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Altered Alpha Oscillatory Power Dynamics Underlie Difficulties with Cognitive Flexibility

Nicole Forner
University of New Hampshire, Durham

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By

Nicole A. Forner

B.A., Carleton College, 2014

M.A., The University of New Hampshire, 2019

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This thesis/dissertation was examined and approved in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Psychology by:

Robert Ross, Associate Professor of Psychology

Laura Allen, Assistant Professor of Psychology

Ronald Croce Professor of Kinesiology

Caitlin Mills, Assistant Professor of Psychology

Amy Janes, Associate Professor of Psychiatry, Harvard Medical School

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Approval signatures are on file with the University of New Hampshire Graduate School.

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Abstract

Cognitive flexibility is an important mental faculty, but there are certain populations that experience reduced flexibility, which may be associated with altered neural activity. Rumination is when an individual becomes mentally stuck on a thought, and they experience difficulty shifting their attention away from the ruminative thought demonstrating reduced cognitive flexibility. In a similar manner, individuals diagnosed with substance use disorder show varying degrees of attentional bias towards drug related stimuli. The drug cues capture attention, and it is difficult for these individuals to shift attention away from thoughts related to drug cues. Both populations experience difficulty shifting attention when they experience highly salient thoughts (high automatic constraints). Here we suggest and demonstrate that reduced cognitive flexibility in these populations is associated with altered activity of alpha oscillations, as alpha oscillations play an important role in supporting cognitive flexibility. In our first study, we assess the relationship between trait tendency to ruminate and resting state alpha power in left frontal and parietal located electrodes. Individuals higher in trait rumination exhibit higher alpha power in left frontal located electrodes. This finding suggests that higher alpha power may contribute to mental inflexibility associated with rumination. In our second study, we assess the relationship between attentional bias towards drug cues and alpha power while automatic constraints on thought are high during an emotional version of the Stroop task and when drug cues are not present and therefore automatic constraints are low, but flexibility is required during a probabilistic reversal learning task. The emotional version of the Stroop task includes traditional congruent and incongruent word meanings as well as drug related and neutral word meanings. Participants in this study were long-term nicotine smokers, therefore the emotional stimuli were smoking related. The probabilistic reversal learning task instructs participants to choose one of two presented stimuli on each trial. The stimuli have different probabilities of reward or punishment. If the participant chooses the stimulus with the higher probability of reward several trials in a row, the reward probabilities reverse, and the participant must adapt to the new

reward contingencies. Participants demonstrate the traditional Stroop effect of lower accuracy and slower reaction time during incongruent trials compared to congruent trials. Additionally, participants show a slowed reaction time during drug trials compared to neutral trials suggesting attentional bias during drug trials. Greater attentional bias is associated with higher alpha power in left frontal electrodes during drug trials. No significant relationship between attentional bias and alpha power during the probabilistic reversal learning task was revealed. Together, these results suggest higher alpha power in left frontal regions may contribute to mental inflexibility prompted by attentional bias when automatic constraints are high, but when automatic constraints are low, flexibility may not be reduced. All together these results reveal a relationship between reduced cognitive flexibility when salient stimuli or thoughts are present and altered alpha power dynamics, which may offer new avenues for behavioral intervention to improve cognitive flexibility.

CHAPTER 1: Introduction

1.1 Introduction

The ability to shift between different modes of thinking is an important aspect of our cognitive lives. However, certain populations demonstrate reduced cognitive flexibility, such as individuals high in trait rumination and individuals suffering from substance use disorder (SUD), which may have a common underlying neural basis. Being able to flexibly shift between different modes of thinking enables us to adapt to changing environmental conditions (Dajani & Uddin, 2015; Ionescu, 2012; Monsell, 2003; Powell & Ragozzino, 2017). For example, a person's thoughts could be focused on writing a paper when a friend asks them a question. The friend's question prompts a shift in thinking from thoughts related to writing, to thoughts related to listening, understanding, and potentially responding to the question. An interplay between the executive functions of shifting and inhibition are thought to underlie this type of cognitive flexibility (Miyake et al., 2000). Shifting is the cognitive act of switching from one mode of thinking to another, while inhibition refers to mentally inhibiting a response or mode of thinking, which can aid shifting to an alternate mode of thinking (Bari & Robbins, 2013; Miyake et al., 2000). A reduced ability to utilize cognitive flexibility is associated with deficits in cognitive functioning (Dajani & Uddin, 2015; Gruner & Pittenger, 2017; Piguet et al., 2016; Waltz, 2017), making an understanding of the different influences on cognitive flexibility of importance. For example, individuals high in trait rumination tend to experience difficulty with tasks that require cognitive flexibility (Altamirano et al., 2010; Davis & Nolen-Hoeksema, 2000; Whitmer & Banich, 2007; Yee lo et al., 2012). Individuals high in trait rumination are more likely to ruminate, which occurs when an individual becomes fixated on a particular thought and they experience difficulty redirecting attention away from the ruminative thought demonstrating cognitive inflexibility (Davis & Nolen-Hoeksema, 2000; Nolen-Hoeksema et al., 2008). Similarly, individuals diagnosed with SUD demonstrate an attentional bias towards cues associated with their drug of choice and they experience difficulty shifting attention away from the drug cues, which demonstrates cognitive inflexibility (Dias et al., 2015; Janes et al., 2010b; Kang et al., 2012;

Luijten et al., 2011; Zhang et al., 2018). Christoff et al. (2016) propose that mental states can be categorized based on two dimensions, automatic constraints, and deliberate constraints. Automatic constraints refer to how attention grabbing a thought is, while deliberate constraints refer to cognitive control, including flexibility. Both high ruminators and individuals with SUD that demonstrate attentional bias experience mental states that are high in automatic constraints and low in deliberate constraints and as such, there may be a unitary alteration in neural functioning at work in both populations. Studying the neural mechanisms that underlie reduced cognitive flexibility in individuals high in trait rumination and individuals diagnosed with SUD who exhibit attentional bias may help shed light on biological alterations that may underlie cognitive inflexibility, especially when automatic constraints are high.

Alterations of brain oscillations in the alpha (8-13 Hz) band may underlie such difficulties with cognitive flexibility. Oscillations reflect patterns of neural firing in the brain and can be separated into different frequency bands that may support cognitive functions in different ways (Engel & Fries, 2010; Hanslmayr et al., 2016; Herrmann et al., 2016; Palva & Palva, 2018). Alpha oscillatory power dynamics modulate neuronal activity in different brain regions as alpha oscillations can inhibit neural firing, but also release inhibition leading to enhanced neural firing (Hanslmayr et al., 2011; Laufs et al., 2003a; Moosmann et al., 2003; Mantini et al., 2007). Specifically, alpha power increases, also referred to as alpha synchronization, lead to less neural activity while alpha power decreases, or alpha desynchronization, leads to enhanced neural firing (Hanslmayr et al., 2011; Laufs et al., 2003a; Moosmann et al., 2003; Mantini et al., 2007). Therefore, alpha oscillatory power dynamics may be a mechanism through which neural resources can be channeled throughout the brain (Bonnefond et al., 2017; Hanslmayr et al., 2016; Jensen & Mazaheri, 2010; Klimesch, 2012). Alpha power dynamics are demonstrated to support performance of tasks that require cognitive flexibility (Buschman et al., 2012; Cooper et al., 2016; Cunillera et al., 2012; Foxe et al., 2014; Phillips et al., 2014; Proskovec et al., 2019;

Sauseng et al., 2006; Verstraeten & Cluydts, 2002; Wolff, Zink, Stock, & Beste, 2017), including the Stroop task (Compton et al., 2011; Ergen et al., 2014; Hanslmayr et al., 2008; Popov et al., 2019; Tafuro et al., 2019; Tang et al., 2013). The Stroop task instructs participants to respond to the font color of words that are also names of colors (Stroop, 1935). The font color and the word can either be congruent (e.g., the word green in green color font) or incongruent (e.g., the word green in red color font). When the word and the font color are incongruent, individuals typically exhibit a slowing in reaction time and decreased accuracy in their response (referred to as the switch cost) that may be a reflection of the cognitive effort needed to inhibit the prepotent response of processing the semantic meaning of the word and process the color font instead (Braver, 2012; Cohen et al., 1990; Jost et al., 2013; Kalanthroff et al., 2018, 2016; Kiesel et al., 2010; MacLeod, 1991; Miyake et al., 2000; Monsell, 2003; Rogers & Monsell, 1995; Scarpina & Tagini, 2018; Shichel & Tzelgov, 2018; Vandierendonck et al., 2010; Washburn, 2016). During incongruent trials in the Stroop task, a decrease in alpha power in midfrontal brain regions is observed suggesting that a greater recruitment of neural resources is needed to shift the mode of thinking from processing the meaning of the word to processing the font color (Compton et al., 2011; Ergen et al., 2014; Hanslmayr et al., 2008; Popov et al., 2019; Tafuro et al., 2019; Tang et al., 2013). Probabilistic reversal learning (PRL) can also be used to assess cognitive flexibility. The PRL task instructs participants to choose one of two presented stimuli for each trial. One stimulus yields positive feedback 80% of the time while the other yields negative feedback 80% of the time. After several trials in which the participant chooses the stimulus with an 80% chance of positive feedback, the reward contingencies for the stimuli reverse and the participant must update their task set accordingly. The reversal relies on cognitive flexibility to abandon the “old” reward contingencies and shift to the “new” reward contingencies. EEG studies of PRL have not assessed the role of alpha oscillations in shifting to new reward contingencies, but because the reversal requires cognitive inhibition (hereafter referred to as inhibition) of an “old” mode of thinking and shifting to a “new” mode of thinking, alpha

oscillations are likely to change their functioning based on their demonstrated role in shifting and inhibition (Cooper et al., 2016; Cunillera et al., 2012; Ergen et al., 2014; Foxe et al., 2014; Hanslmayr et al., 2008; Popov et al., 2019). An increase in alpha power may support inhibition while a decrease in alpha power may support shifting (Bacigalupo & Luck, 2019; Doesburg et al., 2016; Foxe & Snyder, 2011; Haegens et al., 2011; Handel et al., 2011; Ikkai et al., 2016; Klimesch et al., 1998; Minarik et al., 2018; Moorselaar et al., 2018; Okazaki et al., 2015; Poch et al., 2017, 2018; Thut et al., 2006; van Diepen et al., 2016; Vollebregt et al., 2016; Worden et al., 2000). Both inhibition and shifting support cognitive flexibility, and due to alpha power dynamics links to inhibition and shifting, an alteration of alpha power dynamics may underlie difficulties with cognitive flexibility observed when automatic constraints are high such as in high ruminators and individuals with SUD that experience attentional bias.

