors motivating relapses relative to enhanced salience of smoking cues. Both craving and withdrawal seem to involve brain processes that cause long-lasting changes in mood (such as stress), and are likely to involve dysregulation of emotion processing or reward brain systems.

Emotion-related constructs such as negative affect, craving, and anxiety sensitivity have been linked to early lapses (Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996; Abrantes et al., 2008; Shiffman, Engberg, Paty, Perz, Gnys, Kassel, & Hickcox, 1997; Brown et al., 2001). However, the underlying mechanisms responsible for this association are not fully understood. Emotion-related processing is generally thought of as a way for the brain to 'tag' stimuli as being motivationally important. In cigarette addiction, this system undergoes associative learning, which causes cigarette cues to have enhanced incentive salience (Robinson & Berridge, 1993). While there is evidence that drug cues have enhanced motivational value for smokers relative to neural stimuli (Versace, Engelmann, Jackson, Costa, Robinson, Lam, ... & Cinciripini, 2011), this relative elevation in salience is best explained as a result of blunted salience of ordinary

pleasant stimuli instead of strictly hypersensitivity to smoking cues. This effect is enhanced whenever smokers are in a withdrawal state (Curtin, & McCarthy, 2006) and can be voluntarily regulated through reappraisal, or suppression strategies. Interestingly, the voluntary regulation of emotional reactivity to acute stressors does not seem hampered in the state of withdrawal (Piper & Curtin, 2006), which suggests that the influence of executive processes on emotional systems may not be the primary culprit in failed smoking cessation. Conscious emotion regulation strategies based on self-efficacy have also been used to successfully control cue-induced craving (Ono, Kochiyama, Fujino, Sozu, Kawada, Yokoyama, ... & Takahashi, 2018). Self-efficacy is a person's belief in their ability to withstand smoking – and is commonly measured using the Smoking Self-Efficacy (SSE) questionnaire (Colletti, Supnick, & Payne, 1985). These conscious emotion regulation strategies may be helpful in preventing lapses proximally, but the underlying problem may not be resolved through this treatment strategy.

One potential mechanism for craving and withdrawal states in addiction is neuroadaptation in the extended amygdala. This region is thought to have reduced dopaminergic neurotransmitter functioning, and elevated levels of anxiolytic neurotransmitters (Koob, 2003). These findings have been found in conjunction with hypofrontality in medial prefrontal and cingulate cortex, which may be involved in directly regulating the value of rewards through their projections onto the ventral striatum (Goldstein, Tomasi, Rajaram, Cottone, Zhang, Maloney, ... & Volkow, 2007). These regions are well-known to be involved in the processing of emotional stimuli, and reward. The conscious experience of urges to take drugs has been linked to the insula – a well-known region of the salience network (Naqvi 2009). Actively resisting these urges through smoking self-efficacy has been linked to activation in pregenual anterior cingulate and medial prefrontal cortex – regions that have been associated with emotion suppression of

the amygdala and insula (Ono et al., 2018; Goldin, McRae, Ramel, & Gross, 2008). These findings suggest that both the salience network and emotional processing networks are involved in the conscious states and motivating factors associated with craving and may be important regions for tolerating distress more broadly.

Distress Tolerance and Social Stress

Distress tolerance (DT) is the ability to persist while experiencing affective distress. The most common experimental assessment of DT is a behavioral measure of the number of seconds a person can withstand a stressful task (Zvolensky, Vujanovic, Bernstein, & Leyro, 2010). Additionally, self-report has been used to gauge a person's perceived DT through the Distress Tolerance Scale (Simons & Gaher, 2005) and Frustration-Discomfort Scale (Harrington, 2005). A growing body of research suggests that DT is an important factor in the development and maintenance of adult psychopathology broadly (Zvolensky, Bernstein, & Vujanovic, 2011), and nicotine addiction specifically (Brown et al., 2002; Brown et al., 2005). Researchers have used a variety of tasks that induce distress in different ways. For instance, submerging a limb in an ice bath can induce physical distress (Streff, Kuehl, Michaux, & Anton, 2009), while a challenging cognitive task may induce frustration in participants as they fail to meet a goal (Brown et al., 2005). These tasks may provide unique information on how we respond to different types of distressing stimuli. Delineating the utility of these effects to understand addiction is a topic of ongoing research, which may help to identify ideal neurocognitive and emotion-related brain systems to target with clinical treatments.

Cognitive and emotional DT have been explicitly linked to smoking behavior. Smokers that quickly terminate their performance on the Paced Auditory Serial Addition Task (Gronwall, 1977) tend to have earlier smoking lapses in a quit attempt (Brown et al., 2005; Daughters, Ross,

Bell, Yi, Ryan, & Stein, 2017). This suggests that persistence at challenging tasks may recruit the same cognitive resources as the tolerance of distress associated with smoking withdrawal. Similarly, smokers that have a history of early lapses (within the first 24 hours of quitting) also tend to have greater negative affect in response to stress (Brown et al., 2002). This behavioral pattern is further supported by work showing that negative affect induction is associated with decreased latency to smoke, and more 'puffs taken' by participants after viewing negative cues (Heckman, Carpenter, Correa, Wray, Saladin, Froeliger, ... & Brandon, 2015). These studies provide evidence for two potential explanations for the underlying link between DT and success in quit attempts. On one hand, smokers that have high cognitive resilience in the face of stress may be more successful in a quit attempt, and on the other hand, smokers that have an enhanced emotional response to stress may be less successful in their quit attempts. There is mounting evidence that emotional DT, measured with the Distress Tolerance Scale, is higher in smokers that perceive that internal barriers (rather than external, or addiction-related barriers) contribute to their failure in succeeding in a quit attempt (Kraemer, McLeish, Jeffries, Avallone, & Luberto, 2013). This supports the broad view that motivation to smoke occurs as a way to cope with stress and negative affect, including attenuation of the negative emotions experienced during withdrawal (Baker, Brandon, Chassin, 2004). However, more research is needed to fully understand the relative contribution of cognitive and emotional neural mechanisms that lead to these smoking behaviors.

Research focusing on psychosocial stress has been used to identify hormonal and BOLD activation changes that underlie the human stress response. Instead of physical or cognitive challenges, social pressure is used to induce stress in participants. Tasks such as the Trier Social Stress Task (TSST; Kirschbaum, Pirke, & Hellhammer, 1993) and Montreal Imaging Stress Task

(MIST; Dedovic, Renwick, Mahani, Engert, Lupien, & Pruessner, 2005) have been adapted for use in the FMRI environment to induce psychosocial stress in participants. In the TSST, participants perform a 5-minute impromptu oral presentation while being evaluated by a panel of judges, and then perform a mental arithmetic task. This causes an increase in self-reported negative affect, physiological arousal, salivary cortisol concentration (Wardle, Munafò, & De Wit, 2011) and craving among smokers (Childs, & De Wit, 2010). Similarly, in the MIST participants perform a computerized adaptive mathematical test that escalates in difficulty to ensure a high failure rate. These tasks have been used in the past to identify neural correlates of stress (Pruessner, Dedovic, Khalili-Mahani, Engert, Pruessner, Buss, ... & Lupien, 2008). However, fewer studies have investigated the utility of these tasks with regard to smoking specifically. For instance, participants in nicotine withdrawal tend to have enhanced stress responses to the MIST, but this response has not been linked directly to smoking outcomes. Therefore, this body of research is informative in conceptualizing expected stress responses in the brain in the context of healthy and smoking populations. Future research in this area would benefit from tying differences in stress responses to smoking outcomes – and research may additionally benefit from the inclusion of social stressors as a broad category that fits under the DT umbrella.

These recent developments in DT research are primarily centered around subjective and behavioral measures, with few studies having examined the neurocognitive mechanisms underlying DT. In the present study, we minimized the inherent negative emotional reactivity by using the n-Back, a cognitive task (rather than a social stress or negative emotion induction task). We expected to see brain responses similar to the PASAT (Wanger, 2018), which reflects cognitive frustration and has been associated with a moderate level of distress. While emotion-

related systems tend to activate when provided with arousing stimuli, research suggests that they deactivate during stressful situations. We proposed that the level of deactivation of emotional systems during a cognitively distressing task would be associated with the success of a smoking quit attempt. In order to interpret these potential findings at a finer level than overall task-specific activation, we compared cessation-associated brain responses to the n-Back with self-report measures (perceived stress, DT, pre-post PANAS, smoking self-efficacy). Studying psychological factors that relate to, or potentially mediate the expected relationships between brain activation and smoking cessation is an important step that may lead to the development of more effective interventions.

Neural correlates of DT and relevance for addiction models

The most common task used to study the cognitive aspect of DT is the PASAT. Broadly speaking, the PASAT task is expected to activate the fronto-parietal executive control network and salience networks in healthy controls (Audoin, Ibarrola, Duong, Pelletier, Confort-Gouny, Malikova, ... & Ranjeva, 2005) - just as cognitive tasks like the n-Back tend to activate these regions. Using a quantitative meta-analysis, we have demonstrated that the pattern of activation between the PASAT and n-Back is very similar (Wanger, 2018). Researchers have recently used FMRI to identify the neural correlates of DT during this task (Daughters et al., 2017). Daughters et al. demonstrated that higher DT in smokers is associated with less deactivation of the insula, anterior cingulate cortex (ACC), medial frontal gyrus, inferior gyrus, and ventromedial prefrontal cortex during the PASAT. These findings of relative deactivation are interesting because they parallel the widespread deactivation found in psychosocial stress tasks (Dedovic, 2009a). Findings from fMRI studies using the MIST indicate activation in frontal lobes, including the ACC, and relative deactivation of the amygdala, hippocampus, hypothalamus, and nucleus

accumbens (Dedovic, Rexroth, Wolff, Duchesne, Scherling, Beaudry, ... & Pruessner, 2009a; Dedovic, D'Aguiar, & Pruessner, 2009b). In these studies, activation of lateral and medial (e.g., ACC) frontal regions was thought to be related to the cognitive aspect of the task, while deactivation of the limbic regions was thought to be related to the negative emotionality of the social-evaluative aspect of the task. In a similar study, Pruessner (2008) used Positron Emission Tomography to show widespread deactivation of the limbic system during the MIST in smokers. This deactivation included the hippocampus, hypothalamus, medial and orbito-frontal cortex, and ACC. This pattern may be counterintuitive, as prior work investigating emotional regions has found significant activation in response to smoking cues (Janes, Pizzagalli, Richardt, Frederick, Chuzi, Pachas, ... & Kaufman, 2010) or fear stimuli (Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002). However, Pruessner et al. (2008) suggested that perception of arousing stimuli may induce a state of vigilance in subjects. In contrast, the deactivation seen during stress induction was interpreted as a suppression of the default processing occuring in limbic regions. Following these stressful tasks, drug cue reactivity appears to be heightened during FMRI – with elevated activity in the medial prefrontal cortex, posterior cingulate cortex (PCC), and visual association areas (Dagher, Tannenbaum, Hayashi, Pruessner, & McBride, 2009). These regions overlap with the default mode network, which has led to speculation that these activated regions represent neural coding for 'ruminative thoughts about drug use' (Sutherland, McHugh, Pariyadath, & Stein, 2012). These studies show that stressful tasks tend to deactivate limbic regions and motivates our use of these particular regions as *a-priori* regions of interest.

Investigation of DT systems using a Challenging Cognitive Task – the n-Back

Altered brain functioning across both emotional and cognitive regions is evident in smokers, but the extent of these effects during cognitive demands is under-studied. Deactivation

during verbal working memory tasks has been observed in limbic regions (Yun, Krystal, & Mathalon, 2010) in healthy controls and several cortical regions, including nodes of the default mode network, when smokers are in withdrawal (Sweet, Mulligan, Finnerty, Jerskey, David, Cohen, & Niaura, 2010). These point to an overall suppression of emotion-related and default mode network activity when performing an active task. This generalized form of emotion regulation is often overlooked. While FMRI researchers have focused on examining voluntary emotional suppression and cue-reactivity, a confounding factor in these paradigms is that emotionally arousing cues typically activate emotional processing systems – and this may obfuscate the influence of emotion regulation during cognitive demands. By studying emotion regulation in a non-emotional task, we can isolate this aspect of emotion processing and potentially tie it to smoking outcomes.

The verbal n-Back is frequently used in functional neuroimaging as a working memory challenge. This task requires participants to buffer and maintain multiple phonological chunks of information, manipulate the information, sustain attention despite interference, and relay correct answers at a rapid pace (Jonides, Schumacher, Smith, Koeppe, Awh, Reuter-Lorenz, ... & Willis, 1998; Tombaugh 2006; Sweet, Paskavitz, Haley, Gunstad, Mulligan, Nyalakanti, & Cohen, 2008). This task is considered to be cognitively challenging and is sometimes described as distressing (Parmenter, Shucard, Benedict, & Shucard, 2006). However, the n-Back does not typically induce a negative mood, and negative affect scores from the Positive and Negative Affective Schedule (PANAS) do not seem to increase after n-Back task performance in controls (Iida, Nakao, & Ohira, 2012). In smokers this task may be challenging enough induce distress. According to prior research, this may present as widespread limbic deactivation and task-related

activation, and the efficacy of the cognitive or emotional processing of this stressful task may be related to the successfulness of the smoker's quit attempt.