1.2 Rumination and Cognitive flexibility

High trait rumination may serve as a good model for studying reduced cognitive flexibility due to the notion that decreased cognitive flexibility, or cognitive inflexibility, may be the root cause of rumination. When an individual is ruminating, they become mentally stuck on a thought and experience difficulty shifting their attention away from the ruminative thought (Davis & Nolen-Hoeksema, 2000; Nolen-Hoeksema et al., 2008). Ruminative thoughts tend to be negative and self-focused (Nolen-Hoeksema et al., 2008), suggesting negative self-focused thoughts are salient and when these thoughts come to mind, automatic constraints increase and the individual experiences difficulty shifting attention away from the ruminative thought. Davis and Nolen-Hoeksema (2000) suggest that cognitive inflexibility can explain rumination due to the difficulty shifting to a different mode of thinking characteristic of rumination (Joorman & D'Avanzato, 2010; Koster et al., 2011; Nejad et al., 2013; Yee lo et al., 2012). The performance of individuals high in trait rumination (high ruminators) on tasks that require cognitive flexibility for optimal performance, such as task-switching tasks and the Wisconsin Card Sorting Task

(WCST), is in line with Davis and Nolen-Hoeksema's cognitive inflexibility hypothesis, as high ruminators do not perform as well on such tasks as individuals low in trait rumination (Altamirano et al., 2010; Beckwe et al., 2013; Davis & Nolen-Hoeksema, 2000; Owens & Derakshan, 2013; Whitmer & Banich, 2007; Yang et al., 2017; Yee lo et al., 2012; Zetsche et al., 2012). In addition, cognitive training meant to enhance flexibility is associated with less rumination (Cohen et al., 2015; Hoorelbeke et al., 2016). These studies demonstrate that cognitive inflexibility is tied to rumination. High ruminators may generally have trouble shifting from one mode of thinking to another, therefore they may become "stuck" on ruminative thoughts because it is difficult for them to shift their attention to another mode of thinking. In addition, high ruminators may also experience difficulty with inhibition if they attempt, but fail, to inhibit a ruminative thought. As both shifting and inhibition are thought to support cognitive flexibility (Bari & Robbins, 2013; Costa & Friedrich, 2012; Jost et al., 2017; Koch et al., 2004, 2010; Kok, 1999; Liu et al., 2003; Miyake et al., 2000; Monsell, 2003; Pires et al., 2014), it is possible that the two processes may interact so that high ruminators may find it generally more difficult to shift from one mode of thinking to another and when they experience a ruminative thought they also may experience difficulty in attempts to inhibit the ruminative thought. Therefore, an already weakened propensity for shifting may be exacerbated by difficulty inhibiting an "old" mode of thinking. As alpha power dynamics are important for both inhibition and shifting (Bacigalupo & Luck, 2019; Doesburg et al., 2016; Foxe & Snyder, 2011; Haegens et al., 2011; Handel et al., 2011; Ikkai et al., 2016; Klimesch et al., 1998; Minarik et al., 2018; Moorselaar et al., 2018; Okazaki et al., 2015; Poch et al., 2017, 2018; Thut et al., 2006; van Diepen et al., 2016; Vollebregt et al., 2016; Worden et al., 2000), alpha power dynamics may be altered for high ruminators providing a neurobiological explanation for observed difficulties with cognitive flexibility in high ruminators.

1.3 Attention bias in Substance Use Disorder and Cognitive Flexibility

Attentional bias towards drug cues demonstrated by individuals with SUD demonstrates similar cognitive inflexibility to rumination, which may be attributable to common underlying neurobiological alterations in alpha oscillatory functioning. According to the incentive-sensitization model of SUD (Berridge & Robinson, 2016; Olney et al, 2018; Robinson & Berridge, 1993), stimuli in the environment become associated with drug administration through classical conditioning, which leads to increased salience of such stimuli (cue reactivity) and intense “wanting” or craving for the substance (Allenby et al., 2020; Epstein et al., 2009; Fryer et al., 2012; Huang et al., 2018; McClernon et al., 2005, 2009; McHugh et al., 2016; Ostlund et al., 2014; Volkow et al., 2003; Zhou et al., 2011). Cue reactivity may stem from sensitization of the mesolimbic dopamine system in the brain (Berridge & Robinson, 2016; Olney et al, 2018; Robinson & Berridge, 1993). Many drugs of abuse enhance the activity of dopamine in the mesolimbic pathway, which may lead to reinforced associations between objects in the environment while an individual administers a drug and the drug response through classical conditioning (Chiara et al., 1993; Glautier, 1994; Glautier et al, 1994; Hyman et al., 2006; Kelley, 2004; Lazev et al., 1999; Pierce & Kumaresan, 2006; Volkow et al., 2004). Neuroimaging studies consistently show a network of brain regions associated with cognitive control and motivation increase their activity in response to drug cues compared to neutral cues in individuals suffering from SUD suggesting enhanced salience of drug cues (Chase et al., 2011; Courtney et al., 2016; Due et al., 2002; Engelmann et al, 2012; Huang et al., 2018; Janes et al., 2010b, 2015; Jasinska et al., 2014; Kang et al., 2012; McClernon et al., 2005, 2009; Schacht et al., 2013; Wang et al., 2020). Strong cue reactivity is associated with a drug-related attentional bias in which drug cues capture attention and the individual experiences difficulty in attempts to shift attention away from the cues (Dias et al., 2015; Janes et al., 2010b; Kang et al., 2012; Luijten et al., 2011; Zhang et al., 2018). For example, Janes et al. (2010b) demonstrate attentional bias towards drug cues in long-term tobacco smokers during an emotional Stroop

task. In the emotional version of the Stroop task, participants are instructed to respond to the color of the font used for words that are either smoking related or neutral, rather than names of colors used in the traditional Stroop task. In accordance with attentional bias towards drug cues, participants demonstrate a longer reaction time for smoking related versus neutral words (Janes et al., 2010b). In addition, longer reaction times to smoking words during the emotional Stroop task are associated with greater neural reactivity to drug cues (Janes et al., 2010b). These results suggest that drug cues may be salient for individuals with SUD leading to a hijacking of their attention and it may then be difficult to shift attention to other modes of thinking. In terms of constraints, drug related thoughts are salient thus increasing automatic constraints, which may make utilizing deliberate constraints more difficult. The similarities in constraints between rumination and attentional bias suggests there may be a common underlying neural alteration. Due to alpha oscillations relationship with attention and flexibility, altered alpha power dynamics may be present during attentional bias (Bacigalupo & Luck, 2019; Doesburg et al., 2016; Foxe & Snyder, 2011; Haegens et al., 2011; Handel et al., 2011; Ikkai et al., 2016; Klimesch et al., 1998; Minarik et al., 2018; Moorselaar et al., 2018; Okazaki et al., 2015; Poch et al., 2017, 2018; Thut et al., 2006; van Diepen et al., 2016; Vollebregt et al., 2016; Worden et al., 2000). Therefore, altered alpha oscillatory activity may underlie difficulties with cognitive flexibility for both individuals with SUD that demonstrate attentional bias and high ruminators.

1.4 Neurobiological Mechanisms Supporting Cognitive Flexibility

1.4.1 Brain Oscillations

1.4.1.1 An Overview of Brain Oscillations.

Observing the activity of brain oscillations can be a useful tool to study the neural mechanisms that support cognitive processes such as cognitive flexibility. Brain oscillations stem from patterns of neural firing in underlying populations of neurons in the brain. These patterns of neural firing can be separated into different frequency bands which are thought to

support cognitive functions in different ways (Engel & Fries, 2010; Hanslmayr et al., 2016; Herrmann et al., 2016; Palva & Palva, 2018). The power of oscillations, which reflects the degree of synchrony in firing of the underlying population of neurons, creates a dimension of temporal dynamics that adds nuance to how oscillations may alter functioning of the brain (Hanslmayr et al., 2012). Specifically, a high degree of synchrony in firing of a population of neurons is equated with high power, whereas a low degree of synchrony in firing is equated with low power (Hanslmayr et al, 2012). The brain may use an interplay of different oscillatory bands, phase synchrony, and power dynamics to relay information throughout the brain (Bonnefond et al., 2017; Fries, 2015; Jensen & Mazaheri, 2010; Palva & Palva, 2018). Alpha oscillations (8-13 Hz) may be particularly useful to observe when considering cognitive flexibility due to associations between alpha oscillations, attention, and flexibility.

1.4.1.2 Alpha Oscillations and Attention.

Alpha oscillations have demonstrated relationships with attention, which may be important for cognitive flexibility. On a general level, when an individual is engaged in quiet wakefulness with their eyes closed, alpha power tends to be higher globally than when the eyes are opened (Adrian & Matthews, 1934; Bai et al., 2016; Klimesch, 2012; Knyazev et al., 2011; Laufs et al., 2003a, b; Lopez da Silva, 1991). This observation led researchers to suggest that higher alpha power may reflect more of an internal focus of attention and when alpha power lowers, attention may be engaged more towards external stimuli (Adrian & Matthews, 1934; Bai et al., 2016; Bonnefond & Jensen, 2012, 2013; Compton et al., 2019; Cona et al., 2020; Cooper et al., 2003, 2006; Frey et al., 2015; Klimesch, 2012; Knyazev et al., 2011; Laufs et al., 2003a, b; Lopez da Silva, 1991; Magosso et al., 2019; Mo et al., 2013; Palva et al., 2005; Ray & Cole, 1985). When an individual is engaged in a task the requires focused attention, alpha oscillatory power dynamics change in a localized fashion with a decrease in alpha power tending to be observed in brain regions that are considered to be task relevant and an increase in alpha

power tending to be observed in brain regions that are task irrelevant (Bacigalupo & Luck, 2019; Doesburg et al., 2016; Foxe & Snyder, 2011; Haegens et al., 2011; Handel et al., 2011; Ikkai et al., 2016; Klimesch et al., 1998; Minarik et al., 2018; Moorselaar et al., 2018; Okazaki et al., 2015; Poch et al., 2017, 2018; Thut et al., 2006; van Diepen et al., 2016; Vollebregt et al., 2016; Worden et al., 2000). A decrease in alpha power is associated with increased metabolic activity of an underlying population of neurons, whereas higher alpha power is associated with decreased metabolic activity (Hanslmayr et al., 2011; Laufs et al., 2003a; Moosmann et al., 2003; Mantini et al., 2007). Therefore, the observation that alpha power tends to decrease in task relevant regions of the brain and increase in task irrelevant brain regions during task performance suggests that alpha oscillations may be used to dampen neural activity in task irrelevant brain regions and channel neural resources towards regions of the brain that are important for performing the task at hand (Bonnefond et al., 2017; Hanslmayr et al., 2016; Jensen & Mazaheri, 2010; Klimesch, 2012). For example, in tasks that cue participants to allocate attention in preparation for a visual stimulus in either the right or left visual field, such as the Posner attention task, functional magnetic resonance imaging (fMRI) reveals that parts of the occipital lobe contralateral to the cued location increase their activity in anticipation of processing information about the upcoming visual stimulus and ipsilateral parts of the occipital lobe decrease their activity (Blankenburg et al., 2010; Corbetta et al., 2000; Heinze et al., 1994; Hopfinger et al., 2000; Indovina & Macaluso, 2004; Thiel et al., 2004; Yantis et al., 2002). Alpha power during the task increases in the task irrelevant occipital regions ipsilateral to the cued visual field and decreases in the task relevant occipital regions contralateral to the cued visual field (Bacigalupo & Luck, 2019; Doesburg et al., 2016; Foxe & Snyder, 2011; Handel et al., 2011; Ikkai et al., 2016; Moorselaar et al., 2018; Okazaki et al., 2015; Poch et al., 2017; Thut et al., 2006; van Diepen et al., 2016; Vollebregt et al., 2016; Worden et al., 2000). As higher alpha power is associated with less metabolic activity and lower alpha power is associated with greater metabolic activity, lateralization of alpha power dynamics during selective attention may

help inhibit irrelevant sensory information and promote the processing of sensory information that is considered task relevant (Bacigalupo & Luck, 2019; Doesburg et al., 2016; Foxe & Snyder, 2011; Handel et al., 2011; Ikkai et al., 2016; Okazaki et al., 2015; Thut et al., 2006; van Diepen et al., 2016; Vollebregt et al., 2016; Worden et al., 2000). Therefore, alpha oscillations are linked to attention via their association with increasing task relevant and decreasing task irrelevant neural activity. Cognitive flexibility requires a shift in attention from one mode of thinking to another, therefore alpha oscillations likely play a role in flexibility as well.

1.4.1.3 Alpha Oscillations and Cognitive Flexibility.

Properly functioning alpha power dynamics may support cognitive flexibility. Task switching tasks rely on cognitive flexibility to shift from following one rule for the task to a different rule (Dajani & Uddin, 2015; Koch et al., 2018; Monsell, 2003; Rogers & Monsell, 1995; Vandierendonck et al., 2010). During task switching tasks, a lowering of alpha power is typically observed in task relevant brain regions when an individual is cued that a switch in the rule to be followed is going to occur rather than maintaining the current rule (Buschman et al., 2012; Cooper et al., 2016; Cunillera et al., 2012; Foxe et al., 2014; Phillips et al., 2014; Proskovec et al., 2019; Sauseng et al., 2006; Verstraeten & Cluydts, 2002; Wolff, Zink, Stock, & Beste, 2017). A lowering of alpha power in task relevant brain regions prior to a switch suggests that greater neural resources may be devoted to the brain areas necessary to make the switch (Bonnefond et al., 2017; Hanslmayr et al., 2016; Jensen & Mazaheri, 2010; Klimesch, 2012). Performance of the Stroop task also utilizes cognitive flexibility. During the Stroop task, when participants are instructed to respond to the color font of words that are presented, they must ignore the semantic meaning of the words that may be at odds with the color font (Braver, 2012; Cohen et al., 1990; Kalanthroff et al., 2018, 2016; MacLeod, 1991; Scarpina & Tagini, 2018; Shichel & Tzelgov, 2018; Washburn, 2016). Similar to alpha power dynamics during task switching tasks, a decrease in alpha power in task relevant brain regions is observed during incongruent trials in

the Stroop task (Compton et al., 2011; Ergen et al., 2014; Hanslmayr et al., 2008; Popov et al., 2019; Tafuro et al., 2019; Tang et al., 2013). These findings suggest greater neural resources may be needed to successfully shift to a mode of thinking that promotes processing font color from the more automatic mode of thinking for processing the semantic meaning of the words. As semantic processing occurs more readily than color processing, semantic processing may need to be inhibited in order to shift to color processing (Braver, 2012; Cohen et al., 1990; Jost et al., 2013; Kalanthroff et al., 2018, 2016; Kiesel et al., 2010; MacLeod, 1991; Miyake et al., 2000; Monsell, 2003; Rogers & Monsell, 1995; Scarpina & Tagini, 2018; Shichel & Tzelgov, 2018; Vandierendonck et al., 2010; Washburn, 2016). Therefore, parts of the brain associated with semantic processing may exhibit higher alpha power during incongruent trials, while regions associated with shifting and inhibition may show decreased alpha power. The association between alpha power dynamics and cognitive flexibility suggests that higher alpha power may be needed in order to inhibit irrelevant modes of thinking and lower alpha power may enable a shift to task relevant modes of thinking thereby supporting cognitive flexibility. Because high ruminators and individuals with SUD that exhibit attentional bias experience difficulty with cognitive flexibility, this suggests alpha power dynamics may be disrupted.

1.4.1.4. Alpha Oscillations and the Flow of Information Throughout the Brain.

In addition to alpha power dynamics, the phase of alpha oscillations in different populations of neurons may help channel the flow of information throughout the brain (Bonnefond et al., 2017; Fries, 2015; Palva & Palva, 2018; Varela et al., 2001). Phase refers to the start and end of an oscillation cycle. When the phase of alpha oscillations between two groups of neurons is synchronous, the peaks of excitability in firing of the underlying groups of neurons match each other and information may be exchanged between the two regions (Lobier et al., 2018; Michalareas et al., 2016; Mima et al., 2001; Palva et al, 2005; Palva & Palva, 2011; Saalmann et al., 2012; von Stein et al., 2000). Information may be contained within fast

frequency gamma oscillations (>30Hz) that may nest within the peaks of excitability in alpha oscillations (Bastos et al., 2015; Hadjipapas et al., 2015; Jensen et al., 2015; Michalareas et al., 2016; Palva et al., 2005; Ray & Maunsell, 2010; van Kerkoerle et al., 2014; von Stein et al., 2000). The power of oscillations may come into play during phase synchrony by manipulating the window of time in which the groups of neurons are excitable (Bonnefond et al., 2017). Low powered alpha oscillations have a longer period of time in which the underlying group of neurons is excitable whereas high powered alpha oscillations have very short periods of time in which the underlying population of neurons is excitable (Bonnefond et al., 2017). Therefore, a combination of alpha oscillation phase and power may establish channels throughout the brain through which information can flow and help networks of brain regions share information and support processes like flexibility.

1.4.2 Brain Networks

Networks of brain regions support different aspects of attention, which may influence flexibility in different ways. Attention can be influenced by both internal and external factors (Berger et al., 2005; Chica et al., 2013; Corbetta & Shulman, 2002; Hopfinger & West, 2006; Petersen & Posner, 2012). The internal factors that guide attention are typically referred to as top-down control of attention in which cognitive factors such as goals, knowledge, and expectations are used to direct the focus of attention, whereas external influences are salient stimuli in the environment that are attention grabbing due to behavioral relevance, referred to as stimulus-driven attention (Corbetta & Shulman, 2002). For example, when looking for a baseball in a closet, prior knowledge of what a baseball looks like as well as the expectation of where the baseball will be will help guide attention to locate the baseball. The baseball on its own may not be naturally salient (unless it is hurtling towards your body), but because there is a goal to find the baseball, it becomes salient. On the other hand, there are stimuli in the environment that seem to be naturally salient and capture attention without need of a goal. For example, if you

are peacefully eating a picnic lunch when all of a sudden there is an object that is moving quickly towards you, you will likely pay attention to that object to identify what it is and if it is dangerous. Internal and external influences on attention align with Kristoff et al.'s (2016) description of deliberate and automatic constraints respectively. Corbetta & Shulman (2002) proposed a dorsal frontoparietal network including the frontal eye fields and the intraparietal sulcus works to support top-down attention whereas a right ventral frontoparietal network, including ventral frontal cortex and the temporoparietal junction works to support stimulus-driven attention. However, more recent studies of attention control suggest there may be more nuance to these two attention-based systems. Petersen and Posner (2012) provide evidence that the networks identified by Corbetta and Shulman (2002) may serve different purposes than originally proposed and there may be two additional brain networks that support attention control. The dorsal and ventral frontoparietal networks proposed by Corbetta and Shulman (2002) may be subnetworks of a larger network devoted to orienting attention (Petersen & Posner, 2012). A ventral orienting network includes the same brain regions Corbetta and Shulman (2002) identify as the ventral frontoparietal network. However, Petersen and Posner (2012) provide evidence that this network supports shifting attention rather than responding to the salience of objects in the environment. A dorsal orienting network includes the brain regions Corbetta and Shulman (2002) identify as the dorsal frontoparietal network. Whereas Corbetta and Shulman (2002) argue that the dorsal network supports top-down aspects of attention, Petersen and Posner (2012) provide evidence that the dorsal orienting network specifically supports fast control of attention orientation. Petersen and Posner (2012) suggest separate networks for identifying salient information and top-down control of attention. The alerting network which responds specifically to salience of an object includes the reticular formation and right cerebral structures (Petersen & Posner, 2012). The top-down control of attention may be supported by an executive network consisting of two subnetworks: the cingulo-opercular network and the frontoparietal network. The cingulo-opercular network includes the anterior

cingulate cortex (ACC) and the insula and supports maintenance of a task set whereas the frontoparietal control network consists of dorsolateral prefrontal cortex and parietal cortex that supports the identification of goals and goal-relevant material and supports flexibly shifting between task sets (Dosenbach et al., 2008; Fan et al., 2005). Activity of these two executive networks may support cognitive flexibility, as the frontoparietal network may support shifting and the cingulo-opercular network may support inhibition. Altered alpha power dynamics in nodes of these networks may disrupt communication and contribute to difficulties with cognitive flexibility when salient thoughts occur.

1.4.2.1 The Frontoparietal Control Network.

Neuroimaging studies focusing on cognitive flexibility frequently point to roles for dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex in supporting cognitive flexibility. Studies of cognitive flexibility demonstrate that activation of frontal and parietal brain regions occurs when a shift in mode of thinking is required (Berry et al., 2017; Cole et al., 2013; Crone et al., 2005; Hopfinger et al., 2000; Liu et al., 2003; Meyer et al., 1998, Monsell, 2003; Panikratova et al., 2020; Smith et al., 2010; Weidner et al., 2002; Woldorff et al., 2004). In addition, individuals with damage to frontal and/or parietal cortices exhibit behavioral impairment in cognitive flexibility (Barbey et al., 2013; Caeyenberghs, et al., 2014; Mecklinger et al., 1999; Monsell, 2003; Rogers, et al., 1998; Rossi et al, 2007; Sadaghiani et al., 2019). The dlPFC and posterior parietal cortex make up the frontoparietal control network (Badre & Nee, 2018; Berry et al., 2017; Dosenbach et al., 2007, 2008; Marek & Dosenbach, 2018; Petersen & Posner, 2012; Ptak, 2012). Posterior parietal cortex is also part of the orienting network and is demonstrated to be important in selecting input that will be the focus of attention (Chiu & Yantis, 2009; Crone et al., 2005; Esterman et al., 2009; Forstmann et al., 2006; Gurd et al., 2002; Kok, 1999; Petersen & Posner, 2012). The dlPFC, especially the left dlPFC, may identify information that is goal/task-relevant and determine a task set (Banich, 2009; Berry et al., 2017; Crone et

al., 2005; Liu et al., 2003; Kok, 1999; MacDonald et al., 2000; Panikratova et al., 2020; Silton et al, 2011). Left and right dlPFC are demonstrated to serve slightly different functions with left dlPFC showing greater activation when goal hierarchies must be assessed (Kaller et al., 2011), which may be influenced by salience and personal relevance of incoming information (Knight et al., 2020; Turnbull, 2019). Signals sent from dlPFC may influence the posterior parietal cortex to act in a flexible manner shifting between inputs of attentional focus (Badre & Nee, 2018; Braver, 2012; Crone et al., 2005; Kok, 1999; Liu, et al., 2003; Marek & Dosenback, 2018; Miller & Cohen, 2001; Praamstra et al., 2005). Activity of the frontoparietal network exhibits a negative correlation with alpha power and a positive correlation with alpha phase coherence (Laufs et al., 2003a; Mo et al., 2013; Proskovec et al., 2019; Sadaghiani et al., 2012; Van Schouwenburg et al., 2017), meaning alpha activity has smaller oscillations that occur in the same phase. Alpha oscillatory dynamics relation to frontoparietal activity is in line with theories about alpha oscillations channeling neural resources (Bonnefond et al., 2017; Hanslmayr et al., 2016; Jensen & Mazaheri, 2010; Klimesch, 2012). As the frontoparietal control network may support shifting, altered functioning in the frontoparietal control network, possibly attributable to altered automatic constraints and alpha oscillations, may lead to difficulties with cognitive flexibility.