The n-Back activates a bilateral frontoparietal network that includes supplementary motor area, anterior cingulate, dorsolateral prefrontal cortex, and secondary motor regions (Owen, McMillan, Laird, & Bullmore, 2005; Loughead, Wileyto, Ruparel, Falcone, Hopson, Gur, & Lerman, 2015). These regions include regions notable for executive control and the phonological loop (e.g., premotor cortex) from Baddeley's model (2003) of working memory. In terms of relative deactivation, regions of the default mode network (medial frontal cortex and posterior cingulate) are suppressed during the n-Back (Jonides et al., 1998; Qin, Hermans, van Marle, Luo, & Fernández, 2009). Deactivation has also been seen in orbitofrontal cortex (Jonides et al., 1998) and amygdala (Yun et al., 2010) during the n-Back; these regions are associated with emotion regulation (Golkar, Lonsdorf, Olsson, Lindstrom, Berrebi, Fransson, ... & Öhman, 2012). This limbic deactivation is typically not the focus of experiments that use cognitive tasks, and when reported tends to be cautiously interpreted (Jonides et al., 1998), since the trend of greater deactivation under higher load is distinct from tasks that are designed to elicit emotional responses (Yun et al., 2010). Recent research (Loughead et al., 2015) has suggested that there are also task-negative effects in regions during the n-Back (PCC & VMPFC) that have previously been associated with self-referential thought. These regions have also been identified as nodes of the default mode, as well as cognitive control and emotion regulation (Leech, Kamourieh, Beckmann, & Sharp, 2011; Goldin et al, 2008). Interestingly, these early findings mirror the broad deactivation of limbic regions that has been identified using psychosocial stress tasks (Dedovic et al., 2009a; Dedovic et al., 2009b). Thus, both activated regions and deactivated regions are important to consider as potential predictors of smoking relapse.

Rationale

Prior work has shown that reduced left DLPFC activation and reduced suppression of PCC may predict earlier smoking lapses (Lougead et al, 2015). The present study extends these findings by testing whether the n-Back task activation in a wider range of brain regions (Table 1), which have been empirically derived via quantitative meta-analysis, are related to cessation. Deactivation of emotion-related regions during this stressful cognitive task has been associated with behavioral measures of DT in past research (Daughters et al., 2017). We predicted that smokers who are able to deactivate emotion-related brain regions more effectively during the n-Back will exhibit greater self-reported DT and better cessation outcomes. DT has been linked to cessation in previous studies, but more work is needed to directly tie emotion-related brain response to cessation. Since negative affect has been identified as a hallmark of addiction that becomes dysregulated in tandem with executive function (particularly when in withdrawal), this aspect of addiction merits further study.

My dissertation aimed to extend our understanding of DT by determining whether brain responses in cognitive and emotion-related regions during a challenging cognitive task (the n-Back) predict subsequent smoking cessation. The present study used 10 derived *a-priori* regions of interest that originate from a meta-analysis of clusters that are typically activated by the n-Back (Wanger, 2018). These regions include bilateral clusters in the DLPFC, inferior parietal lobules, insula, premotor area, and supplementary motor area. Of these regions, only left DLPFC has been previously associated with smoking cessation. Furthermore, the study examined 6 emotion-related regions and one region associated with the default mode network (posterior cingulate cortex; PCC) that were expected to exhibit relative deactivation. The emotion-related regions examined include bilateral amygdala, bilateral ventromedial prefrontal

cortex (VMPFC), subgenual anterior cingulate cortex (sgACC), and pregenual anterior cingulate cortex (pgACC). Of these regions, only PCC has previously been associated with cessation (Loughead et al., 2015). These regions have typically been studied in the context of emotion reactivity or emotion regulation task paradigms. Instead, we examined their responses during a challenging cognitive task, to determine whether their activation or deactivation is predictive of cessation.

Additionally, the present study tested whether potential cessation-associated brain activation is related to self-reported measures (perceived stress, DT, pre-post PANAS, smoking self-efficacy). These measures represent potential psychological constructs that could potentially be investigated in future studies as correlates or mediators of brain response and behaviors that are associated with smoking cessation. My explicit aims and hypotheses included:

Aims and Hypotheses

Aim 1. Determine whether brain response to the n-Back predicts subsequent smoking cessation. Based on information from prior literature, brain response to this cognitive DT was expected to result in increased activation of the brain's frontoparietal attention network and decreased activation in the default mode network. We also investigated whether self-reported stress measures are associated with brain regions significantly associated with cessation.

H.1.1. Primary nodes of the frontoparietal attention network (lateral prefrontal, frontal poles, and parietal cortices) were expected to be active during the n-Back and the magnitude of these relative activation effects was expected to be positively associated with subsequent cessation outcomes (i.e., greater brain response in these regions would be associated with better cessation outcomes).

H.1.2. Primary nodes of the DM network (dorsomedial prefrontal cortex, ventromedial prefrontal cortex, posterior cingulate) were expected to be suppressed during the n-Back and the magnitude of these relative deactivation effects were expected to be associated with better outcome (i.e., greater relative deactivation was expected to be associated with better cessation outcomes).

H.1.3. The magnitude of brain responses (i.e., greater relative activation or greater relative deactivation) in regions associated with cessation outcome was also expected to be associated with better scores on self-reported DT (Distress Tolerance Scale), smoking self-efficacy (SSE), perceived stress (PSS), and pre-scan to post-scan change in self-reported negative affect (PANAS).

Aim 2. Determine whether the magnitude of brain response to the n-Back in emotion-processing regions, including the anterior salience network, at baseline was related to subsequent smoking cessation. We also investigated whether self-reported stress measures were associated with brain regions that predicted cessation.

H.2.1. Primary nodes of the emotion processing network (amygdala, orbitofrontal cortex) were expected to be significantly suppressed during the n-Back and greater magnitude of suppression at baseline was expected to be associated with more successful cessation outcomes.

H.2.2. Primary nodes of the SN (anterior insula and anterior cingulate) were expected to be significantly active during the n-Back at baseline, and their magnitude of response was expected to be positively associated with successful cessation outcomes.

H.2.3. The absolute magnitude of brain responses (i.e., greater relative activation or greater relative deactivation) in regions associated with cessation outcome was also

expected to be significantly correlated with better scores on self-reported DT (Distress Tolerance Scale), smoking self-efficacy (SSE), perceived stress (PSS), or a pre-scan to post-scan change in self-reported negative affect (PANAS).

Aim 3. In order to explore the additive value of brain imaging assessments, we tested whether the variance in BOLD response in significantly activated/deactivated regions (Aim 1 or Aim 2) predicted cessation outcomes beyond known predictors of smoking outcome. These data were then added to a backwards stepwise multiple regression model with conventional measures of smoking severity and craving that have significant zero-order correlations with cessation.

H.3.1. Patterns of predictive validity expected in Aims 1 and 2 will remain after variance associated with cigarettes per day and FTND score (and other empirically defined predictors of outcome) are statistically controlled.

Exploratory Aim. Although days to lapse was our primary outcome measure in Aims 1-3, we explored two other outcome measures: days to relapse and complete abstinence. Therefore, we also tested the sensitivity and specificity of days to relapse and complete abstinence. Each of these measures has unique ecological significance that complements the primary outcome measure. While divergent validity would be informative, the overall results were expected to be convergent.

CHAPTER 2

METHOD

Overview

This study examined fifty 10-cigarette/day smokers aged 18-65 who were motivated to quit. Participants in this study provided smoking history and demographic information, assessments of withdrawal, craving, smoking self-efficacy, and two measures of smoking severity: reported cigarettes per day (CPD) and the Fagerstrom Test for Nicotine Dependence (FTND). Whole brain functional MRI data were obtained, which included an n-Back paradigm. Smokers then began a nine-week quit attempt with the assistance of nicotine replacement therapy (NRT) and cognitive-behavioral therapy, including motivational interviewing. Weekly follow-up assessments yielded outcome variables such as the time to first lapse (days to lapse) and time until full relapse (days to relapse). A relapse is defined as having occurred when the participant has seven consecutive days where they have smoked at least one cigarette. Successful abstinence is a dichotomous variable that was be derived from 'days to relapse.'. Participants who refrained from smoking at least one cigarette for 7 days in a row during their quit attempt are considered to have remained abstinent. In this experiment, if participants reach the 49th day of follow-up without relapsing, they are considered to have been successfully abstinent.

Two primary *a-priori* region of interest (ROI) analyses were carried out using these data. The first included 10 ROIs from a prior meta-analysis of regions activated by the n-Back (Wanger, 2018). The findings of this meta-analysis include clusters in the bilateral dorsolateral prefrontal cortex (DLPFC), supplementary motor area (SMA), left frontal pole, bilateral inferior parietal lobules (IPL), bilateral anterior insula (INS), and bilateral premotor areas. The second

used emotion-related regions, including the anterior salience network, and the default mode network that we hypothesized would be relatively deactivated during the n-Back. These include the bilateral amygdala, bilateral ventromedial prefrontal cortex (VMPFC), subgenual anterior cingulate cortex (sgACC), and pregenual anterior cingulate cortex (pgACC), and posterior cingulate cortex (PCC).

For brain regions where n-Back response predicts future cessation, we used linear regression to determine whether their variance in response magnitude predicts cessation above and beyond traditional predictors of quitting success (e.g., smoking severity, DT). This aimed to potentially link important psychological constructs such as DT, perceived stress, and negative affect, which have previously been independently linked to cessation, directly to brain activation patterns associated with successful cessation.

Participants

All procedures described herein were approved by the University of Georgia Institutional Review Board and are in compliance with the declaration of Helsinki. We recruited 50 right-handed treatment-seeking smokers from the Athens community using advertisements. Participants were comprised of 31 men and 17 women, aged 18-60 (M = 40.8, SD = 11.6). Participants smoked greater than 10 cigarettes per day (M = 22.6, SD = 14.2), reported a motivation to quit of at least 5 on a scale of 1-10, and scored an average of 5.00 on the FTND, which represents a moderate level of dependence. Recent use of alcohol, marijuana, or other psychoactive drugs was assessed during screening session with a substance use checklist but was not used as an exclusion criterion to improve generalizability. Participants were excluded if they had diagnosed medical, psychiatric, or neurologic disorders, as these may confound interpretations of results. Participants were also screened for MRI contraindications to ensure

that they could be safely scanned using MRI. Participants were excluded if they had an estimated IQ less than 70, as measured by the Wechler Test of Adult Reading. This criterion was implemented to ensure that participants would be able to follow instructions, benefit from treatment and perform above chance on cognitive assessments.

Procedures

Overview

This experiment involves secondary analyses of data from a study examining the neural correlates of smoking relapse. The study had a longitudinal design with two study visits and a nine-week intervention with nine weekly research follow-ups. Following the two baseline screening and scanning sessions, participants began a quit attempt with the assistance of weekly therapist meetings and NRT.

Screening and Baseline visit

Participants who responded to advertisements were first screened over the phone for inclusion and exclusion criteria. After passing this initial screening, participants met study personnel in-person to verify smoking behavior, and to ensure that participants met the safety requirements for MRI. Informed consent was obtained from all participants after introducing them to the study's protocols. During this visit participants provided demographic information, medical history, cognitive assessments, and various self-reports related and other assessments unrelated to this study.

Scanning session

Subjects were instructed to smoke as usual prior to their MRI session in order to standardize the level of craving and withdrawal present in participants. During the MRI scanning session, participants underwent pre-scan assessments, which included the Positive and Negative

Affect Schedule (PANAS), Shiffman Craving Scale (SCS), and the Minnesota Nicotine Withdrawal Scale. Next participants underwent a T1-weighted anatomical scan and functional MRI during a 90-minute task battery that included the n-Back. Following these MRI procedures, participants filled out post-scan assessments that included craving, PANAS, Perceived Stress Scale, and Distress Tolerance Scale (DTS).

Intervention and weekly follow-up

After the scanning session, participants met with researchers to form a 9-week smoking cessation treatment plan, which included therapist-guided counseling sessions and nicotine replacement therapy (NRT). Participants planned to begin their quit attempt 2 weeks after the scanning session on average, meeting with their therapist for 60 minutes on the day they began their quit attempt, and 30 minutes weekly, for nine weeks. These meetings used motivational interviewing and cognitive behavioral therapy approaches to aid in cessation attempts. Nicotine patches were dispensed on a bi-weekly basis. In accordance with the manufacturer's instructions, participants received 21 mg nicotine patches for 4 weeks, with dosage reducing to 14mg and 7mg for two weeks each, and finally full nicotine abstinence in the final (ninth) week.

Participants were instructed to keep a record of their smoking, if any, and their use of the nicotine patch on a timeline follow-back calendar. These data allowed us to verify the adherence to NRT, obtain information about subjects' first lapse, and whether the participant fully relapsed.

Self-report measures

Demographic information was obtained prior to the scanning session. This included measures of socioeconomic status, education, income level, sex, and medical history. Assessments for nicotine dependence, withdrawal, craving, affect, stress, and DT were also obtained using questionnaires.

Fagerstrom Test for Nicotine Dependence

Cigarettes smoked per day and the Fagerstrom Test for Nicotine Dependence (FTND) score were used to measure the severity of smoking dependence (Piper & Curtin, 2006). The FTND is a questionnaire that assesses the frequency and volume of smoking. Scores on this scale range from 0-10, indicating the level of dependence on nicotine. Higher scores on the FTND are reliably linked to cessation outcomes (Kozlowski, Porter, Orleans, Pope, & Heatherton, 1994; Breslau, & Johnson, 2000; Johnson, Morgan-Lopez, Breslau, Hatsukami, & Bierut, 2008).

Minnesota Nicotine Withdrawal Scale

Levels of withdrawal were obtained using the Minnesota Nicotine Withdrawal scale (Hughes, Hatsukami, 1986). This 8-item scale measures withdrawal symptoms such as craving, irritability, restlessness, weight gain, and others. Participants rate their recent symptomology on a Likert scale where 0 = none, 1 = slight, 2= mild, 3 = moderate, and 4 = severe. Mean withdrawal is calculated by averaging the score of the first seven items (Hatsukami, Dalgren, & Hughes, 1988)

Shiffman-Jarvik Withdrawal Scale (Craving Subscale)

Craving was measured using the Shiffman-Jarvik Withdrawal Scale (Shiffman, Jarvik, 1976). This questionnaire consists of 25 items that measure symptoms of withdrawal. There are five subscales that assess domains of withdrawal symptoms (i.e. craving, psychological symptoms, physical symptoms, arousal disturbance, and appetite disturbance). Scores on the craving subscale have been associated with an increased likelihood of lapsing (Shiffman, Engberg, Paty, Perz, Gnys, Kassel, & Hickcox, 1997).

Positive and Negative Affect Schedule

Self-reported levels of positive and negative affect before and after the scanning session were obtained using the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988). This questionnaire consists of 10 items for positive affect and 10 items for negative affect. Participants rate their current level of an emotion (e.g. distressed, excited) on a 5-point Likert scale from 1= "very slightly or not at all", to 5 = "extremely". Scores on the negative affect items have been linked with urge to smoke, specifically in cases where smokers indicate that their desire to smoke is for negative affect relief (Leventhal, Greenberg, Trujillo, Ameringer, Lisha, Pang, & Monterosso, 2013). This study showed that baseline negative affect mediated the current state of negative affect, which was associated with higher smoking urges. Levels of positive affect and negative affect have been associated with treatment outcomes (Serafini, Malin-Mayor, Nich, Hunkele, & Carroll, 2016; Martens, Neighbors, Lewis, Lee, Oster-Aaland, & Larimer, 2008). Furthermore, this questionnaire is sensitive to changes in state affect, meaning pre-task and post-task score differences can be used to identify changes in affectivity that occur as a result of performing a task (Díaz-García, González-Robles, Mor, Mira, Quero, García-Palacios, ... & Botella, 2020).

Perceived Stress Scale

The Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1994) assesses the frequency of stressful events that have occurred in the most recent month. Participants answer questions such as "In the last month, how often have you felt nervous and 'stressed'?" according to a Likert scale with the following options: 0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, 4 = very often. This scale is used to identify how unpredictable, uncontrollable, and overloaded respondents find their lives (Cohen et al., 1994). This test has good internal validity

(Cronbach's alpha = 0.75-0.9) and tends to be moderately correlated with measures of depression and anxiety (Lee, 2012). Feelings of stress are often cited as potential motivations for relapse, and lower scores on this scale are associated with abstinence generally, and tend to increase after a failed quit attempt, and decrease after a successful quit attempt (Cohen, & Lichtenstein, 1990).

Distress Tolerance Scale

Post-scan DT was measured using the Distress Tolerance Scale (DTS; Simons & Gaher, 2005). This scale consists of 15 statements that describe how participants might feel about being in distress, and how they react towards being in distress (e.g. "When I feel distressed or upset, I must do something about it immediately"). Each question is rated on a 5-point Likert scale. The DTS has good internal validity (Cronbach's alpha = 0.84) and there are two confirmatory factor analysis models that fit the data best (Simons & Gaher, 2005). The first model, which explains 88% of variance is a one-factor model for DT. While the four-factor model of the DTS is considered to be a better fit (according to many confirmatory factor analysis metrics), there are significant correlations (r>.85) between the first-order factors, demonstrating that they co-vary strongly. Thus, we used the superordinate factor rather than the four subscales in these analyses. Averaging responses to all items of the scale yields a single value that represents self-perceived DT for each participant. Low levels of self-reported DT on this scale is correlated with self-reported external and internal barriers to quitting (Kraemer et al., 2013), is correlated with anxiety sensitivity, and leads to greater smoking volume after short term abstinence (Perkins, Karelitz, Giedgowd, Conklin, & Sayette, 2010).

Smoking Self-Efficacy Questionnaire

Smoking self-efficacy was measured using the smoking self-efficacy questionnaire (Colletti et al., 1985). This scale is comprised of 12 questions that measure the confidence in

ability to refrain from smoking when facing internal stimuli, and external stimuli. Participants rate their prospective behavior on a Likert scale with the options: not at all tempted, somewhat tempted, very tempted, and extremely tempted. Lower total scores for this scale (less temptation) are associated with successful long term cessation in smokers (Baer, Holt, & Lichtenstein 1986; Etter, Bergman, Humair, & Perneger, 2000).

Wechler Test of Adult Reading

Estimated IQ was obtained via the Wechler Test of Adult Reading (WTAR). The validity and reliability of the WTAR to estimate IQ is supported by prior literature and extensive norms are available (Matarazzo, 1972; Axelrod, 2002).

Cognitive task: the n-Back

The n-Back task was presented as a part of a larger task battery that included delayed discounting, cue reactivity, and resting state data acquisition. The n-Back procedure was comprised of the 2-Back and 0-Back. It consisted of two imaging runs that lasted for 258 seconds each. Each run contained two blocks of the 0-Back (27 seconds per block), three blocks of the 2-back (45 seconds per block), two blocks of rest (fixation cross for 27 seconds), and five 3-second instruction screens to indicate transition between blocks.

During the 2-Back task, participants were asked to view series of 15 consonants that are presented every 3 seconds. These stimuli were randomly presented as capital letters or lower-case letters via a goggle system using E-Prime software (Psychology Software Tools, 2016). Using a keypress, participants indicate whether each letter is the same as the letter presented two previously. During the 0-Back, participants were shown a target letter (i.e., H) prior to the sequence of letters and were asked to respond to upper- and lower-case letters that matched the target letter. During the rest condition, participants were asked to remain still with eyes open

while viewing a fixation cross. Our primary hypotheses used the rest condition as the control for the 2-Back, and the 0-Back condition was available for secondary analyses.

Functional Neuroimaging

Data acquisition. We used a General Electric Signa HDx 3.0T MRI scanner to obtain imaging data for each subject. Structural images were acquired for anatomical reference using a high-resolution T1-weighted SPGR sequence (voxel size = 1 mm^3, a field of view = 256^2 mm, matrix = 256^2 and axial slice thickness = 1 mm). Whole-brain echoplanar FMRI was obtained using a T2* echoplanar imaging with a single-shot gradient echo pulse sequence (TR 2500 ms, TE 25 ms, FOV = 22.5 cm, matrix = 64^2, axial slices = 3.5 mm). This procedure yielded blood-oxygen-level-dependent (BOLD) signal values across time for each voxel.

Image processing. Functional activation data was processed using Analysis of Functional NeuroImages (AFNI; Cox, 1996) software using block design protocols. The FMRI response during blocks of 2-Back data was contrasted with the blocks of data during rest periods. BOLD activation effects were averaged across voxels for each ROI, and then correlated with smoking dependence variables.

Each participant's functional images were despiked, slice time corrected, and registered over time and aligned to their anatomical dataset. Each run of data was transformed into Talairach space (Talairach & Tournoux, 1988) and spatially aligned to its third volume (i.e., registered). These data had a spatial mask applied to exclude data outside of the brain, and spatially smoothed using a 7mm full-width half-maximum 3D spatial blur.

Linear Modelling. Functional imaging data was entered into a General Linear Model (GLM) that includes regressors for each condition (0-Back, 2-Back), instruction screens, and six nuisance regressors to account for motion (x, y, and z displacement and roll, pitch, and yaw).

Using this GLM, the variance accounted for by these regressors represents a comparative effect relative to the variance attributed to the rest condition. The GLM yielded beta values for each effect in each voxel, which represents an estimation of BOLD signal change associated with performance of the task.

Quality Control

Data was visually inspected to ensure that the functional and anatomical data has been aligned properly. Volumes that had moved greater than 0.35mm along the x, y, or z axes were censored. Furthermore, volumes with greater than 10% of voxels identified as outliers were censored. Participants with greater than 30% of volumes censored were excluded from our analyses. Participants who did not perform above 50% on the 2-back or 0-back were excluded from the analysis.

Region of Interest specification

Ten regions of interest are derived from an Activation Likelihood Estimation meta-analysis of the n-Back (Wanger, 2018). These clusters represent regions that are known to be active during the n-Back and were resampled to fit the Talairach space of the BOLD data for the study. Eight of these regions are members of the frontoparietal attention network, and two belong to the salience network. Full information on the Talairach coordinates, number of voxels, expected activation, and hypotheses that reference these regions is summarized in Table 1.

Seven ROIs were generated in AFNI by forming a 5mm sphere around the central coordinates of well-known emotion-related regions and PCC. The PCC is a node of the default mode network, and the other six regions are part of the emotion processing network. Pregenual and subgenual ACC are cross listed as members of the salience network. The mean coordinates for all seven ROIs were empirically derived from a large set of neuroimaging studies (Nielsen,

2003). Full information on the Talairach coordinates, number of voxels, expected activation, and hypotheses that reference these regions is summarized in Table 1.

For these analyses, each ROI were resampled and transformed into Talairach space, and task-associated changes in BOLD FMRI signal (beta values representing the 2-Back vs rest contrast) were averaged across the voxels of each ROI. This yielded a single value per subject, per ROI, which will represent the estimated change in BOLD signal associated with performance of the 2-Back task relative to rest. This captures effects that are associated with both cognitive and emotional responses. These averaged beta values were used for group level t-tests, correlational and regression analyses to test hypotheses.

Voxel-wise activation maps

Group-level activation maps were created by contrasting the 2-Back and rest conditions. AFNI was used to perform a mass univariate analysis, in which each voxel undergoes a single sample t-test versus a hypothetical mean of zero, thresholded using a two tailed $p<0.05$. These data were corrected for multiple comparisons using AFNI's built-in false discovery rate procedure using a two-tailed alpha of 0.05. This map was examined alongside activation and deactivation maps from prior literature to compare the observed response of this sample to prior n-Back FMRI data (e.g., Owen, McMillan, Laird, & Bullmore, 2005; Loughead et al., 2015).

Statistical Analyses

Quality control

Prior to conducting hypothesis testing, assumptions for multiple linear regression (linearity, homoscedasticity, normality, independence, multicollinearity) will be assessed for all predictor variables (behavioral and self-report measures) and ROI BOLD signal estimates (Cohen, Cohen, West, & Aiken 2003). Linearity refers to the relationship between the predictors

and outcome being linear, instead of curvilinear or exponential. Linearity was assessed by plotting a non-linear best-fit line on scatter plot of the predicted value against residuals (Jacoby, 2000). If the residuals are randomly scattered around zero, this indicates linearity between the response variable and predictor variables. Homoscedasticity means having an equal level of variance in residuals across levels of the variable. The homoscedasticity of the data was also visually assessed using the scatterplot of predicted values against residuals. Linear regression also assumes that the standardized residuals are normally distributed, which was assessed visually using a Q-Q plot in SPSS (IBM Corp, 2017). Multicollinearity between variables was assessed using variance inflation factors (Hair, Anderson, Tatham, & Black, 1995). Outliers are observations that have very large residuals that disproportionately influence the linear regression model. Outliers with standardized regression residuals greater than 3 standard deviations away from the mean were identified and excluded for all predictors and BOLD signal parameter estimates. After quality control for our BOLD FMRI signal parameter estimates and predictor variables, aims were addressed using t-tests and regression analyses conducted with SPSS.

Correlations

A zero-order correlation matrix was generated for reference and reported for all self-report measures: withdrawal, craving, smoking severity, cessation, perceived stress, DT, and PANAS scores (pre-, post- and difference).

Activation & Deactivation

We tested whether each ROI is significantly active or deactive by performing single sample two tailed t-test of each. This compares all subjects' mean BOLD FMRI beta values per ROI to a hypothetical mean of zero.

Regression Analyses

Linear multiple regression is frequently used to identify associations between variables that have linear relationships (Cohen, Cohen, West, & Aiken 2003). Using univariate multiple regression, we determined whether significant changes in activity in ROIs are associated with cessation outcome, and then self-reported measures of stress. Goodness of fit (R-squared), F-values, and significance were obtained and reported for each multiple regression. Brain activation or deactivation that correlated with cessation was then entered into a stepwise multiple regression equation with other measures that significantly correlated with cessation. In backwards stepwise multiple regression models, predictor variables are removed from the model based on the Wald test statistics of the estimated coefficients (Bursac, Gauss, Williams, & Hosmer, 2008). All predictors added to the model besides BOLD signal parameter estimates (i.e., mean betas) were chosen because they exhibited significant zero-order correlations with the outcome variable. Variables that are strongly correlated with each-other ($r>0.8$), or no longer meet the significance cutoff of $p<0.05$ in the omnibus model will be removed from the model. The resultant multiple regression model demonstrates whether brain response to the n-Back adds predictive power beyond what would be predicted by other measures confirmed to be associated with cessation.

Hypothesis Testing: Aim 1

First, we examined 8 *activating a-priori* ROIs that have been associated with performance of the n-Back in prior research (summarized in Table 1). These regions are primarily nodes of the frontoparietal attention network and were hypothesized (H.1.1.) to be active during the n-Back in this sample. We tested whether each ROI is significantly active using single sample t-tests versus a hypothetical mean of zero. Then we used multiple regression

to determine whether significantly activated or deactivated ROIs are related to cessation outcome measures. Therefore eight univariate multiple regressions were conducted using a single ROI's BOLD FMRI beta values as the predictor variable, days to lapse as the outcome variable, and age, sex, and years of education as covariates.