1.4.2.1.1 Evidence for Altered Functioning in Rumination.

Neurobiological alterations of the frontoparietal control network may underlie difficulties with cognitive flexibility characteristic of rumination. Neuroimaging studies demonstrate that high trait rumination is associated with reduced activity in dlPFC, particularly the left dlPFC (Ferdek et al., 2016; Nejad et al., 2013; Putnam & McSweeney, 2008). The dlPFC may be important for identifying different task sets and modulating activity of parietal regions that focus attention accordingly in the frontoparietal control network (Badre & Nee, 2018; Braver, 2012; Kok, 1999; Liu, et al., 2003; Marek & Dosenback, 2018; Miller & Cohen, 2001; Praamstra et al., 2005). Reduced activity of left dlPFC suggests task sets may not be updated when flexibly shifting

between modes of thinking. Therefore, if posterior parietal regions do not receive signals from dlPFC to change the focus of attention, then the posterior parietal cortex may focus attention on whatever the most salient stimulus is, which in the case of rumination may be negative self-focused thoughts (Nolen-Hoeksema et al., 2008). Therefore, reduced cognitive flexibility during rumination may be associated with reduced effectiveness of left dlPFC.

1.4.2.2 The Cingulo-Opercular Control Network.

Neurobiological evidence also points to a role for the ACC in cognitive flexibility. The ACC is part of the Cingulo-Opercular control network, which is thought to support task set maintenance by monitoring conflict and signaling an increase in attention towards task related information when a conflict is detected (Banich, 2009; Botvinick, 2001;Braver, 2012; Berry et al., 2017; Dosenbach et al., 2008; Fan et al., 2005; Kropotov et al., 2017; Petersen & Posner, 2012; Silton et al., 2010, 2011.) The ACC increases its activity during flexibility tasks when there may be competing task sets or distracting information (Berry et al., 2017; Botvinick et al., 2001; Chen et al., 2013; Derrfuss et al., 2005; Dosenbach et al., 2006; MacDonald et al., 2000; Nee et al., 2007; Pardo et al., 1990; Silton et al., 2010; Weissman et al., 2005). For example, during the Stroop task the ACC typically increases its activity during incongruent trials in which the task sets of semantic processing and color processing are in conflict (Banich, 2009; Botvinick et al., 2001; MacDonald et al., 2000; Pardo et al., 1990; Ruff et al., 2001; Silton et al., 2010). However, with practice of the Stroop task, conflict between semantic processing and color processing task sets may be reduced and activity of the ACC during incongruent trials does not increase as much as it does without practice (Bush et al., 1998; Chen et al., 2013; Erickson et al., 2004; Milham et al., 2003). This suggests that activity of the ACC is specific to increasing attention when there are task sets that may be interfering with one another. Alpha power decreases are observed near the ACC when flexibility is necessary (Javadi et al., 2019; Proskovec et al., 2019). As the ACC is sensitive to conflicting task sets, or modes of thought, decreased alpha

power and increased activity of the ACC may help direct neural resources towards task-relevant information and identify task irrelevant information that may be high in automatic constraints and need to be inhibited via alpha power increases to support cognitive flexibility.

1.4.2.2.1 Evidence for Altered Functioning in Rumination.

Altered functioning of the Cingulo-Opercular network in high ruminators may disrupt flexibility by impacting inhibition. State rumination is associated with reduced activity in the ACC, the degree of which is positively correlated with trait rumination (Zhu et al., 2012) and with reduced gray matter volume in the ACC (Kuhn et al., 2012). Reduced activity of the ACC may relate to the difficulties with cognitive flexibility high ruminators experience. If the ACC monitors conflict and its activation is associated with enhanced allocation of attention to overcome conflict stemming from competing task sets, the ACC in high ruminators may not be as efficient at deploying greater attention to shift to a new task set and signal inhibition of a highly salient ruminative thought, which would be reflected by higher alpha power in mid-frontal, left frontal, and parietal located electrodes.

1.4.2.2.2 Evidence for Altered Functioning in Attention Bias in SUD.

Findings from studies of attentional bias in SUD also implicate altered functioning of the ACC possibly contributing to attention bias. The ACC is one of several brain regions that typically increases its activity during cue reactivity (Courtney et al., 2016; Engelmann et al, 2012; Huang et al., 2018; Janes et al., 2010a; Jasinska et al., 2014; Kuhn & Gallinat, 2011; McClernon et al., 2005, 2009; Schacht et al., 2013; Wang et al., 2020). In addition, when an individual suffering from SUD exhibits strong reactivity to drug cues and a corresponding attentional bias towards those cues, the ACC shows reduced connectivity with other brain regions (Janes et al. 2010a). Because the ACC becomes more active when drug cues are present, alpha power would be expected to decrease in midfrontal electrodes. However, because connectivity between the ACC and nodes of the frontoparietal control network may be

diminished for individuals that exhibit attentional bias, alpha power in nodes of the frontoparietal network may be higher when drug cues are present. If the ACC is not able to effectively send signals to enhance attention and increase cognitive effort to inhibit a highly salient thought, in this case drug cues, then the individual may not be able to inhibit thoughts about drug cues in order to shift to a new task set.

1.5 Summary

Cognitive flexibility allows us to switch from one mode of thinking to another with relative ease, but in populations such as individuals high in trait rumination and individuals with SUD that exhibit attentional bias, cognitive flexibility can be impaired, which may negatively impact cognition. A better understanding of the neurobiological underpinnings of reduced cognitive flexibility may offer new avenues for behavioral intervention. In order to shift from one mode of thinking to another, an "old" mode of thinking may need to be inhibited to help shift attention to a "new" mode of thinking (Bari & Robbins, 2013; Costa & Friedrich, 2012; Jost et al., 2017; Koch et al., 2004, 2010; Kok, 1999; Liu et al., 2003; Miyake et al., 2000; Monsell, 2003; Pires et al., 2014). Individuals high in trait rumination can become mentally stuck on negative self-referential thoughts and experience difficulty shifting attention away from the ruminative thought demonstrating cognitive inflexibility (Davis & Nolen-Hoeksema, 2000; Joorman & D'Avanzato, 2010; Koster et al., 2011; Nejad et al., 2013; Yee lo et al., 2012). Individuals with SUD exhibit attentional bias towards drug cues in which drug cues capture attention and it is difficult to shift attention away from drug cues (Dias et al., 2015; Janes et al., 2010b; Kang et al., 2012; Luijten et al., 2011; Zhang et al., 2018). In both populations, individuals experience difficulty disengaging from thoughts that are highly salient (high automatic constraints), which may increase difficulty in shifting to a different mode of thinking. The similarities in the dimensions of thought in high ruminators and individuals with SUD that exhibit attentional bias suggest there may be a common alteration of neural functioning. Specifically, the functioning of alpha

oscillations may be altered in these populations. Alpha oscillatory power dynamics modulate the activity of populations of neurons by inhibiting their activity or releasing inhibition allowing for greater activity (Bonnefond et al., 2017; Hanslmayr et al., 2011, 2016; Jensen & Mazaheri, 2010; Klimesch, 2012; Laufs et al., 2003a; Moosmann et al., 2003; Mantini et al., 2007). By increasing or decreasing alpha power in different brain regions, alpha power may channel neural resources away from task irrelevant brain regions towards brain regions that are important for task performance, respectively (Bonnefond et al., 2017; Hanslmayr et al., 2016; Jensen & Mazaheri, 2010; Klimesch, 2012). During tasks that require cognitive flexibility, alpha power decreases are observed in dorsolateral prefrontal, mid-frontal, and parietal cortices when a switch in mode of thinking is required (Buschman et al., 2012; Compton et al., 2011; Cooper et al., 2016; Cunillera et al., 2012; Ergen et al., 2014; Foxe et al., 2014; Hanslmayr et al., 2008; Phillips et al., 2014; Popov et al., 2019; Proskovec et al., 2019; Sauseng et al., 2006; Tafuro et al., 2019; Tang et al., 2013; Verstraeten & Cluydts, 2002; Wolff, Zink, Stock, & Beste, 2017), suggesting greater recruitment of neural resources may help enable a shift in mode of thinking. Dorsolateral prefrontal, midfrontal, and parietal brain regions are included in the frontoparietal and cingulo-opercular control networks, which are demonstrated to support cognitive flexibility (Berry et al., 2017; Botvinick et al., 2001; Chen et al., 2013; Cole et al., 2013; Crone et al., 2005; Derrfuss et al., 2005; Dosenbach et al., 2006; Hopfinger et al., 2000; Liu et al., 2003; MacDonald et al., 2000; Meyer et al., 1998, Monsell, 2003; Nee et al., 2007; Panikratova et al., 2020; Pardo et al., 1990; Petersen & Posner, 2012; Silton et al., 2010; Smith et al., 2010; Weidner et al., 2002; Weissman et al., 2005; Woldorff et al., 2004). In the frontoparietal control network, dlPFC, especially the left dlPFC, may maintain task relevant information and influence the posterior parietal cortex to act in a flexible manner shifting between inputs of attentional focus (Badre & Nee, 2018; Braver, 2012; Crone et al., 2005; Kok, 1999; Liu, et al., 2003; Marek & Dosenback, 2018; Miller & Cohen, 2001; Praamstra et al., 2005). The cingulo-opercular network may be important for maintaining a task set by monitoring conflict and signaling an

increase in attention towards task related information when a conflict is detected, particularly through activation of the ACC (Banich, 2009; Botvinick, 2001; Braver, 2012; Berry et al., 2017; Dosenbach et al., 2008; Fan et al., 2005; Kropotov et al., 2017; Petersen & Posner, 2012; Silton et al., 2010, 2011). As both networks support cognitive flexibility, alpha power dynamics in these regions may help channel neural resources to support cognitive flexibility. Studies of individuals high in trait rumination and individuals with SUD demonstrate altered functioning in nodes of these networks (Courtney et al., 2016; Engelmann et al, 2012; Ferdek et al., 2016; Huang et al., 2018; Janes et al., 2010a, b; Jasinska et al., 2014; Kuhn et al., 2012; Kuhn & Gallinat, 2011; McClernon et al., 2005, 2009 Nejad et al., 2013; Putnam & McSweeney, 2008; Schacht et al., 2013; Wang et al., 2020; Zhu et al., 2012). Altered alpha power dynamics may be at the root of such alterations in functioning. In a series of experiments, we will explore the relationship between alpha power dynamics, trait rumination, and attentional bias towards drug cues with a focus on brain regions that are nodes of the frontoparietal and cingulo-opercular control networks that exhibit altered functioning in these populations.