Next, we examined one *deactivating a-priori* ROI (the PCC) that has been associated with default mode network deactivation during the n-Back (Loughead et al., 2015). While the relationship of the DMN to stress or emotional processing is not well understood, the PCC has been associated with n-Back deactivation in smokers. We attempted to replicate these findings, to assess potential links to stress processing in H.1.3. Similar to H.1.1, we tested whether the PCC was significantly deactive using a single sample t-test versus a hypothetical mean of zero. We then used multiple regression to determine whether significant activation in the PCC is related to cessation outcome measures. A linear multiple regression was conducted using the BOLD FMRI beta values from the PCC as the predictor variable, days to lapse as the outcome variable, and age, sex, and years of education as covariates.

Following these initial hypotheses, we used multiple regression to determine whether the magnitude of response to the n-Back in regions significantly associated with cessation (from H.1.1 or H.1.2) were also associated with self-reported DT, SSE, PSS, or change in positive or negative affect. Univariate multiple regressions included BOLD FMRI data as the outcome variable, a single self-report measure, age, sex, and years of education as predictors (H.1.3.).

Hypothesis Testing: Aim 2

We examined 6 *a-priori* emotion-related regions, which are thought to be deactivated during distress and cognitive processing. We tested whether there was increased suppression of emotion-related regions (H.2.1.) We tested whether each ROI was significantly deactive with

single sample two tailed t-tests versus a hypothetical mean of zero. Then we used multiple regression to determine whether significantly activated or deactivated regions were related to cessation outcome measures. Therefore, six univariate multiple regressions were conducted using a single ROI's BOLD FMRI beta values as the predictor variable, days to lapse as the outcome variable, and age, sex, and years of education as covariates.

We also tested activation of 2 salience network regions, left and right insula (H.2.2.). We tested whether each region was significantly active using single sample two tailed t-tests versus a hypothetical mean of zero. Then we used two univariate multiple regressions with BOLD FMRI beta values from an ROI as the predictor variable, days to lapse, and age, sex, and years of education as covariates. As with H.1.2, we then tested whether activation of regions significantly associated with outcome were also associated with self-reported DT, SSE, PSS, or change in positive or negative affect.

Hypothesis Testing: Aim 3

Prior work has shown that smoking volume and FTND scores are able to predict cessation (Kozlowski et al, 1994). We entered cigarettes per day, FTND, and other variables that significantly correlated with outcome with the BOLD FMRI parameter estimates for regions that were associated with outcome into two stepwise linear regression models that predicting days to relapse and abstinence. These analyses determined if the brain regions provided additional predictive power beyond self-report measures.

Hypothesis Testing: Exploratory Aim

Days to lapse served as our primary cessation outcome measure for Aims 1, 2 and 3. However, we also entered the FMRI BOLD beta values for each ROI into multiple regressions

with time until full relapse and successful abstinence as alternate outcome measures. For abstinence, we used binary logistic regressions due to the dichotomous nature of the variable.

Power analysis

Loughead et al. (2015) examined FMRI activation during the n-Back and correlated activation in working memory-related ROIs (DLPFC, medial frontal gyrus, posterior cingulate cortex, and ventromedial frontal cortex) with abstinence. They found that reduced left DLPFC activation during the n-Back was correlated with lapsing (odds ratio=0.14, p=0.02). In order to calculate the needed power for our experiment, we used the left DLPFC results obtained by their study as an estimate of the effect size we expected to find. We used G*Power v3.1.9.4 (Faul, Erdfelder, Lang, & Buchner, 2007) to determine the required sample size (n=37) to detect similar effects in our sample, using a logistic regression z-test for an alpha of 0.05.

CHAPTER 3

RESULTS

Quality Control

Assumptions of linearity, homoscedasticity, normality, independence, and multicollinearity were tested and met for the variables of each multiple regression. No outlier data were observed in standardized regression residuals for our multiple regression analyses. Two participants were excluded due to below-chance performance during the 2-Back. Additionally, bilateral ventromedial prefrontal cortex and subgenual anterior cingulate cortex ROIs were excluded due to unreliable or lack of BOLD signal.

Sample Characteristics

Demographic information for the final set of 48 subjects is presented in Table 2. The study sample were middle-aged adults between the ages of 20 and 61 (M = 40.8 years, SD = 11.6). It was comprised of 31 males and 17 females that were ethnically diverse: 34 were Caucasian (71%), 12 were African American (25%), and 2 were multiracial (4%). Participants had an average of 13.4 years of education (SD = 2.4), where 12 years is equivalent to graduating high school or passing the General Educational Development test. The intelligence of sample was estimated to be 100.7 (SD = 15.5) from the Wechsler Test for Adult Reading.

Behavioral Performance and Self-Report Measures

Behavioral performance and self-report measures are shown in Table 3. Participants performed at above-chance levels on the n-Back. Percentage of correct responses averaged 97.2% (SD = 2.9) on the 0-Back and 81.7% (SD = 10.5) on the 2-Back. The average days to lapse was 12.1 (SD = 19.9), days to relapse was 24.2 (SD = 23.4), and abstinence was achieved

in 21 smokers (43.8%). Our study sample smoked an average of 22.6 cigarettes per day (SD = 14.2) and reported scores on the Fagerstrom Test for Nicotine Dependence (M = 5.00, SD = 2.55), indicating a moderate level of addiction. Scores for the Minnesota Nicotine Withdrawal Scale (M = 1.97, SD = 0.67), Shiffman-Jarvik Withdrawal Scale – Craving Subscale (M = 26.3, SD = 29.5), Distress Tolerance scale (M = 3.44, SD = 0.82), Perceived Stress Scale (M = 2.63, SD = 0.54), and Smoking Self-Efficiency Questionnaire (M = 3.03, SD = 1.13). Participants reported positive and negative affect before and after performance of the n-Back. We calculated average change in positive affect (M = -0.16, SD = 0.53) and negative affect (M = 0.06, SD = 0.32) that occurred during the scanning session.

Functional Neuroimaging Measures

Group Summary Response

The group-level whole-brain voxelwise brain response map is shown in Figure 2 and summary information for ROIs is in Table 1. As noted above, two regions were excluded from hypothesis testing because of significant data loss due to susceptibility artifact. An average of 38% of voxels in subgenual ACC, and 80% of voxels in bilateral VMPFC ROIs contained no data. We observed significant activation in all regions we predicted to be activated, and significant deactivation in all regions we predicted to be deactivated (Figure 2). Each ROI overlapped fully with the observed whole-brain voxel-wise map, such that all included voxels were significantly active or deactive. Consistent with the whole-brain voxel-wise results, the mean activation or relative deactivation response of each included *a-priori* ROI was significant (see Table 4).

Hypothesis testing

All initial zero-order correlations

Zero order correlations among all key study variables are presented in Tables 5 and 6. We hypothesized that greater activation in nodes of the frontoparietal and anterior salience networks (H.1.1 & H.2.2.), as well as greater deactivation in nodes of emotion processing and default mode networks (H.1.2. & H.2.1.) would be associated with better cessation outcomes. Correlations with our primary outcome, days to lapse, were examined first. After finding that no regions were significantly associated with days to lapse, we examined the zero-order correlations of days to relapse and complete abstinence. They indicated that less deactivation of right amygdala activity was associated with lower likelihood of abstinence $r(48) = -0.328$, $p = 0.012$; less deactivation of left amygdala was associated with lower likelihood of abstinence $r(48) = -0.321$, $p = 0.013$; and less deactivation of the PCC was associated fewer days to relapse $r(48) = -0.285$, $p = 0.05$.

Regressions including ROIs, covariates (age, sex, education)

When including age, sex, and education as covariates in multiple regressions with individual brain regions, the associations between brain regions and cessation outcomes were no longer observed. Instead, we found that age was negatively associated with days to lapse, and education was associated with days to lapse, days to relapse, and abstinence. These effects were seen in all linear multiple regressions (days to lapse & days to relapse) and binomial logistic regressions (abstinence) regardless of brain region entered into the model (Tables 7-12). Furthermore, no new associations with cessation were discovered when performing multiple regressions that included age, sex, and education. As a result, regions identified in bivariate zero-order correlations were used for the remaining hypotheses (H.1.3, H.2.3., H.3.1).

Regressions including significantly active ROIs and stress-related variables

We used linear multiple regression to determine whether self-reported measures of distress tolerance, perceived stress, smoking self-efficacy, and change in positive or negative affect are related to BOLD response in the PCC, right amygdala, and left amygdala (H.1.3 & H.2.3). These regressions did not identify any associations that were not previously identified by bivariate zero-order correlations. A summary of these regressions can be found in Tables 13-15. Two cessation outcome types were associated with deactivating brain regions, demographic and self-report measures. This necessitated the use of two backwards stepwise regressions (linear and logistic) to determine whether PCC, right amygdala, and left amygdala predict cessation beyond self-report predictors derived from our data (H.3.1).

The first backwards stepwise linear regression included the brain response of the PCC, CPD, FTND score, SCS score, and years of education. The final model included only FTND (standardized $\beta = -0.508$, $p < .001$, $R^2 = 0.258$). These results demonstrate that higher FTND scores are associated with earlier relapse. A full summary of each step of this regression can be found in Table 16.

The second backwards stepwise binary logistic regression included the brain response of the left amygdala, right amygdala, CPD, FTND score, SCS score, and years of education. The final model included both FTND and right amygdala ($p < .001$, Cox & Snell $R^2 = 0.306$). In this model, higher FTND scores (standardized $\beta = -0.532$, $p = .004$) and greater right amygdala activity (standardized $\beta = -0.120$, $p = .031$) were associated with a lower likelihood of abstinence. A full summary of each step of this regression can be found in Table 17.

CHAPTER 4

DISCUSSION

The present study examined responses to a cognitive stressor in brain regions associated with cognitive and emotional processing to determine whether they are related to successful outcomes during a smoking cessation intervention. Previous studies have identified several self-report measures that are associated with cessation, and elaborate brain-based models have been proposed to explain these relationships (Robinson & Berridge, 1993, Volkow et al., 2016). In this study, we quantified BOLD response to a stressful cognitive task (the n-Back) to determine whether the strength of response would predict subsequent smoking cessation.

Overall, smoking cessation rates were high and brain and behavioral responses were consistent with prior n-Back literature, with all ROIs responding significantly in the predicted directions. We found mixed support for hypotheses about regions associated with cognitive function (H.1.1, H.1.2) and hypotheses regarding emotion-related regions (H.2.1, H.2.2). Specifically, none of the task-related regions that have previously been associated with activation during the n-Back (Owen et al., 2005; Wanger, 2018) were related to cessation outcomes, which was contrary to our hypotheses. The only cognition-related region associated with cessation was the suppression of the PCC, in agreement with one of our hypotheses (H.1.2.) and prior findings (Loughead et al, 2015). In emotion-related regions, we observed bilateral suppression effects in the amygdala and the magnitude of each ROI was significantly associated with higher likelihood of abstinence, which supports our hypothesis (H.2.1.). None of the three significant neuroimaging predictors of outcome were associated with self-reported measures of distress

tolerance, stress, affect, or smoking self-efficacy (H.1.3.). After accounting for known significant predictors of smoking cessation outcome, the suppression observed in the right amygdala accounted for unique variance in subsequent abstinence, supporting H.2.1.

Responses to the n-Back

Brain and behavioral responses to the n-Back task appeared to be valid, as they were consistent with prior literature and followed predictions in terms of direction and significance. As expected, we observed activation during the n-Back in a broad frontoparietal network (Figure 2). This activation pattern has been demonstrated for the n-Back through meta-analysis of healthy controls (Owen et al., 2005, Wanger 2018), as well as prior studies of smokers (Sweet et al., 2010). Additionally, we also observed expected widespread deactivation in limbic regions and resting state networks, such as the DMN. This deactivation resembles the BOLD activation response to stress, which has been reported in prior research using stress-inducing tasks such as the Trier Social Stress Task and Montreal Imaging Stress Task (Dedovic et al., 2009a, Dedovic et al., 2009b). Behavioral performance on the 2-Back was also consistent with prior literature (Braver, Cohen, Nystrom, Jonides, Smith, & Noll, 1997), including smokers (Sweet, et al., 2010).

Hypothesis testing

BOLD response to n-Back in the PCC, but not task-activated regions, is associated with days to relapse

We did not find support for the hypothesis that task-positive regions activated during the n-Back would be associated with outcome (H.1.1.). This may be due to differences in the experimental design of our study and a prior study that demonstrated that relapse was predicted by decreased left DLPFC signal (Loughead et al. 2015). Loughead et al. used a 3-Back, which is

a more challenging working memory task. In the past, the DLPFC has shown to have working memory load effects (Yun et al., 2010). This may have led to an increase in signal for task-positive regions that are related to working memory demands, and likely reduced performance. These differences may have introduced variance in DLPFC that the present study was unable to capture.

Another significant difference is that Loughead et al.'s participants had been abstinent for three days prior to their neuroimaging session. Previous work has shown that smokers who are in a state of satiety perform the 2-Back at a level comparable to healthy controls, and have worse performance when they have been abstinent leading up to the scanning session (Mendrek, Monterosso, Simon, Jarvik, Brody, Olmstead, ... & London, 2006). Smokers who have briefly been abstinent before performing the n-Back display weaker responses in the n-Back's task-active regions, and reduced suppression in default mode network regions (Falcone, Wileyto, Ruparel, Gerraty, LaPrate, Detre, ... & Lerman, 2014). This pattern is corroborated by functional connectivity research that has demonstrated that the cross-network correlations between the salience network and both the task-positive network and default mode network are weaker in abstinence compared to smoking satiety (Lerman, Gu, Loughead, Ruparel, Yang, & Stein, 2014). Therefore, if brain responses in task-active regions that correlate with outcome are strongly mediated by being in a state of abstinence, our experiment may not have been sensitive to these effects.