1.5.1 How Might Altered Alpha Oscillatory Functioning Underlie Difficulties with Cognitive Flexibility Experienced by High Ruminators?

Higher alpha power in nodes of the frontoparietal and cingulo-opercular network may underlie the difficulties with cognitive flexibility demonstrated in individuals high in trait rumination. Individuals high in trait rumination are more likely to engage in state rumination, which draws attention inwards, typically towards negative self-referential thoughts (Nolen-Hoeksema et al., 2008). Higher alpha power is associated with an internal focus of attention (Adrian & Matthews, 1934; Bai et al., 2016; Bonnefond & Jensen, 2012, 2013; Compton et al., 2019; Cona et al., 2020; Cooper et al., 2003, 2006; Frey et al., 2015; Klimesch, 2012; Knyazev et al., 2011; Laufs et al., 2003a, b; Lopez da Silva, 1991; Magosso et al., 2019; Mo et al., 2013; Palva et al., 2005; Ray & Cole, 1985). Therefore, individuals high in trait rumination may have

more of an internal focus of attention, which may be reflected in elevated alpha power, particularly in left frontal and parietal brain regions that are part of the frontoparietal control network (Adrian & Matthews, 1934; Allen et al., 2018; Cicek & Nalcaci, 2001; Ferdek, et al., 2016; Knyazev et al., 2011; Kuhn et al., 2012; Laufs et al., 2003 a, b; Lopez da Silva, 1991; Mantini et al., 2007; Putnam & McSweeney, 2008; Zhu et al., 2012). Observing alpha power in these regions during resting state can demonstrate whether individuals high in trait rumination exhibit higher alpha power. Therefore, in our first study, trait rumination is used as a predictor of average alpha power at rest in left frontal and posterior parietal located electrodes. We expected to see that higher trait rumination would be predictive of higher average alpha power at rest in all regions of interest. This finding would suggest that individuals high in trait rumination may have more of an internal focus of attention, which may promote state rumination and contribute to cognitive inflexibility.

1.5.2 How Might Altered Alpha Oscillatory Functioning Underlie Difficulties with Cognitive Flexibility Experienced by Individuals that Exhibit Attentional Bias?

Attentional bias towards drug cues in individuals with SUD may be associated with greater decreases in alpha power in midfrontal brain regions, and higher alpha power in parietal and left frontal brain regions in response to drug cues, which may increase automatic constraints on thoughts towards drug cues and make utilizing deliberate constraints more difficult. Strong cue reactivity in individuals with SUD can lead to attentional bias, in which drug cues capture attention and increases the difficulty to shift attention away from drug cues (Dias et al., 2015; Janes et al., 2010b; Kang et al., 2012; Luijten et al., 2011; Zhang et al., 2018). An emotional version of the Stroop task in which drug related words are used as stimuli can prompt attentional bias towards drug related words in individuals with SUD and measure cognitive flexibility during the task (Cox et al., 2006; Janes et al., 2010a, b; Ma et al., 2019; Munafo et al., 2003; Waters et al., 2003). Drug related thoughts are salient and therefore would be expected to

increase automatic constraints on thought and lessen deliberate constraints (Christoff et al., 2016). Mid frontal brain regions consistently demonstrate cue reactivity for individuals with SUD, which may reflect high saliency of drug cues (Courtney et al., 2016; Engelmann et al, 2012; Huang et al., 2018; Janes et al., 2010a; Jasinska et al., 2014; Kuhn & Gallinat, 2011; McClernon et al., 2005, 2009; Schacht et al., 2013; Wang et al., 2020). Decreases in alpha power in mid frontal regions may reflect increased automatic constraints tied to drug cues. In addition, attentional bias is associated with reduced connectivity between midfrontal brain regions and other parts of the brain (Janes et al. 2010a), which suggests midfrontal signals to the frontoparietal network to shift attention may be diminished. Therefore, higher alpha power in lateral frontal and parietal regions may underlie difficulties shifting attention away from drug cues. In our second study we will assess alpha power and inter-trial phase coherence (ITC) in left frontal, mid-frontal, and parietal located electrodes during an emotional Stroop task designed for long-term nicotine smokers. ITC is a measure of the phase of alpha across trials. We expect to see a slowing in reaction time and decreased accuracy on trials that use smoking related words along with greater desynchronization of alpha power in midfrontal electrodes and higher alpha power in left frontal and parietal located electrodes for individuals with greater attentional bias and thus stronger automatic constraints on thought. We also expect to see that individuals with greater attentional bias will demonstrate greater alpha ITC during drug trials. These findings would demonstrate that individuals with SUD may devote greater neural resources to processing drug related thoughts, which may increase automatic constraints and make cognitive flexibility more difficult.

1.5.3 Does Reduced Cognitive Flexibility Associated with Attentional Bias Only Occur When Drug Cues are Present and Automatic Constraints are High?

Attentional bias may be attributable to reduced cognitive flexibility even when automatic constraints are not high, which may be linked to alterations of alpha power dynamics when

flexibility is required. It is consistently reported that cognitive flexibility is reduced when drug cues are present (Dias et al., 2015; Janes et al., 2010b; Kang et al., 2012; Luijten et al., 2011; Zhang et al., 2018). However, factors that account for individual differences in attentional bias are less well studied. One theory to account for individual differences in attentional bias is that individuals who exhibit reduced cognitive flexibility in the absence of drug cues may be more likely to experience attentional bias (Field & Cox, 2008). Probabilistic reversal learning can be used to assess cognitive flexibility in the absence of drug cues when automatic constraints on thought are low. Individuals diagnosed with SUD demonstrate impaired performance on PRL tasks, with a bias towards reward (Ersche et al., 2011; Izquierdo & Jentsch, 2012; Kanen et al., 2019; Lesage et al., 2017; Moreno-Lopez et al., 2014). Because individuals with SUD experience difficulty shifting from a learned set of reward contingencies to a new set when automatic constraints are expected to be low, alpha oscillatory power may be higher near nodes of the cingulo-opercular and frontoparietal networks when they attempt to shift to a new mode of responding making shifting more difficult. As an additional part of our second study, we will observe alpha oscillations in the same group of long-term nicotine smokers during a probabilistic reversal learning task. We expect to see that individuals with greater attentional bias, as assessed in the Stroop task, will exhibit higher alpha power during lose/shift trials when cognitive flexibility is being utilized near midfrontal, left frontal, and parietal brain regions. These results would demonstrate that reduced cognitive flexibility is tied to higher alpha power and that individual differences in cognitive flexibility may account for differences in the degree of attention bias experienced.

Together, these studies will demonstrate that altered alpha power dynamics near nodes of the frontoparietal and cingulo-opercular control networks may underlie differences in cognitive flexibility, possibly due to disruptions of voluntary allocation of attention influenced automatic constraints.

CHAPTER 2: Trait Rumination is Associated with Higher Alpha Oscillatory Power During Resting State

2.1 Introduction

Cognitive flexibility allows an individual to shift attention from one mode of thinking to another with relative ease, but occasionally attention can become stuck on a thought. The experience of being stuck on a thought is called rumination (Nolen-Hoeksema et al., 2008). Rumination may occur due to cognitive inflexibility, which is difficulty or inability to change from one mode of thought to another (Davis, & Nolen-Hoeksema, 2000; Koster et al., 2011; Nejad et al., 2013; Yee lo et al., 2012). Behavioral studies support the notion that rumination is related to cognitive inflexibility by demonstrating that individuals high in trait rumination (the tendency of an individual to ruminate) perform more poorly on tasks that require cognitive flexibility than those low in trait rumination (Altamirano et al., 2010; Davis, & Nolen-Hoeksema, 2000; Whitmer & Banich, 2007; Yee lo et al., 2012). For example, Altamirano et al. (2010) had participants complete the Ruminative Responses Scale-Revised (RRS-R) to measure trait rumination followed by performance of a letter naming task in which participants were cued to name a letter based on the side of the computer screen it was presented on. The letter naming task utilizes cognitive flexibility to switch modes of thinking based on the cue presented for each trial. Trait rumination score is negatively correlated with accuracy in the letter naming task, suggesting individuals higher in trait rumination experience greater difficulty with cognitive flexibility (Altamirano et al., 2010). These results demonstrate that there is a behavioral link between high trait rumination and decreased cognitive flexibility. Therefore, the link between trait rumination and cognitive inflexibility may have a neural basis.

Altered brain activity patterns in prefrontal and/or parietal cortices may underlie the cognitive inflexibility that appears to be characteristic of high trait rumination. During tasks that require cognitive flexibility for successful performance, it is generally observed that parts of the frontal and parietal lobe become more active when flexibility is necessary (Berry et al., 2017; Cole et al., 2013; Rosenbach et al., 2006; Hopfinger et al., 2000; Liu et al., 2003; Meyer et al.,

1998, Monsell, 2003; Panikratova et al., 2020; Smith et al., 2010). In addition, damage to frontal and parietal cortices is linked to impaired cognitive flexibility (Barbey et al., 2013; Caeyenberghs, et al., 2014; Mecklinger et al., 1999; Monsell, 2003; Rogers, et al., 1998; Sadaghiani et al., 2019). Frontal and parietal brain regions make up the frontoparietal control network, which is a collection of frontal and parietal brain regions that are demonstrated to work together to support flexible aspects of task performance and cognition (Badre & Nee, 2018; Berry et al., 2017; Marek & Dosenback, 2018; Petersen & Posner, 2012; Ptak, 2012). In the frontoparietal control network, the posterior parietal cortex is thought to be important for selecting input that will be the focus of attention, whereas the prefrontal cortex (PFC) may identify and maintain task-relevant information and modulate activity of the posterior parietal cortex accordingly (Badre & Nee, 2018; Braver, 2012; Kok, 1999; Liu, et al., 2003; Marek & Dosenback, 2018; Miller & Cohen, 2001; Praamstra et al., 2005). Rumination is associated with reduced neuronal activity in the PFC, particularly in left frontal regions, which are included as part of the frontoparietal control network (Ferdek et al., 2016; Nejad et al., 2013; Putnam & McSweeney, 2008). Due to their demonstrated roles in supporting cognitive flexibility, a deviation from normal activity in the PFC and/or posterior parietal cortex may underlie difficulties associated with cognitive flexibility and rumination, which could be further explored by examining brain oscillations.