We observed that activity in the PCC was inversely related to days to relapse, supporting our hypothesis (H.1.2). Because activity in the PCC decreased in response to the n-Back, greater magnitude of relative deactivation in the PCC was associated with greater success. This finding is similar to Loughead et al.'s study (2015), which found an association between PCC

suppression and a lower likelihood of lapsing within the first 7 days of a quit attempt. However, the results of the current study extend the previous findings by demonstrating this effect in smoking satiety.

The PCC is a well-documented node in the default mode network, which has been theorized to mediate shifts in attention toward goal directed behavior (Small, Gitelman, Gregory, Nobre, Parrish, & Mesulam, 2003). Prior work has demonstrated that activity in the salience network positively correlates with the task-positive network and negatively with the default mode network (Menon & Uddin, 2010). This coupling is thought to reflect the salience network's ability to direct cognitive resources toward internal stimuli (default mode processing) or external stimuli (task-positive network) based on motivational relevance. In healthy controls, these networks are anticorrelated (Fox, Snyder, Vincent, Corbetta, Van Essen, & Raichle, 2005), with higher activity in the salience network being associated with greater task-positive network activity and reduced activity in the default mode network.

Weaker anticorrelations between the salience network and default mode network has been demonstrated in children with Attention Deficit Hyperactivity Disorder (Fassbender, Zhang, Buzy, Cortes, Mizuiri, Beckett, & Schweitzer, 2009). Less effective suppression of activity in the default mode network was speculated as a potential mechanism for greater distractibility (Fassbender et al., 2009. One consequence of failure to suppress the PCC may be the inability to maintain focus on a goal-directed task such as the n-Back. Moreover, as suggested by Loughead et al., this may also apply to the goal of maintaining abstinence over time. However, participants in this study demonstrated strong performance on the n-Back, which may have been possible because they were allowed to smoke prior to the scanning session.

With regard to early models of addiction, the PCC may contribute to incentive salience by biasing attention towards smoking-related stimuli associated with reward. Brain response in the nucleus accumbens towards drug cues has been demonstrated to positively correlate with PCC activity (Dagher et al., 2009). Since PCC activity is typically deactivated during cognitive tasks, this indicates that smokers with less deactivated PCC may have greater drug cue induced reactivity in reward regions. Alternatively, the PCC may be associated with ruminative thoughts about future smoking. Rumination has been linked to earlier lapses, which may occur as a result of negative affect, craving, and withdrawal (Nosen & Woody, 2014). Our findings demonstrate that the PCC is a predictor of cessation, even in smoking satiety, and should be considered in future studies designed to examine cognitive distress tolerance, reward, and rumination.

BOLD response to n-Back in bilateral amygdala is associated with abstinence

Participants who exhibited greater deactivation of amygdala activity during successful performance of the n-Back were more likely to successfully abstain, supporting our hypothesis (H.2.1). This finding is similar suppression of the PCC (H.1.2), though it is not clear whether the suppression of activity in these regions is mediated by the same, or different pathways. Elevated amygdala activation occurs when viewing smoking cues, and is attenuated through extinction-based treatment, leading to successful cessation (McClernon, Hiott, Liu, Salley, Behm, & Rose, 2007). This is evidence that the amygdala is strongly engaged in emotional stimulus perception but maintains a low baseline level of function that may be important to suppress during cognitive tasks. In the context of stressful social and cognitive tasks, widespread deactivation of limbic regions is thought to be specifically related to the suppression of negative emotionality of the social-evaluative aspect of the MIST (Dedovic et al, 2009a; Dedovic et al. 2009b). However, because the n-Back does not have an explicit social element, these effects are likely due to

frustration encountered when performing the cognitive challenge. We suggest that a common underlying factor that could explain the similar activation between stressful social and cognitive tasks is emotion regulation, rather than social engagement.

Potential functions of the amygdala in addiction have been explored in studies that use pharmacotherapies to curtail withdrawal symptoms. Varenicline is a pharmacotherapy that is thought to aid in cessation by ameliorating abstinence-induced withdrawal symptoms. In one study, administration of varenicline was shown to modify the resting-state functional connectivity between the amygdala and insula, as well as between the insula and the default mode network, but only in abstinent smokers (Sutherland, Carroll, Salmeron, Ross, Hong, & Stein, 2013). These findings were not observed in control subjects, which indicates that withdrawal may be mediated in part by the interactions of the insula, amygdala, and default mode network. One proposed mechanistic explanation for these network interactions is that salience network nodes mediate the identification of appetitive stimuli and coordinate with the default mode network to pursue a course of action that responds to the stimuli appropriately.

Relationships between outcome-associated brain response and self-report

In order to contextualize the brain response to the n-Back as a function of self-reported stress, we examined bivariate correlates of regions that were significantly associated with cessation (H.2.3). We observed that bilateral amygdala responses were inversely associated with smoking self-efficacy. Participants who reported greater smoking self-efficacy tended to exhibit greater suppression of the bilateral amygdala. Conceptually, this measures smokers' perceived attitudes about how well they can resist cravings and is worse in smokers with greater negative affect (Gwaltney, Shiffman, Balabanis, & Paty, 2005). We found a significant inverse relationship between smoking self-efficacy and both pregenual cingulate cortex and bilateral

amygdala activation. Prior work has shown that the pregenual anterior cingulate is associated with self-efficacy (Ono et al., 2018), resisting craving, regulating negative emotion (Brody, Mandelkern, Olmstead, Jou, Tiongson, Allen, ... & Korb, 2007), and lower relapse rate (Bandura, Freeman, & Lightsey, 1997). In the broader context of our study, more efficient deactivation of emotion and salience regions would be associated with less attention allocation toward drug-related stimuli during a stressful cognitive task.

Demographic variables associated with cessation

Unrelated to our aims, we observed that several measures of smoking severity (CPD, FTND, craving) were strongly associated with outcome, and distress tolerance. These findings confirm prior literature, which has identified these as potent predictors of outcome (Kozlowski et al., 1994). Furthermore, years of education were associations with all cessation outcomes, several measures of smoking severity, and brain response. Correlations between age and days to lapse, cigarettes per day, and change in negative affect were observed. Older participants smoked more cigarettes per day and were more likely to lapse early. Additionally, older participants were less likely to report an increase in negative affect after performance of the n-Back. Due to the strong effects of age and education in predicting outcome that were identified from multiple regression, these factors will be discussed.

Non-smoking elderly individuals have been observed to have lower levels of negative affect as they age (Mroczek, & Kolarz 1998). These lower levels of negative affect may be a more stable baseline as the result of experiencing fewer stressful events per day in older populations (Charles, Luong, Almeida, Ryff, Sturm, & Love, 2010), but one interpretation of our findings is that older smokers are desensitized to stressful events and situations that are less severe than withdrawal. In older smoking populations, higher levels of depressive symptoms are

observed (Colsher, Wallace, Pomrehn, LaCroix, Cornoni-Huntley, Blazer, ... & Hennekens, 1990), and greater levels of depressive symptoms are associated with a lower likelihood of cessation (Kenney, Holahan, Holahan, Brennan, Schutte, & Moos, 2009). This comorbidity might suggest that smoking is used as a coping mechanism to alleviate negative affect. This is supported by research indicating that negative reinforcement is a stronger motivator than positive reinforcement when compared to younger adults (Oei, Tilley, & Gow, 1991).

We observed differential brain response associated with age, with older participants exhibiting less deactivation in PCC, pregenual ACC, and right amygdala. These findings suggest that older individuals may have more difficulty in suppressing or suspending default mode and limbic regions activity when performing challenging cognitive tasks. These regions have been implicated in prior research as being involved in the processing of emotional experiences (Bush, Luu, & Posner, 2000), self-referential thought and emotion regulation (Leech et al., 2011; Goldin et al., 2008). This may indicate that older populations are more likely to have negative emotional experiences when under stress, when these thoughts could be considered detrimental toward performance of an active task.

Education was also observed to be strongly related to measures of smoking cessation, in agreement with prior literature (Wetter, Cofta-Gunn, Irvin, Fouladi, Wright, Daza, ... & Gritz, 2005). More years of education was associated with longer time to lapse, relapse, and a higher chance of abstinence. Socioeconomic factors were proposed by Wetter et al. (2005) to explain these findings, though psychological factors such as stress, income, and social factors require more research. We observed a moderate correlation between education and self-reported distress tolerance, and associations with both cognitive (right DLPFC, PCC) and emotion-related regions (bilateral anterior insula, bilateral amygdala). We followed up these bivariate correlations with a

mediation model to test whether PCC BOLD response to the n-Back task mediated the effect of education on smoking outcome, but the results were non-significant. Future research could examine the effects of education on brain response during cognitive tasks, and other covariates to determine how these factors may be related to successful cessation.

Incremental predictive validity

We found that smoking severity (FTND score) and amygdala response predict subsequent smoking cessation above and beyond other variables. Many prior studies have found links between cessation and various demographic, self-report, behavioral, and brain response (Brown et al., 2002; Brown et al., 2005, Loughead et al., 2015). Our findings are in agreement with the broader literature. We observed significant bivariate correlations between cessation and CPD, FTND, SCS, amygdala, and posterior cingulate. However, only FTND and amygdala activation survived a backwards stepwise regression onto abstinence. It's possible that the variance shared between CPD, SCS, and FTND are best encapsulated by FTND, while the variance associated with amygdala activity is unique. This may indicate that the function of the amygdala could be distinct from the factors represented by the FTND scale. The FTND scale items are skewed towards measuring smoking volume, the urge to smoke immediately in the morning after waking up, and the urge to smoke in cases where it might be inappropriate or unhealthy. Broadly speaking, these seem to be measures of the compulsion to smoke. Interestingly, the only self-report measure we observed as related to amygdala activation was the smoking self-efficacy questionnaire, which measures the smoker's perceived ability to resist the temptation to smoke in the face of internal stimuli (e.g., when depressed, anxious, angry) or when in normative smoking circumstances (e.g., when celebrating something, after a meal, when drinking beer). Therefore, we suggest that the amygdala activity, which is associated with levels

of smoking self-efficacy and smoking cessation, may modulate the urge to smoke under various social or emotional circumstances, where FTND is a measure of the physical dependence and craving for nicotine.

Strengths, limitations, future directions

This study had strengths and weaknesses to consider when interpreting findings and could be improved for future investigations into the neural correlates of cognitive distress tolerance in smokers. The study's smoking cessation intervention was thorough and successful, with 22 of 48 participants maintaining abstinence for the full duration of the experiment. Responses to the n-Back were robust and consistent with prior literature (Owen et al, 2005; Wanger 2018), all self-report measures were normally distributed and met parametric statistical assumptions for multiple regression testing. Our sample population was diverse, and overall representative of the broader population of smokers in terms of age, gender, and other demographic variables. This study also provides a novel contribution to literature by identifying suppression during the n-Back in satiated smokers, which opens new avenues to study predictors of cessation using cognitive tasks. While some of our hypotheses were not fully supported, our findings reveal broad, consistent, and coordinated network activity in response to a stressful cognitive task.

One weakness of the study was the lack of a behavioral measure of distress tolerance, which would measure the persistence of smokers to perform a task while under distress. This measure does not significantly correlate with self-reported measures of distress tolerance, which capture a smoker's perceived sensitivity to distress (McHugh, Daughters, Lejuez, Murray, Hearon, Gorka, & Otto, 2011). Future studies examining DT as a construct would benefit from the inclusion of both measures, as it is currently unclear which method is the better predictor of

behavioral outcomes. Furthermore, we were unable to directly tie self-report measures to brain regions associated with outcome. Future work is needed to validate psychological factors that are related to, or mediate, these findings. We did not observe statistically significant changes in positive or negative affect, which agrees with prior literature (Parmenter et al., 2006) even though participants often report the n-Back as being stressful. We observed a decrease in positive affect, and an increase in negative affect after performance of the n-Back, but the effect sizes were very small and did not reach significance. Future studies could utilize more reliable measures of stress, such as hormonal measurement of serum cortisol to demonstrate the stressful nature of the n-Back.

Additionally, we did not observe a significant brain response that was related to our primary outcome measure, days to lapse. Using secondary outcomes with less variance may have led to Type 1 errors despite each measure having its own unique and meaningful ecological validity. We observed high intercorrelation between days to relapse and abstinence, which suggests that future studies should use only one of the two measures. The sample size in the present study was well-powered to detect strong and medium effect sizes but may not have been able to detect small effect sizes. Another potential limitation of this study is the ratio of men to women, which was 31:17. These findings may be less generalizable to women. Sex effects in brain regions have been identified during cognitive reappraisal of emotional stimuli (Domes, Schulze, Böttger, Grossmann, Hauenstein, Wirtz, ... & Herpertz, 2010), smoking cue reactivity (McClernon, Kozink, & Rose, 2008), resting state network activity (Beltz, Berenbaum, & Wilson, 2015), and default mode network suppression (Dumais, Chernyak, Nickerson, & Janes 2018). Potential sex effects are worthwhile to investigate in future studies examining addiction.

Future studies would benefit from using both cognitive and emotional distress tolerance tasks to test how different types of distress are reflected in these responses. Additionally, the precise relationship between the networks (salience, default mode, and task-positive) should be explored further in the context of both smoking satiation and brief abstinence. The prevailing view is that nodes of the salience network are responsible for mediating the activation or suppression of brain response in the other networks, however this should be verified using causal analyses. We did not observe direct evidence of a region clearly suppressing limbic regions, or the PCC – and inferences of this process may overlook alternate explanations for these effects.

Conclusions

Basic measures of smoking severity such as cigarettes per day and FTND score are reliable indicators of the likelihood to relapse. In this study, we observed that less deactivation of the PCC and bilateral amygdala lead to worse cessation outcomes in smokers. This suggests that both cognitive and emotion-related systems may potentially mediate smoking cessation. With this study, we demonstrated that brain response to a cognitive distress tolerance task provides additional predictive utility for abstinence. While the underlying function of these brain-based activation patterns are unresolved by our findings, they warrant future research. The findings reported here may be important for understanding the social, cognitive, or emotional factors that contribute to the development of or maintenance of substance abuse – and importantly, attempts at smoking cessation.

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TABLE 1

Summary Information for Regions of Interest.

	Talairach Coordinates (center of mass)					Expected direction	Aim &	
Region Name	x	y	z	# Voxels	ROI type	of response	Hypothesis	Network
L DLPFC	-45	9	35	138	cluster	+[12]	H.1.1.	Frontoparietal Attention
R DLPFC	-37	-37.1	25.8	121	cluster	+[1]	H.1.1.	Frontoparietal Attention
R premotor	-29.7	1.1	52	74	cluster	+[1]	H.1.1.	Frontoparietal Attention
L premotor	28	2	53	67	cluster	+[1]	H.1.1.	Frontoparietal Attention
Bilateral SMA	1.7	-12.2	47.9	115	cluster	+[1]	H.1.1.	Frontoparietal Attention
L frontal	36.4	-46.1	14.1	30	cluster	+[1]	H.1.1.	Frontoparietal Attention
R Inferior Parietal Lobule	-33.5	55.1	42.5	186	cluster	+[1]	H.1.1.	Frontoparietal Attention
L Inferior Parietal Lobule	35.9	52.9	38.9	176	cluster	+[1]	H.1.1.	Frontoparietal Attention
PCC	0	43.7	25.4	10	sphere	-[2]	H.1.2.	Default Mode
R amygdala	-21	6.2	-14.5	12	sphere	-[3]	H.2.1.	Emotion Processing
L amygdala	21	6.2	-14.5	12	sphere	-[3]	H.2.1.	Emotion Processing
R VMPFC	-12.2	-35.8	-15.4	8	sphere	-[3]	H.2.1.	Emotion Processing
L VMPFC	12.2	-35.8	-15.4	8	sphere	-[3]	H.2.1.	Emotion Processing
R INS	-31.7	-19.2	1.9	58	cluster	+[1]	H.2.2.	Salience
L INS	31.1	-19.7	2.7	71	cluster	+[1]	H.2.2.	Salience
pregenual ACC	0	-42.8	8.6	20	sphere	+[3]	H.2.2.	Salience, Emotion Processing
subgenual ACC	0	-21.6	-7.5	26	sphere	+[3]	H.2.2.	Salience, Emotion Processing

Note. Information for each region of interest (ROI) includes: center of mass Talairach coordinates (x, y, and z), number of 3.5mm^3 voxels, ROI type (cluster = meta-analysis derived; sphere = manually created using database coordinates), expected relative activation and source supporting inclusion of this region (+ denotes activation; - denotes deactivation; [1] = Wanger, 2018; [2] = Loughead et al. 2015; [3] = Nielsen, 2003), Aim and Hypothesis that involves specified region, and brain network membership. Region abbreviations include: L (left), R (right), DLPFC (dorsolateral prefrontal cortex), SMA (supplementary motor area), PCC (posterior cingulate cortex), VMPFC (ventromedial prefrontal cortex), INS (insula), ACC (anterior cingulate gyrus).

TABLE 2

Descriptive Statistics for Participants

Demographic variables		
	mean	*SD*
Age (years)	40.8	11.6
Education (years)	13.4	2.11
Estimated IQ	100.7	15.5
Gender	*N*	*percent*
male	31	65%
female	17	35%
Race/Ethnicity		
White	34	71%
Black / African American	12	25%
Multiracial	2	4%

Note. Summary of descriptive statistics for participants. IQ = intelligence quotient, SD = standard deviation.

TABLE 3

Summary of Behavioral Performance and Self-Report Data

Behavioral Performance	mean	SD
0-Back % correct	97.2	2.9
2-Back % correct	81.7	10.5
Self-report		
Abstinence (n = 21, 43.8%)	-	-
Days to lapse	12.1	19.9
Days to relapse	24.2	23.4
Cigarettes per day	22.6	14.2
Fagerstrom Test for Nicotine Dependence score	5.00	2.55
Minnesota Nicotine Withdrawal Scale score	1.97	0.67
Shiffman Craving Scale score	26.3	29.5
Distress Tolerance Scale score	3.44	0.82
Smoking Self-Efficacy Questionnaire score	3.03	1.13
Perceived Stress Scale score	2.63	0.54
Change in Positive Affect	-0.16	0.53
Change in Negative Affect	0.06	0.32

Note. Summary of behavioral performance and self-report measures. This table contains the number and percentage of participants who maintained abstinence for the duration of the study. Mean and standard deviations (SD) are reported for 0-Back and 2-Back performance, days to lapse, days to relapse, cigarettes per day, scores for the Fagerstrom Test for Nicotine Dependence, Shiffman Craving Scale, Distress Tolerance Scale, Smoking Self-Efficacy Questionnaire, and change in Positive Affect and Negative Affect measures of the Positive and Negative Affect Schedule.

TABLE 4

Significance of Brain Response in Regions of Interest

Region of Interest	*df*	*mean z-scores*	*t-value*	*p-value*
Left dorsolateral prefrontal	48	16.70	9.44	< .001
Right dorsolateral prefrontal	48	13.94	8.41	< .001
Left premotor area	48	15.23	9.10	< .001
Right premotor area	48	10.58	10.43	< .001
Supplementary motor area	48	18.51	9.99	< .001
Left frontal pole	48	11.89	10.00	< .001
Right inferior parietal lobule	48	14.25	11.14	< .001
Left inferior parietal lobule	48	14.03	10.67	< .001
Posterior Cingulate	48	-22.48	19.41	< .001
Pregenual Anterior Cingulate	48	-14.75	10.60	< .001
Left Anterior Insula	48	8.85	5.91	< .001
Right Anterior Insula	48	8.30	6.81	< .001
Left Amygdala	48	-6.62	6.73	< .001
Right Amygdala	48	-6.52	7.31	< .001

Note. df = degrees of freedom. β = beta values from general linear modeling of the blood-oxygen-level-dependent (BOLD) brain response.

TABLE 5

Bivariate Zero-order Correlation Matrix for Aim 1

	Demographic			Outcome			Severity of Addiction				Self-Report					Brain Region Response								
	D1	*D2*	*D3*	*O1*	*O2*	*O3*	*S1*	*S2*	*S3*	*S4*	*R1*	*R2*	*R3*	*R4*	*R5*	*B1**	*B2**	*B3**	*B4**	*B5**	*B6**	*B7**	*B8**	*B9***
D1	1	-0.14	0.22	-0.07	0.06	0.05	-0.16	-0.12	-0.02	0.10	0.05	-0.23	0.25	0.02	0.15	0.14	0.36	0.19	0.21	0.13	0.19	0.10	0.15	-0.04
D2		1	-0.19	**-0.33**	-0.25	-0.22	**0.35**	0.20	0.15	0.07	-0.25	0.08	-0.07	0.08	**-0.34**	-0.06	-0.15	-0.13	-0.22	-0.06	-0.11	0.10	-0.03	**0.40**
D3			1	**0.33**	**0.40**	**0.44**	**-0.29**	**-0.46**	-0.06	-0.22	0.24	**0.44**	-0.13	-0.18	0.20	0.10	0.32	0.02	0.22	**0.39**	0.16	0.23	-0.06	**-0.30**
O1				1	**0.62**	**0.58**	**-0.29**	**-0.48**	-0.18	**-0.29**	0.12	0.26	-0.19	-0.06	-0.04	-0.02	0.05	0.01	-0.07	0.10	0.01	0.00	-0.05	-0.18
O2					1	**0.94**	**-0.33**	**-0.52**	-0.12	**-0.44**	0.06	0.24	-0.13	-0.13	0.20	0.06	0.03	0.09	0.18	0.09	-0.16	0.05	0.01	**-0.26**
O3						1	**-0.29**	**-0.48**	-0.09	**-0.39**	0.12	0.27	-0.15	-0.17	0.13	0.10	0.11	0.04	0.24	0.18	-0.06	0.08	0.05	-0.23
S1							1	**0.63**	0.09	**0.52**	0.07	-0.31	-0.22	-0.05	-0.29	-0.22	-0.07	-0.12	-0.09	-0.06	-0.19	-0.13	-0.16	0.23
S2								1	.280*	**0.50**	-0.01	**-0.33**	0.11	0.10	-0.12	0.01	-0.12	-0.06	0.08	-0.11	-0.06	-0.17	-0.04	0.06
S3									1	0.14	-0.21	**-0.34**	**0.33**	0.09	0.25	0.00	-0.14	0.04	0.09	-0.04	-0.17	0.03	0.06	0.02
S4										1	0.04	**-0.46**	0.15	0.13	-0.02	-0.22	-0.02	-0.13	-0.06	0.04	-0.03	0.08	-0.21	0.06
R1											1	0.02	-0.06	-0.21	0.19	-0.11	0.07	-0.07	0.02	-0.02	0.23	-0.10	-0.09	-0.24
R2												1	**-0.56**	0.13	-0.08	0.11	0.14	-0.02	0.12	**0.37**	0.22	0.20	-0.05	-0.21
R3													1	-0.09	0.16	0.02	-0.06	0.21	0.07	-0.25	0.05	0.02	0.24	0.16
R4														1	0.20	-0.11	-0.08	-0.09	-0.09	0.08	0.09	-0.03	0.06	0.07
R5															1	-0.11	-0.10	0.10	-0.05	-0.17	-0.20	-0.03	-0.05	-0.18
*B1**																1	**0.50**	**0.50**	**0.68**	**0.50**	**0.44**	**0.54**	**0.61**	0.18
*B2**																	1	**0.59**	**0.54**	**0.72**	**0.68**	**0.41**	**0.48**	-0.06
*B3**																		1	**0.38**	**0.38**	**0.34**	**0.46**	**0.43**	0.02
*B4**																			1	**0.54**	**0.36**	**0.41**	**0.52**	-0.23
*B5**																				1	**0.65**	**0.56**	**0.34**	0.02
*B6**																					1	**0.37**	**0.56**	0.12
*B7**																						1	**0.28**	0.23
*B8**																							1	0.20
*B9***																								1

Note. * = H.1.1. ; ** = H.1.2. ; **Bold** = Benjamini-Hochberg corrected 1-tailed p-value < .05; Demographic variables (D) include: 1.gender, 2.age, 3.education ; Outcome variables (O) include 1.days to lapse, 2.days to relapse, 3.abstinence ; Severity of addiction variables (S) include 1.cigarettes per day, 2.Fagerstrom Test for Nicotine Dependence score, 3.Minnesota Nicotine Withdrawal Scale score, 4.Shiffman Craving Scale score ; "Self-Report" scores (R) include: 1.Smoking Self-Efficacy Questionnaire, 2.Distress Tolerance Scale, 3.Perceived Stress Scale, 4. Change in Positive Affect, 5. Change in Negative Affect ; Brain Region Response variables (B) include 1.Left dorsolateral prefrontal cortex, 2.Right

inferior parietal lobule, 3.Left inferior parietal lobule, 4.Supplementary motor area, 5.Right dorsolateral prefrontal cortex, 6.Right premotor area, 7.Left frontal pole, 8.Left premotor area, 9.Posterior cingulate cortex.