Brain oscillations in the alpha band (8-13 Hz) are of interest when considering rumination because alpha oscillatory power dynamics may support cognitive flexibility. The brain may use alpha oscillatory power dynamics as a mechanism to direct neural resources towards task-related brain areas (Bonnefond et al., 2017; Hanslmayr et al., 2016; Jensen & Mazaheri, 2010; Klimesch, 2012). For example, during task switching tasks in which cognitive flexibility is heavily relied on, a lowering of alpha power in posterior parietal brain regions is observed when participants are cued to switch from one mode of thinking to another (Cooper et al., 2016;

Cunillera et al., 2012; Foxe et al., 2014; Phillips et al., 2014; Thut et al., 2006; Wolff et al., 2017; Worden et al., 2000). Lower alpha power is associated with increased activity in an underlying population of neurons (Hanslmayr, et al., 2011; Laufs et al., 2003a; Moosmann et al., 2003; Mantini et al., 2007). Together, these findings suggest that a lowering of alpha power may help channel neural resources to posterior parietal brain regions important for flexibly shifting between different modes of thinking (Braver, 2012; Foxe et al. 2014; Jensen & Mazaheri, 2010; Liu, et al., 2003; Marek & Dosenback, 2018; Miller & Cohen, 2001; Praamstra et al., 2005). Individuals high in trait rumination experience greater difficulty in completing tasks that require cognitive flexibility (Altamirano et al., 2010; Davis, & Nolen-Hoeksema, 2000; Whitmer & Banich, 2007) suggesting alpha power dynamics may be functioning differently in high ruminators due to the relationship between alpha power desynchronization and cognitive flexibility (Cooper et al., 2016; Cunillera et al., 2012; Foxe et al., 2014; Phillips et al., 2014; Wolff et al., 2017; Worden et al., 2000). As low alpha power is associated with cognitive flexibility, individuals high in trait may have higher alpha power, which may be revealed by assessing resting state alpha power dynamics.

In the current study we examine the hypothesis that higher trait rumination is predictive of higher alpha power during resting state in left frontal and posterior parietal located electrodes (Adrian & Matthews, 1934; Allen et al., 2018; Cicek & Nalcaci, 2001; Ferdek, et al., 2016; Knyazev et al., 2011; Laufs et al., 2003 a, b; Lopez da Silva, 1991; Mantini et al., 2007; Putnam & McSweeney, 2008). In order to examine this hypothesis, participants completed the RRS-R to measure trait rumination, followed by collection of resting state EEG data.

2.2 Materials and Methods

2.2.1 Subjects

Participants for this study were recruited from the University of New Hampshire Durham campus. A total of forty-seven participants gave written informed consent to participate in the

study in accordance with the Institutional Review Board of the University of New Hampshire. This review board follows the guidelines of the Declaration of Helsinki. Resting state data for this study was acquired in the same visit as performance of a source memory task, results published separately (Forner-Phillips et al., 2020). Two of the participants were excluded from analysis due to malfunction of the EEG equipment, while two additional participants were excluded due to their performance on the source memory task (see Forner-Phillips et al., 2020). Sample size was determined by consulting Miles and Shelvin (2001, Discovering Statistics using IBM SPSS Statistics, Fig. 8.9), planning for three independent variables (RRS-R, BDI, and BAI) and a small effect size for the previously published source memory study. The remaining participants included in the data analysis were between 18-35 years of age (m=21.26, SD=3.92), able to speak English, and had normal or corrected to normal vision. The participants also indicated that they had no history of head trauma or intracranial surgery, history or current neurological or psychiatric problems, current use of antidepressants or anxiolytics, or learning disabilities. For compensation, participants were given the choice between course credit or an Amazon gift card at a rate of $10/hour.

2.2.2 Questionnaires

Participants completed the RRS-R to assess trait levels of rumination. The RRS-R is a shortened version of the original Ruminative Responses Scale in which questions with depressive ideology were removed in order to assess rumination more accurately (Treynor et al., 2003). The RRS-R contains 10 statements about personal responses to feeling sad. For each statement, the participant rates on a scale of 1-4 how often they engage in the behavior described. The total score (range 10-40) is a sum of the ratings with higher total scores indicative of a greater tendency to ruminate. Participants also completed the Beck Depression Inventory-II (BDI-II; Beck et al., 1996) and the Beck Anxiety Inventory (BAI; Beck et al., 1988) to account for variance attributable to trait levels of depression and anxiety in our analysis as

rumination is often associated with depression and anxiety (Lyubomirsky, & Nolen-Hoeksema, 1993; McLaughlin, & Nolen-Hoeksema, 2011; Nolen-Hoeksema et al., 1993; Nolen-Hoeksema et al., 2008).

2.2.3 EEG Data Acquisition

A 64-channel BrainVision ActiChamp EEG system with Ag-AgCl electrodes (Brain Products GmbH, Munich, Germany) was used for EEG data acquisition. EEG data recording took place in a radiofrequency-shielded room (Universal Shielding Corp., Deer Park, NY). The data was collected using BrainVision's Pycorder software, vertex referenced, and sampled at 500 Hz using an analog filter of 0.1-200 Hz. Electrode impedances were kept below 25 kΩ. The P1 electrode could not be kept below 25 kΩ for four participants, so the channel was excluded from the final EEG analysis for those four participants. Resting state EEG data was collected before participants completed the source memory task. While resting state EEG data was recorded, participants were instructed to relax, let their minds wander freely, and focus their eyes on a fixation cross on a computer monitor for six minutes with eyes open. We chose to collect eyes open resting state data because we were interested in comparing individual differences in resting state alpha power rather than within subjects differences between eyes open and eyes closed (Inagaki & Meyer, 2019; Jennings, et al., 2016; Mennes, et al., 2010).

2.2.4. EEG Data Analysis

EEG data was processed using the MATLAB (Mathworks, Natick, MA) plug-in EEGLAB (Delorme & Makeig, 2004). For each participant's data, the EEGLAB tool for automatic channel rejection was used to identify any electrodes with kurtosis greater than five standard deviations from that channel's mean. Identified channels were not completely removed from processing, but they were excluded during re-referencing to the average EEG signal. First, the EEG data was filtered between 1-100 Hz followed by re-referencing to the average EEG signal. An average of 4 channels (SD= 5) were excluded from re-referencing for each participant. After re-

referencing, the EEG data was then segmented into 4.5-second-long epochs. Each epoch was visually inspected for any non-blink related changes in voltage greater than 75 microvolts. If an epoch contained a change in voltage exceeding 75 microvolts, the epoch was manually removed from the data and excluded from further processing. Upon completion of epoch rejection, Infomax Independent Component Analysis (ICA; Bell & Sejnowski, 1995) was used to separate the data into independent components. Epochs for the resulting independent components were visually inspected for noise characterized by large uniform changes in voltage. Upon completion of the independent component epoch rejection, infomax ICA was run again. An average of 25 epochs (SD=14) in total were rejected for each participant leaving an average of 55 epochs for averaging resting state alpha power. The EEGLAB plug-in function ADJUST (Mognon et al., 2011) was used on the processed data for each participant to identify artifact components. Identified artifact components were excluded from further analysis and data was converted back into sensor space. An average of 10 components (SD=4) were excluded for each participant. All oscillatory analyses were done using channel data in sensor space.

Two regions of interest were used for oscillatory analyses, a left frontal region including electrodes AF7, AF3, F7, F5, and F3 (Fig. 2.1A) and a posterior parietal region including electrodes P5, P3, P1, Pz, P2, P4, P6, PO3, POz, and PO4 (Fig. 2.1B). These regions were selected *apriori* based on EEG resting state studies focused on alpha oscillatory power (Adrian & Matthews, 1934; Allen et al., 2018; Cicek & Nalcaci, 2001; Knyazev et al., 2011; Laufs et al., 2003 a, b; Lopez da Silva, 1991; Mantini et al., 2007; Putnam & McSweeney, 2008). Average alpha power (8-13 Hz) values were extracted from EEGLAB for each participant to be further analyzed in SPSS v25 (IBM Corporation, Armonk, NY). Separate averages were calculated for the left frontal and posterior parietal regions of interest.

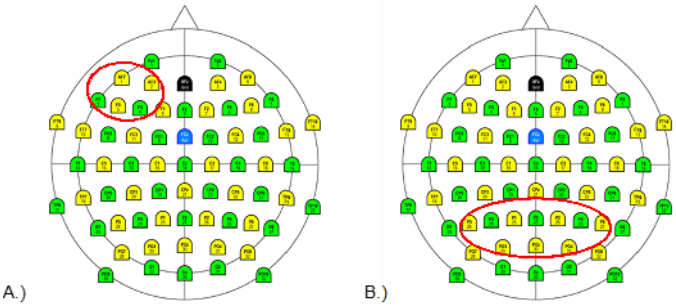


Figure 2.1. Electrodes used in EEG Analysis. Pictured is a diagram of the layout of electrodes for the 64 channel Brain Vision Actichamp EEG system. The triangle at the top of the circle represents a nose in order to orient where on the scalp the electrodes are located. The red ovals highlight the electrodes used in our analyses. A.) Electrodes analyzed in the left frontal region of interest. B.) Electrodes analyzed in the posterior parietal region of interest.

We sought to test whether trait rumination predicts average alpha power during resting state when accounting for variance attributable to trait anxiety and depression. To answer this question, we performed two separate linear regressions with average alpha power as the dependent variable for both the left frontal and posterior parietal regions of interest. RRS-R, BDI, and BAI scores, as well as their interaction terms, were used as predictor variables in each model. All predictor variables were entered into the model at the same time rather than in a stepwise fashion. An alpha level of .05 was used to determine statistical significance.

2.3 Results

Trait rumination, depression, anxiety, and their interaction terms (rumination x depression, rumination x anxiety, and depression x anxiety) were used as predictor variables in standard linear regressions with average alpha power in decibels (dB) at rest as the dependent variable. The part correlation squared (sr^2), beta (b), standard error of beta (SEb), and standardized beta value are reported for any individual predictor variables that uniquely account for a significant proportion of variance in the dependent variable. Means and standard deviations for each variable can be found in Table 2.1. The variables included in the models had

no outliers, impossible scores, or missing scores. All quantitative variables were normally distributed, and pairs of quantitative variables had a normal bivariate distribution, no evidence of heteroscedasticity, and there were no bivariate outliers. An alpha level of .05 was used to determine significance.

Table 2.1.
Means and Standard Deviations of Variables

Variables	**Mean**	**SD**
BDI-II score	5.53	4.31
BAI Score	5.51	5.43
RRS-R Score	20.09	4.06
Average Power for Left Frontal Alpha (dB)	56.44	3.50
Average Power for Posterior Parietal Alpha (dB)	59.50	4.09

Notes: Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory (BAI), Ruminative Responses Scale-Revised (RRS-R),

2.3.1 Left Frontal Region of Interest

A standard linear regression was used to examine whether trait rumination, depression, anxiety and their interactions predict average alpha power at rest in left frontal located electrodes. Zero order correlations between variables can be found in Table 2.2. The overall regression model was not significant (R=.36, F(6,36)= .91, p=.50). However, rumination alone uniquely accounts for 9.73% of the variance in average alpha power at rest when accounting for variance attributed to all other variables in the model (sr^2=.097, b=.30, *SEb*=.15, *standardized beta*= .35; t(36)=2.01, p=.05; Fig. 2.2; Table 2.3.). For each one-unit change in RRS-R score, average alpha power at rest increases by .3 dB. The range in RRS-R score in our sample was 13-26 predicting a difference of 4 dB between the average alpha power at rest from our participants with the lowest and highest RRS-R scores.

Table 2.2
Zero order correlations of variables for Alpha Regressions

	Average alpha power left frontal	Average alpha power posterior parietal	BDI-II	BAI	RRS-R	Interaction of BDI-II and RRS-R	Interaction of BAI and RRS-R	Interaction of BDI-II and BAI
Average alpha power left frontal	-	-	-.01	-.06	.25	.05	-.02	.032
Average alpha power posterior parietal	-	-	-.07	.02	.24	.14	.13	.12
BDI-II	-.01	-.07	-	.78	.37	.48	.48	.69
BAI	-.06	.02	.78	-	.39	.50	.66	.80
RRS-R	.25	.24	.37	.39	-	.23	.20	.24
Interaction of BDI-II and RRS-R	.05	.14	.48	.50	.23	-	.80	.71
Interaction of BAI and RRS-R	-.02	.13	.48	.66	.20	.80	-	.83
Interaction of BDI-II and BAI	.03	.12	.69	.80	.24	.71	.83	-

Notes: Ruminative Responses Scale-Revised (RRS-R), Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory (BAI).

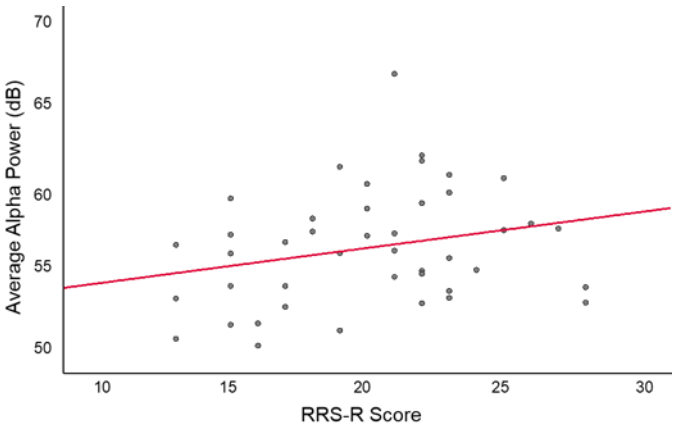


Figure 2.2. Left frontal ROI EEG results. As RRS-R score significantly predicts average alpha power at rest, the scatterplot depicts a dot for each participant and their corresponding RRS-R score (horizontal axis) and their average alpha power at rest (vertical axis) calculated from the left frontal region of interest. A line of best fit for the data points is displayed. As trait rumination increases, the average alpha power at rest increases.

Table 2.3.
Results from left frontal alpha regression

Variables	**b**	**SEb**	**Standardized beta**	**Sr^2**	**p value**
BDI-II score	-.053	.219	-.065	.001	.81
Beck Anxiety Inventory BAI Score	-.243	.215	-.376	.031	.27
RRS-R Score	.300*	.150*	.348*	.097*	.05*
Interaction of RRS-R and BDI-II	.011	.050	.064	.001	.82
Interaction of RRS-R and BAI	-.029	.049	-.209	.008	.56
Interaction of BDI-II and BAI	.026	.023	.423	.031	.26

Notes: An asterisk denotes significance at the .05 level. Ruminative Responses Scale-Revised (RRS-R), Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory (BAI), beta (b), standard error of beta (SEb). Sr^2 is the unique variance explained by a predictor variable.

2.3.2. Posterior Parietal Region of Interest.

A standard linear regression was used to examine whether trait rumination, depression, anxiety and their interactions predict average alpha power at rest in posterior parietal located electrodes. Zero order correlations between variables can be found in Table 2.2. The overall regression model was not significant (R=.40, F(6,36)= 1.14, p=.36). The unique proportion of variance in average alpha power at rest accounted for by rumination when accounting for variance attributed to all other variables in the model approached significance (sr^2=.092, b=.34, *SEb*=.17, *standardized beta*= .34; t(36)= 1.99, p=.06; Fig. 2.3; Table 2.4). Though not statistically significant, the effect of rumination on resting state alpha power in the posterior

parietal region is similar in size to the left frontal effect with a predicted difference of 4.42 dB between our lowest and highest RRS-R score participants.

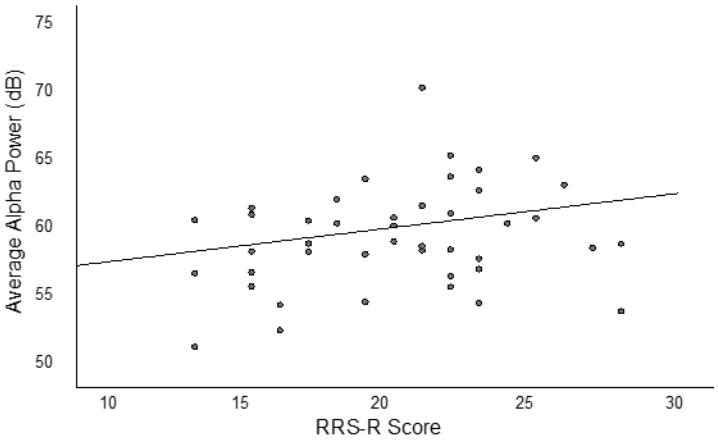


Figure 2.3. Posterior Parietal ROI EEG results. The scatterplot depicts a dot for each participant and their corresponding RRS-R score (horizontal axis) and their average alpha power at rest (vertical axis) calculated from the posterior parietal region of interest. A line of best fit for the data points is displayed. As trait rumination increases, the average alpha power at rest increases. However, in this region of interest the relationship between RRS-R score and average alpha power at rest was not statistically significant.

Table 2.4.
Results from posterior parietal alpha regression

Variables	**b**	**SEb**	**Standardized Beta**	**Sr^2**	**p value**
BDI-II score	-.333	.251	-.350	.041	.19
BAI Score	-.138	.247	-.184	.007	.58
RRS-R Score	.341	.172	.339	.092	.06
Interaction of RRS-R and BDI-II	.013	.057	.061	.001	.82
Interaction of RRS-R and BAI	-.006	.056	-.111	.000	.91
Interaction of BDI-II and BAI	.030	.026	.417	.030	.26

Notes: Ruminative Responses Scale-Revised (RRS-R), Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory (BAI), beta (b), standard error of beta (SEb). Sr^2 is the unique variance explained by a predictor variable.

2.4. Discussion

Elevated alpha power in left frontal located electrodes while at rest suggests that altered alpha power dynamics may be related to cognitive inflexibility associated with high trait rumination and possible engagement in state rumination. Our EEG results are in line with our original hypothesis and reveal that high trait rumination is associated with higher average alpha power in left frontal located electrodes (Fig. 2.2) and a similarly sized non-significant effect in posterior parietal located electrodes (Fig. 2.3). These results suggest that there are altered alpha oscillatory dynamics at rest in individuals high in trait rumination possibly due to internally directed attention.

Higher power in the alpha oscillatory band associated with higher trait rumination may be indicative of internally directed attention. Our results reveal that trait rumination accounts for 9% of the variance in average alpha power in left frontal and posterior parietal located electrodes. The left frontal result is a moderate, but significant effect whereas the posterior parietal is a moderate non-statistically significant effect. In both the left frontal and posterior parietal electrodes, individuals higher in trait rumination exhibit higher average alpha power during resting state (Fig. 2.2 & 2.3). Alpha power at rest is generally observed to be high when an individual is in a state of quiet wakefulness with their eyes closed and alpha power lowers when the eyes are opened and attentional focus is engaged externally, suggesting higher alpha power may be reflective of internally directed attention (Adrian & Matthews, 1934; Bai et al., 2016; Klimesch, 2012; Knyazev et al., 2011; Laufs et al., 2003a, b; Lopez da Silva, 1991). Indeed, studies that instruct participants to engage in tasks that require internally directed attention, such as mental math or imagery, find that performance of such tasks is associated with

increased alpha power (Cooper et al., 2003, 2006; Magosso et al., 2019; Mo et al., 2013; Palva et al., 2005; Ray & Cole, 1985). Findings from resting state network studies also support the notion that higher alpha power may be indicative of internally directed attention. The default-mode network is a collection of brain regions that are often active when individuals are in a state of quiet wakefulness, as in the current study, and its activation is linked to internal self-focused thoughts (Buckner et al., 2008; Fomina et al., 2015; Greicius et al., 2003; Gusnard et al., 2001; Raichle, 2015). Alpha power at rest is positively correlated with activation of the default-mode network further suggesting a link between higher alpha power at rest and an internal focus of attention (Bowman et al., 2017; Knyazev et al., 2011; Mantini et al., 2007; Mo et al., 2013). Therefore, our results showing that higher rumination scores predict higher resting state alpha may be due to high ruminators directing their attention inwards more frequently.

An internal focus of attention combined with high trait rumination may set the stage for state rumination to occur. State rumination occurs when an individual becomes mentally stuck on a thought and they experience difficulty redirecting their attention away from the ruminative thought (Nolen-Hoeksema et al., 2008). Additionally, state rumination tends to be associated with an internal focus of attention as rumination is often self-focused (Koster et al., 2011; Lyubomirsky & Nolen-Hoeksema, 1993; Nolen-Hoeksema et al., 2008; Rude et al., 2007). Our EEG results show that higher trait rumination is associated with higher alpha power, which may be reflective of an internal focus of attention (Cooper et al., 2003, 2006; Magosso et al., 2019; Mo et al., 2013; Palva et al., 2005; Ray & Cole, 1985). In addition, alpha power is positively correlated with activity of the default-mode network (Bowman et al., 2017; Knyazev et al., 2011; Mantini et al., 2007; Mo et al., 2013) which is linked to self-focused thoughts (Buckner et al., 2008; Fomina et al., 2015; Greicius et al., 2003; Gusnard et al., 2001; Raichle, 2015). As state rumination tends to be self-focused (Koster et al., 2011; Lyubomirsky & Nolen-Hoeksema, 1993; Nolen-Hoeksema et al., 2008; Rude et al., 2007), these findings suggest individuals high in trait

rumination may engage in state rumination at rest. However, we did not measure state rumination in the current study, so the notion that high ruminators may have engaged in state rumination is speculative. Future studies may be able to measure state rumination more directly at rest. Higher alpha power at rest observed as a function of trait rumination suggests individuals high in trait rumination may be directing their attention internally activating the default-mode network and engaging in state rumination more often than individuals low in trait rumination, which may underlie difficulties with cognitive flexibility.