TABLE 6

Bivariate Zero-order Correlation Matrix for Aim 2

Demographic			Outcome			Severity of Addiction				Self-Report					Emotion-related Brain Region Response					
	D1	*D2*	*D3*	*O1*	*O2*	*O3*	*S1*	*S2*	*S3*	*S4*	*R1*	*R2*	*R3*	*R4*	*R5*	*E1**	*E2**	*E3***	*E4***	*E5***
D1	1	-0.14	0.22	-0.07	0.06	0.05	-0.15	-0.12	-0.02	0.10	0.05	-0.23	0.25	0.02	0.15	0.20	0.26	0.14	0.01	0.02
D2		1	-0.19	**-0.33**	-0.25	-0.22	**0.35**	0.20	0.15	0.07	-0.25	0.08	-0.07	0.08	**-0.34**	0.00	0.01	**0.31**	0.16	**0.33**
D3			1	**0.33**	**0.40**	**0.44**	**-0.29**	**-0.46**	-0.06	-0.22	0.24	**0.44**	-0.13	-0.18	0.20	**0.26**	**0.27**	-0.25	**-0.35**	-0.20
O1				1	**0.62**	**0.58**	**-0.29**	**-0.48**	-0.18	**-0.29**	0.12	0.26	-0.19	-0.06	-0.04	-0.06	-0.12	-0.14	-0.09	-0.11
O2					1	**0.94**	**-0.33**	**-0.52**	-0.12	**-0.44**	0.06	0.24	-0.13	-0.13	0.20	-0.03	-0.15	-0.09	-0.24	-0.29
O3						1	**-0.29**	**-0.48**	-0.09	**-0.39**	0.12	0.27	-0.15	-0.16	0.13	0.05	-0.10	-0.08	**-0.32**	**-0.33**
S1							1	**0.63**	0.09	**0.52**	0.07	-0.31	-0.22	-0.05	-0.29	-0.08	-0.02	-0.08	0.08	0.11
S2								1	**0.28**	**0.50**	-0.01	-0.33	0.11	0.10	-0.12	0.02	0.04	0.05	0.08	0.08
S3									1	0.14	-0.21	**-0.34**	**0.33**	0.09	0.25	-0.07	0.02	0.16	0.03	0.15
S4										1	0.04	**-0.46**	0.15	0.13	-0.02	-0.01	0.01	-0.07	0.18	0.12
R1											1	0.02	-0.06	-0.21	0.19	-0.20	-0.05	**-0.46**	**-0.31**	**-0.35**
R2												1	**-0.56**	0.13	-0.08	0.19	0.16	-0.10	-0.25	-0.21
R3													1	-0.09	0.16	-0.09	-0.11	0.04	0.06	0.10
R4														1	0.20	-0.22	-0.02	0.15	0.23	0.19
R5															1	-0.13	0.03	-0.03	0.01	0.03
*E1**																1	**0.72**	**0.39**	0.05	0.18
*E2**																	1	**0.26**	0.16	0.20
*E3***																		1	**0.63**	**0.70**
*E4***																			1	**0.86**
*E5***																				1

Note. * = H.2.2. ; ** = H.2.1. ; **Bold** = Benjamini-Hochberg corrected 1-tailed p-value < .05; Demographic variables (D) include: 1.gender, 2.age, 3.education ; Outcome variables (O) include 1.days to lapse, 2.days to relapse, 3.abstinence ; Severity of addiction variables (S) include 1.cigarettes per day, 2.Fagerstrom Test for Nicotine Dependence score, 3.Minnesota Nicotine Withdrawal Scale score, 4.Shiffman Craving Scale score ; "Self-Report" scores (R) include: 1.Smoking Self-Efficacy Questionnaire, 2.Distress Tolerance Scale, 3.Perceived Stress Scale, 4. Change in Positive Affect, 5. Change in Negative Affect ; Emotion-related Brain Region Response variables (E) include 1.Left anterior insula, 2.Right anterior insula, 3.Pregenual anterior cingulate, 4.Left amygdala, 5.Right amygdala.

TABLE 7

Linear Multiple Regressions Predicting Days to Lapse H.1.1 & H.1.2.

Brain Regions of Interest	*B1**	*B2**	*B3**	*B4**	*B5**	*B6**	*B7**	*B8**	*B9***
Omnibus Model									
Goodness of fit (R^2)	0.222	0.221	0.22	0.249	0.22	0.222	0.221	0.22	0.221
F-value	3.071	3.051	3.035	3.556	3.04	3.059	3.049	3.036	3.05
Significance (p-value)	**0.026**	**0.027**	**0.027**	**0.014**	**0.027**	**0.026**	**0.027**	**0.027**	**0.027**
Predictor coefficients									
ROI (beta, p-value)	-0.046, 0.738	-0.033, 0.825	0.002, 0.990	-0.178, 0.209	-0.019, 0.895	-0.038, 0.784	-0.019, 0.895	-0.009, 0.950	0.033, 0.829
Sex (beta, p-value)	-0.18, 0.204	-0.176, 0.234	-0.186, 0.195	-0.158, 0.258	-0.185, 0.191	-0.180, 0.208	-0.185, 0.191	-0.184, 0.198	-0.188, 0.184
Age (beta, p-value)	**-0.301, 0.034**	**-0.302, 0.034**	**-0.300, 0.036**	**-0.330, 0.021**	**-0.300, 0.035**	**-0.303, 0.034**	**-0.300, 0.035**	**-0.300, 0.035**	**-0.312, 0.041**
Education (beta, p-value)	**0.321, 0.027**	**0.326, 0.029**	**0.318, 0.028**	**0.345, 0.017**	**0.325, 0.037**	**0.322, 0.027**	**0.325, 0.037**	**0.317, 0.029**	**0.326, 0.029**

Note. * = H.1.1. ; ** = H.1.2. ; **Bold** = p-value < .05; Brain Regions of Interest (B) include 1.Left dorsolateral prefrontal cortex, 2.Right inferior parietal lobule, 3.Left inferior parietal lobule, 4.Supplementary motor area, 5.Right dorsolateral prefrontal cortex, 6.Right premotor area, 7.Left frontal pole, 8.Left premotor area, 9.Posterior cingulate cortex. Predictor beta coefficients for each region of interest (ROI), determined by the column header, are listed in the "ROI" row.

TABLE 8

Linear Multiple Regressions Predicting Days to Relapse for H.1.1 & H.1.2.

Brain Regions of Interest	*B1**	*B2**	*B3**	*B4**	*B5**	*B6**	*B7**	*B8**	*B9***
Omnibus Model									
Goodness of fit (R^2)	0.193	0.206	0.198	0.198	0.197	0.248	0.193	0.194	0.2
F-value	2.575	2.782	2.649	2.648	2.642	3.546	2.572	2.591	2.686
Significance (p-value)	0.051	**0.038**	**0.046**	**0.046**	**0.047**	**0.014**	**0.051**	**0.05**	**0.044**
Predictor coefficients									
ROI (beta, p-value)	0.018, 0.900	-0.125, 0.414	0.070, 0.618	0.072, 0.619	-0.071, 0.634	-0.242, 0.083	-0.009, 0.950	0.036, 0.799	-0.094, 0.544
Sex (beta, p-value)	-0.054, 0.706	-0.015, 0.919	-0.065, 0.653	-0.063, 0.660	-0.049, 0.731	-0.014, 0.919	-0.051, 0.719	-0.058, 0.687	-0.046, 0.747
Age (beta, p-value)	-0.185, 0.195	-0.193, 0.173	-0.177, 0.215	-0.173, 0.229	-0.184, 0.196	-0.201, 0.145	-0.184, 0.203	-0.184, 0.196	-0.152, 0.318
Education (beta, p-value)	**0.374, 0.012**	**0.405, 0.008**	**0.378, 0.011**	**0.364, 0.015**	**0.402, 0.012**	**0.403, 0.006**	**0.377, 0.014**	**0.379, 0.011**	**0.352, 0.021**

Note. * = H.1.1. ; ** = H.1.2. ; **Bold** = p-value < .05; Brain Regions of Interest (B) include 1.Left dorsolateral prefrontal cortex, 2.Right inferior parietal lobule, 3.Left inferior parietal lobule, 4.Supplementary motor area, 5.Right dorsolateral prefrontal cortex, 6.Right premotor area, 7.Left frontal pole, 8.Left premotor area, 9.Posterior cingulate cortex. Predictor beta coefficients for each region of interest (ROI), determined by the column header, are listed in the "ROI" row.

TABLE 9

Binomial Logistic Regressions Predicting Abstinence H.1.1 & H.1.2.

Brain Regions of Interest	*B1**	*B2**	*B3**	*B4**	*B5**	*B6**	*B7**	*B8**	*B9***
Omnibus Model									
Cox & Snell R^2	0.212	0.211	0.209	0.228	0.209	0.230	0.209	0.215	0.214
Significance (p-value)	0.022	**0.023**	**0.024**	**0.014**	**0.024**	**0.014**	**0.024**	**0.021**	**0.021**
Predictor coefficients									
ROI (beta, p-value)	0.016, 0.664	-0.010, 0.765	0.004, 0.899	0.039, 0.287	0.001, 0.990	-0.037, 0.268	-0.002, 0.956	0.022, 0.557	-0.010, 0.598
Sex (beta, p-value)	0.409, 0.573	0.295, 0.693	0.376, 0.603	0.522, 0.482	0.362, 0.613	0.210, 0.774	0.359, 0.616	0.453, 0.539	0.314, 0.662
Age (beta, p-value)	-0.031, 0.274	-0.032, 0.261	-0.031, 0.280	-0.026, 0.362	-0.031, 0.269	-0.033, 0.250	-0.031, 0.278	-0.031, 0.274	-0.026, 0.387
Education (beta, p-value)	**0.523, 0.009**	**0.542, 0.009**	**0.528, 0.009**	**0.518, 0.012**	**0.525, 0.017**	**0.576, 0.007**	**0.529, 0.011**	**0.541, 0.008**	**0.511, 0.012**

Note. * = H.1.1. ; ** = H.1.2. ; **Bold** = p-value < .05; Brain Regions of Interest (B) include 1.Left dorsolateral prefrontal cortex, 2.Right inferior parietal lobule, 3.Left inferior parietal lobule, 4.Supplementary motor area, 5.Right dorsolateral prefrontal cortex, 6.Right premotor area, 7.Left frontal pole, 8.Left premotor area, 9.Posterior cingulate cortex. Predictor beta coefficients for each region of interest (ROI), determined by the column header, are listed in the "ROI" row.

TABLE 10

Linear Multiple Regressions Predicting Days to Lapse H.2.1 & H.2.2

Emotion-related Brain Regions of Interest	*E1**	*E2**	*E3***	*E4***	*E5***
Omnibus Model					
Goodness of fit (R^2)	0.22	0.222	0.249	0.222	0.22
F-value	3.036	3.059	3.556	3.071	3.04
Significance (p-value)	**0.027**	**0.026**	**0.014**	**0.026**	**0.027**
Predictor coefficients					
ROI (beta, p-value)	-0.009, 0.950	-0.038, 0.784	-0.178, 0.209	-0.046, 0.738	-0.019, 0.895
Sex (beta, p-value)	-0.184, 0.198	-0.180, 0.208	-0.158, 0.258	-0.18, 0.204	-0.185, 0.191
Age (beta, p-value)	**-0.300, 0.035**	**-0.303, 0.034**	**-0.330, 0.021**	**-0.301, 0.034**	**-0.300, 0.035**
Education (beta, p-value)	**0.317, 0.029**	**0.322, 0.027**	**0.345, 0.017**	**0.321, 0.027**	**0.325, 0.037**

Note. * = H.2.2. ; ** = H.2.1. ; **Bold** = p-value < .05; Emotion-related Brain Region Response variables (E) include 1.Left anterior insula, 2.Right anterior insula, 3.Pregenual anterior cingulate, 4.Left amygdala, 5.Right amygdala. Predictor beta coefficients for each region of interest (ROI), determined by the column header, are listed in the "ROI" row.

TABLE 11

Linear Multiple Regressions Predicting Days to Relapse H.2.1 & H.2.2

Emotion-related Brain Regions of Interest	*E1**	*E2**	*E3***	*E4***	*E5***
Omnibus Model					
Goodness of fit (R^2)	0.232	0.245	0.225	0.225	0.223
F-value	3.242	3.488	3.113	3.113	3.092
Significance (p-value)	**0.021**	**0.015**	**0.025**	**0.025**	**0.025**
Predictor coefficients					
ROI (beta, p-value)	-0.113, 0.426	-0.168, 0.241	0.074, 0.623	0.091, 0.532	0.061, 0.676
Sex (beta, p-value)	-0.168, 0.235	-0.149, 0.294	-0.203, 0.162	-0.195, 0.168	-0.192, 0.176
Age (beta, p-value)	**-0.292, 0.039**	**-0.285, 0.043**	**-0.322, 0.031**	**-0.310, 0.030**	**-0.319, 0.033**
Education (beta, p-value)	**0.344, 0.020**	**0.357, 0.015**	**0.336, 0.025**	**0.350, 0.023**	**0.328, 0.026**

Note. * = H.2.2. ; ** = H.2.1. ; **Bold** = p-value < .05; Emotion-related Brain Region Response variables (E) include 1.Left anterior insula, 2.Right anterior insula, 3.Pregenual anterior cingulate, 4.Left amygdala, 5.Right amygdala. Predictor beta coefficients for each region of interest (ROI), determined by the column header, are listed in the "ROI" row.

TABLE 12

Binomial Logistic Regressions Predicting Abstinence H.2.1 & H.2.2

Emotion-related Brain Regions of Interest	*E1**	*E2**	*E3***	*E4***	*E5***
Omnibus Model					
Cox & Snell R^2	0.213	0.258	0.215	0.242	0.256
Significance (p-value)	**0.022**	**0.006**	**0.020**	**0.010**	**0.007**
Predictor coefficients					
ROI (beta, p-value)	-0.030, 0.632	-0.095, 0.094	0.021, 0.543	-0.087, 0.180	-0.090, 0.107
Sex (beta, p-value)	0.285, 0.696	-0.009, 0.990	0.501, 0.510	0.169, 0.818	0.182, 0.804
Age (beta, p-value)	-0.030, 0.290	-0.028, 0.337	-0.036, 0.221	-0.029, 0.305	-0.018, 0.549
Education (beta, p-value)	**0.550, 0.008**	**0.648, 0.004**	**0.555, 0.008**	**0.472, 0.023**	**0.525, 0.013**

Note. * = H.2.2. ; ** = H.2.1. ; **Bold** = p-value < .05; Emotion-related Brain Region Response variables (E) include 1.Left anterior insula, 2.Right anterior insula, 3.Pregenual anterior cingulate, 4.Left amygdala, 5.Right amygdala. Predictor beta coefficients for each region of interest (ROI), determined by the column header, are listed in the "ROI" row.

TABLE 13

Self-Report Measures Predicting Posterior Cingulate Cortex Activity

	DTS	PSS	SSE	PA change	NA change
Omnibus Model					
Goodness of fit (R-squared)	0.231	0.230	0.220	0.210	0.211
F-value	3.228	3.220	3.039	2.864	2.874
Significance (p-value)	**0.021**	**0.021**	**0.027**	**0.034**	**0.034**
Predictor coefficients					
self-report (beta, p-value)	-0.175, 0.289	0.150, 0.294	-0.106, 0.459	-0.008, 0.953	-0.028, 0.851
Sex (beta, p-value)	0.007, 0.962	0.022, 0.877	0.063, 0.653	0.066, 0.640	0.068, 0.631
Age (beta, p-value)	**0.382, 0.009**	**0.368, 0.010**	**0.336, 0.022**	**0.359, 0.013**	**0.350, 0.021**
Education (beta, p-value)	-0.146, 0.381	-0.210, 0.146	-0.219, 0.133	-0.243, 0.097	-0.238, 0.101

Note. Linear multiple regressions of self-report measures upon Posterior Cingulate Cortex brain response, using sex, age, and education as covariates. **Bold** = p-value < .05; DTS = Distress Tolerance Scale score; PSS = Perceived Stress Scale score ; SSE = Smoking Self-Efficacy Questionnaire score ; PA change = change in Positive Affect score, NA change = change in Negative Affect score. Predictor beta coefficients for each self-report measure, determined by the column header, are listed in the "self-report" row.

TABLE 14

Self-Report Measures Predicting Left Amygdala Activity

	DTS	PSS	SSE	PA change	NA change
Omnibus Model					
Goodness of fit (R-squared)	0.154	0.145	0.190	0.171	0.157
F-value	1.953	1.828	2.528	2.212	2.003
Significance (p-value)	0.119	0.141	0.054	0.084	0.111
Predictor coefficients					
self-report (beta, p-value)	-0.113, 0.514	-0.010, 0.949	-0.224, 0.129	0.162, 0.258	0.118, 0.441
Sex (beta, p-value)	0.066, 0.671	0.107, 0.485	0.098, 0.490	0.093, 0.519	0.094, 0.520
Age (beta, p-value)	0.125, 0.393	0.110, 0.452	0.063, 0.665	0.102, 0.480	0.147, 0.336
Education (beta, p-value)	-0.295, 0.095	**-0.358, 0.021**	**-0.310, 0.039**	**-0.326, 0.031**	**-0.370, 0.015**

Note. Linear multiple regressions of self-report measures upon Left Amygdala brain response, using sex, age, and education as covariates. **Bold** = p-value < .05; DTS = Distress Tolerance Scale score; PSS = Perceived Stress Scale score ; SSE = Smoking Self-Efficacy Questionnaire score ; PA change = change in Positive Affect score, NA change = change in Negative Affect score. Predictor beta coefficients for each self-report measure, determined by the column header, are listed in the "self-report" row.

TABLE 15

Self-Report Measures Predicting Right Amygdala Activity

	DTS	PSS	SSE	PA change	NA change
Omnibus Model					
Goodness of fit (R-squared)	0.165	0.143	0.200	0.154	0.162
F-value	2.127	1.792	2.692	1.962	2.084
Significance (p-value)	0.094	0.148	0.043	0.117	0.100
Predictor coefficients					
self-report (beta, p-value)	-0.209, 0.226	0.088, 0.558	-0.268, 0.070	0.139, 0.338	0.176, 0.250
Sex (beta, p-value)	0.029, 0.851	0.073, 0.631	0.092, 0.516	0.090, 0.539	0.084, 0.565
Age (beta, p-value)	**0.335, 0.025**	**0.313, 0.036**	0.250, 0.087	**0.300, 0.043**	**0.362, 0.020**
Education (beta, p-value)	-0.054, 0.756	-0.149, 0.327	-0.112, 0.445	-0.142, 0.345	-0.188, 0.206

Note. Linear multiple regressions of self-report measures upon Right Amygdala brain response, using sex, age, and education as covariates. **Bold** = p-value < .05; DTS = Distress Tolerance Scale score; PSS = Perceived Stress Scale score ; SSE = Smoking Self-Efficacy Questionnaire score ; PA change = change in Positive Affect score, NA change = change in Negative Affect score. Predictor beta coefficients for each self-report measure, determined by the column header, are listed in the "self-report" row.

TABLE 16

Backwards Stepwise Linear Multiple Regression for Days to Relapse

Model	*Predictor*	*Standardized Beta Coefficient*	*t-value*	*p-value*	R^2
1	(Constant)		0.588	0.56	0.381
	CPD	0.162	0.943	0.35	
	FTND	-0.392	-2.19	0.03	
	Education	0.142	0.976	0.34	
	SCS	-0.287	-1.927	0.06	
	PCC	-0.203	-1.521	0.14	0.368
2	(Constant)		0.603	0.55	
	FTND	-0.31	-1.985	0.05	
	Education	0.153	1.055	0.30	
	SCS	-0.243	-1.721	0.09	
	PCC	-0.171	-1.327	0.19	0.351
3	(Constant)		5.683	0.01	
	FTND	-0.379	-2.681	0.01	
	SCS	-0.24	-1.698	0.10	
	PCC	-0.213	-1.733	0.09	0.307
4	(Constant)		5.499	0.01	
	FTND	-0.498	-3.963	0.01	
	PCC	-0.222	-1.77	0.08	0.258
5	(Constant)		7.119	0.01	
	FTND	-0.508	-3.956	0.01	

Note. CPD = cigarettes per day; FTND = Fagerstrom Test for Nicotine Dependence score; SCS = Shiffman Craving Scale score; PCC = Brain Response to the n-Back of Posterior Cingulate Cortex.

TABLE 17

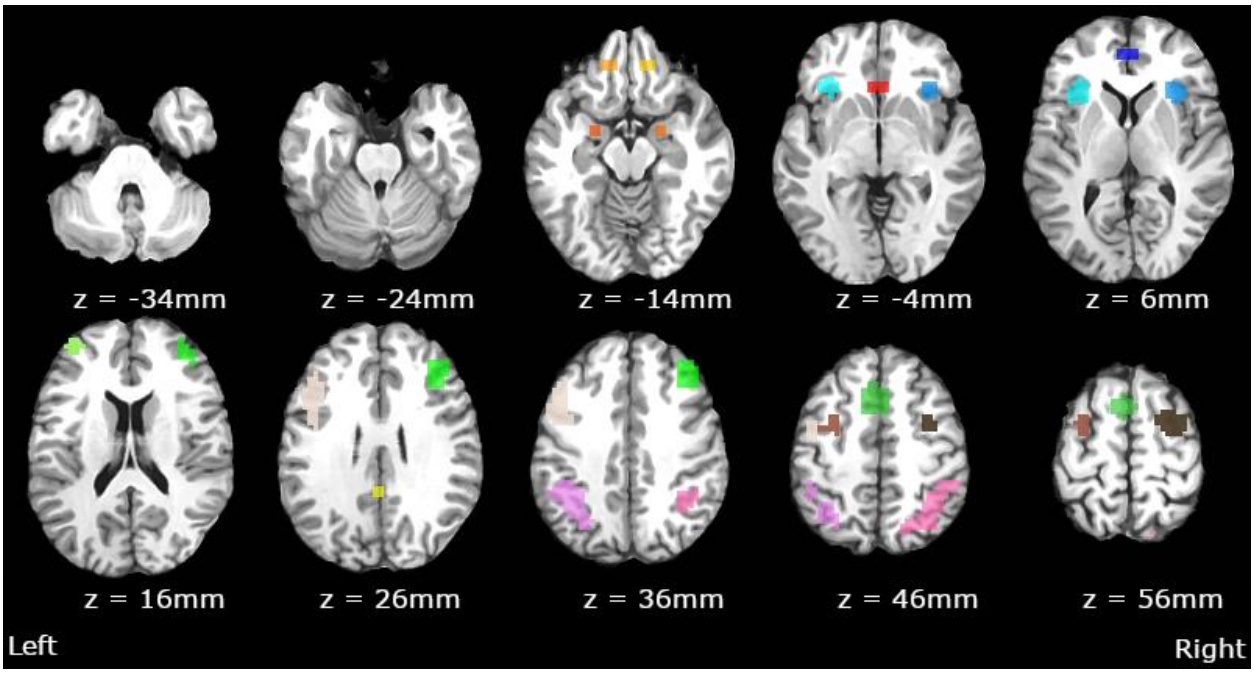
Backwards Stepwise Logistic Multiple Regression for Abstinence

Model	*Predictor*	*Standardized Beta Coefficient*	*Wald value*	*p-value*	*Cox & Snell R^2*
1	Education	0.390	2.51	0.11	0.392
	CPD	0.037	0.86	0.36	
	FTND	-0.473	3.72	0.05	
	SCS	-0.028	2.95	0.09	
	L_AMYG	-0.007	0.00	0.96	
	R_AMYG	-0.128	1.45	0.23	
	Constant	-4.270	1.31	0.25	
2	Education	0.394	2.82	0.09	0.392
	CPD	0.037	0.89	0.35	
	FTND	-0.472	3.73	0.05	
	SCS	-0.028	3.07	0.08	
	R_AMYG	-0.133	4.35	0.04	
	Constant	-4.317	1.43	0.23	
3	Education	0.356	2.52	0.11	0.381
	FTND	-0.381	3.16	0.08	
	SCS	-0.025	2.65	0.10	
	R_AMYG	-0.127	4.04	0.04	
	Constant	-3.483	1.03	0.31	
4	FTND	-0.489	6.10	0.01	0.343
	SCS	-0.022	2.38	0.12	
	R_AMYG	-0.129	4.45	0.04	
	Constant	1.808	3.52	0.06	
5	FTND	-0.532	8.43	0.00	0.306
	R_AMYG	-0.120	4.66	0.03	
	Constant	1.464	2.79	0.10	

Note. CPD = cigarettes per day; FTND = Fagerstrom Test for Nicotine Dependence score; SCS = Shiffman Craving Scale score; L_AMYG = Brain Response to the n-Back of left amygdala; R_AMYG = Brain Response to the n-Back of right amygdala.

FIGURE 1

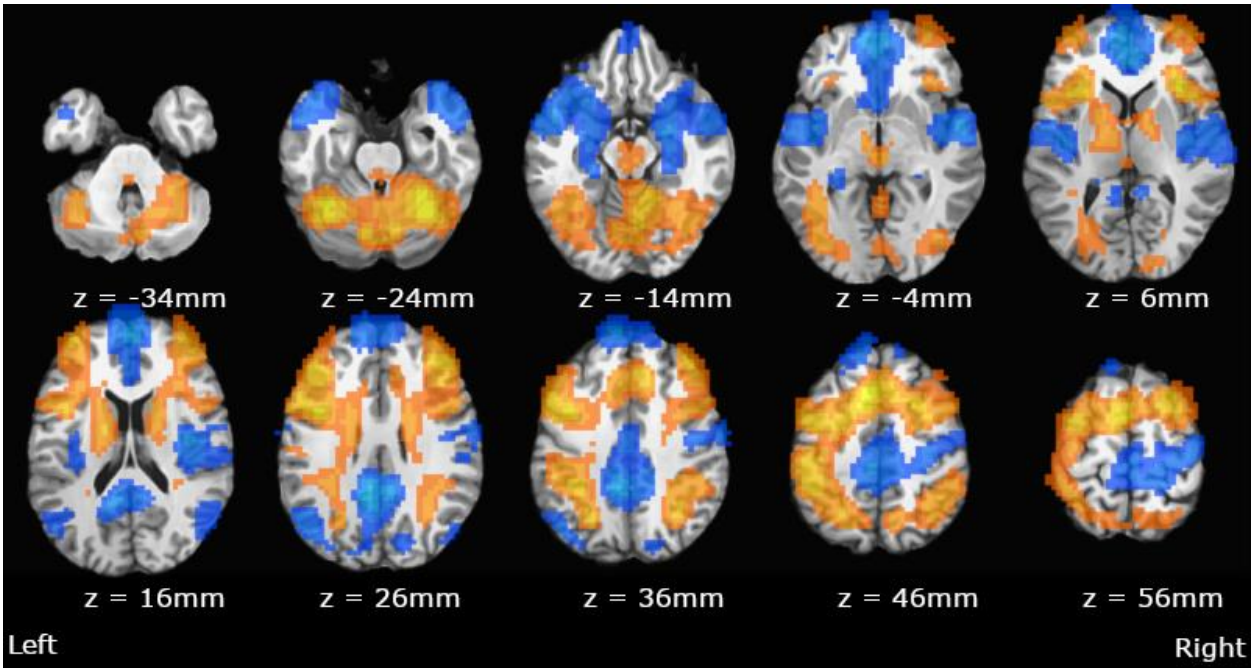
Regions of Interest



Note. Colored regions indicate voxels contained within each the following regions of interest: left ventromedial prefrontal cortex (yellow-orange), right ventromedial prefrontal cortex (light yellow-orange), left amygdala (dark orange), right amygdala (orange), left anterior insula (cerulean), right anterior insula (sky blue), subgenual anterior cingulate cortex (red), pregenual anterior cingulate cortex (blue), left frontal pole (light green), right dorsolateral prefrontal cortex (green), left dorsolateral prefrontal cortex (tan), posterior cingulate cortex (yellow), left inferior parietal lobule (purple), right inferior parietal lobule (pink), left premotor area (brown), right premotor area (dark brown), supplementary motor area (dark green).

FIGURE 2.

Voxel-wise Activation Map for the 2-Back



Note. Voxel-wise activation map for the [2-Back – rest] contrast. Axial slices are presented at 10mm intervals along the z-axis, ranging from -34 to +56. Orange voxels represent significant activation, blue voxels represent significant deactivation at a false-discovery-rate-corrected significance level of q = .001.