Elevated resting state alpha oscillatory power may underlie cognitive inflexibility associated with high trait rumination. Behavioral studies of trait rumination demonstrate that individuals high in trait rumination exhibit impaired performance on tasks that require cognitive flexibility (Altamirano et al., 2010; Davis, & Nolen-Hoeksema, 2000; Whitmer & Banich, 2007; Yee lo et al., 2012). A difference in behavior suggests there may be underlying differences in neural functioning in high ruminators. Previous studies show hypoactivation of frontal brain regions is associated with rumination (Ferdek et al., 2016; Nejad et al., 2013; Putnam & McSweeney, 2008). Our result of higher alpha power near left frontal electrodes associated with higher trait rumination is in line with these previous studies as higher alpha power is associated with decreased activity in an underlying population of neurons (Hanslmayr, et al., 2011; Laufs et al., 2003a; Moosmann et al., 2003; Mantini et al., 2007). Activation of frontal and parietal brain regions, particularly those included in the frontoparietal control network, are demonstrated to be important for the performance of tasks that utilize cognitive flexibility (Barbey et al., 2013; Berry et al., 2017; Caeyenberghs, et al., 2014; Cole et al., 2013; Dosenbach et al., 2006; Hopfinger et al., 2000; Liu et al., 2003; Mecklinger et al., 1999; Meyer et al., 1998, Monsell, 2003; Panikratova et al., 2020; Rogers, et al., 1998; Sadaghiani et al., 2019; Smith et al., 2010). In the frontoparietal control network, frontal brain regions are thought to be important for identifying a task set and modulating activity of parietal brain regions in order to orient attention in line with

current task goals (Badre & Nee, 2018; Braver, 2012; Kok, 1999; Liu, et al., 2003; Marek & Dosenback, 2018; Miller & Cohen, 2001; Praamstra et al., 2005). Therefore, dampened activity near frontal regions in high ruminators at rest suggests frontal brain regions may not be able to effectively modulate the activity of parietal regions, which may underlie the difficulties with cognitive flexibility these individuals experience. Future studies utilizing effective connectivity may reveal differences in connectivity between frontal and parietal brain regions in high ruminators to support the notion that frontal regions may not be effectively communicating with parietal regions leading to cognitive inflexibility.

2.4.1. Limitations

Although we selected specific regions of interest to analyze, we did not attempt to localize the source of signal being picked up by the EEG electrodes. As the variance in signal accounted for in the left frontal (9.7%) and posterior parietal (9.2%) regions of interest is very similar, it may be the case that both regions of interest picked up signals from the same source, but the left frontal electrodes may have picked up a clearer signal from the source, which may explain why the left frontal effect is statistically significant while the posterior parietal effect is not.

2.4.2. Conclusions

High trait rumination is associated with higher resting state alpha oscillatory power. Higher alpha power may reflect an internal focus of attention and activation of the default-mode network, suggesting high ruminators may spend more time directing their thoughts inwards, possibly engaging in state rumination. Higher alpha power is associated with decreased activity of an underlying population of neurons. Decreased activity of brain regions in the frontoparietal control network may underlie difficulties with cognitive flexibility experienced by high ruminators.

CHAPTER 3: Attentional Bias is Associated with Higher Alpha Oscillatory Power

3.1 Introduction

According to the World Health Organization, around 35 million people meet the criteria for substance use disorder (SUD) and there are an estimated .5 million drug related deaths annually. There are many factors that may influence an individual's likelihood of continuing use of a substance of abuse. One such factor is attentional bias towards drug related stimuli (drug cues). Attentional bias refers to when stimuli associated with the effects of a substance are highly salient, which may make shifting attention away from drug related thoughts and drug abstinence more difficult (Dias et al., 2015; Janes et al., 2010b; Kang et al., 2012; Luijten et al., 2011; Zhang et al., 2018). Many drugs of abuse enhance the activity of dopamine in the mesolimbic pathway, which may reinforce associations between stimuli in the environment while an individual administers a drug and the drug response through classical conditioning (Chiara et al., 1993; Glautier, 1994; Glautier et al, 1994; Hyman et al., 2006; Kelley, 2004; Lazev et al., 1999; Pierce & Kumaresan, 2006; Volkow et al., 2004). Prolonged drug use can lead to sensitization of the mesolimbic dopamine system making drugs and drug related stimuli highly salient (Berridge & Robinson, 2016; Olney et al, 2018; Robinson & Berridge, 1993). Indeed, the brains of individuals diagnosed with SUD demonstrate cue reactivity, which is heightened activity in reward and motivation related brain regions when drug related stimuli are present (Chase et al., 2011; Courtney et al., 2016; Due et al., 2002; Engelmann et al, 2012; Huang et al., 2018; Janes et al., 2010b, 2015; Jasinska et al., 2014; Kang et al., 2012; McClernon et al., 2005, 2009; Schacht et al., 2013; Wang et al., 2020). Strong cue reactivity is linked to attentional bias (Janes et al., 2010b), therefore heightened salience may increase automatic constraints and attract attention to drug cues and subsequently make shifting attention away from drugs cues more difficult. For example, when drug related stimuli are presented during a Stroop task, individuals that exhibit attentional bias experience a slowing in reaction time reflecting attention directed towards word meaning rather than font color (Dias et al., 2015; Janes et al., 2010b; Kang et al., 2012; Luijten et al., 2011; Zhang et al., 2018). Cognitive

flexibility is the ability to flexibly shift attention from one mode of thinking to another (Dajani & Uddin, 2015; Miyake et al., 2000). Because attentional bias is associated with difficulty shifting attention away from drug cues, attentional bias may decrease cognitive flexibility by altering neurobiological mechanisms that support flexibility.

Studies of cue reactivity in the brain suggest key attentional networks may alter their functioning and contribute to difficulties with cognitive flexibility during attentional bias. Neuroimaging methods, such as functional magnetic resonance imaging (fMRI), can be used to observe how the brain changes its activity in response to drug related stimuli. fMRI studies consistently observe cue reactivity in anterior cingulate cortex and the insula, which are brain regions included in the cingulo-opercular control network (Chase et al., 2011; Courtney et al., 2016; Due et al., 2002; Engelmann et al, 2012; Huang et al., 2018; Janes et al., 2010b, 2015; Jasinska et al., 2014; Kang et al., 2012; McClernon et al., 2005, 2009; Schacht et al., 2013; Wang et al., 2020). The cingulo-opercular network plays a role in cognitive flexibility by increasing its activity in response to salient stimuli and when conflict is detected and forwarding this information to the frontoparietal control network in order to reorient attention in line with goals (Banich, 2009; Botvinick, 2001; Braver, 2012; Berry et al., 2017; Dosenbach et al., 2008; Fan et al., 2005; Kropotov et al., 2017; Petersen & Posner, 2012; Silton et al., 2010, 2011). The frontoparietal control network consists of dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex and is thought to support shifting attention in a goal driven manner (Berry et al., 2017; Cole et al., 2013; Crone et al., 2005; Hopfinger et al., 2000; Liu et al., 2003; Meyer et al., 1998, Monsell, 2003; Panikratova et al., 2020; Petersen & Posner, 2012; Smith et al., 2010; Weidner et al., 2002; Woldorff et al., 2004). Posterior parietal cortex is particularly important for selecting a focus for attention, while dlPFC may hold onto task relevant information and influence posterior parietal cortex to focus attention in a goal driven manner (Badre & Nee, 2018; Braver, 2012; Crone et al., 2005; Kok, 1999; Liu, et al., 2003; Marek & Dosenback, 2018;

Miller & Cohen, 2001; Praamstra et al., 2005). Attentional bias is associated with reduced connectivity between nodes of the cingulo-opercular network and other parts of the brain (Janes et al. 2010a), which suggests cingulo-opercular signals to the frontoparietal network to shift attention may be diminished. Altered brain oscillatory activity may underlie functional alterations near nodes of these networks and underlie difficulties with cognitive flexibility during attentional bias.

Brain oscillations in the alpha band (8-13 Hz) support cognitive flexibility and may be altered during attentional bias and contribute to difficulty shifting attention away from drug cues. During tasks that require cognitive flexibility, decreases in alpha power are observed in posterior parietal brain regions (Cooper et al., 2016; Cunillera et al., 2012; Foxe et al., 2014; Phillips et al., 2014; Thut et al., 2006; Wolff et al., 2017; Worden et al., 2000), which play an important role in orienting attention (Chiu & Yantis, 2009; Crone et al., 2005; Esterman et al., 2009; Forstmann et al., 2006; Gurd et al., 2002; Kok, 1999; Petersen & Posner, 2012). More generally, it is observed that alpha power lowers in brain regions important for completion of the task at hand (Bacigalupo & Luck, 2019; Doesburg et al., 2016; Foxe & Snyder, 2011; Haegens et al., 2011; Handel et al., 2011; Ikkai et al., 2016; Klimesch et al., 1998; Minarik et al., 2018; Moorselaar et al., 2018; Okazaki et al., 2015; Poch et al., 2017, 2018; Thut et al., 2006; van Diepen et al., 2016; Vollebregt et al., 2016; Worden et al., 2000). Decreases in alpha power are associated with increased activity in an underlying population of neurons (Hanslmayr, et al., 2011; Laufs et al., 2003a; Moosmann et al., 2003; Mantini et al., 2007). These findings suggest that alpha oscillatory power dynamics may be used as a mechanism to channel neural resources towards task relevant brain regions (Bonnefond et al., 2017; Hanslmayr et al., 2016; Jensen & Mazaheri, 2010; Klimesch, 2012). Attentional bias is associated with difficulty shifting attention, therefore alpha oscillatory power dynamics may be altered during attentional bias, especially in brain regions that support cognitive flexibility.

In the current study, we investigate the hypothesis that individuals diagnosed with SUD that exhibit greater attentional bias will exhibit higher alpha power near nodes of the frontoparietal network and lower alpha power near nodes of the cingulo-opercular network when drug cues are present and automatic constraints are high. To answer this question, nicotine dependent participants completed a Stroop task that included classic and emotional stimuli while their brain activity was recorded using EEG. The emotional stimuli included smoking related words to prompt attentional bias. An attentional bias score was calculated for each participant and was used as a predictor of alpha power during the different trial types. We expected to see that alpha power during drug trials would be lower near midfrontal electrodes and higher near left frontal and parietal located electrodes for participants with greater attentional bias due to the drug cues being highly salient and difficulty shifting attention away from drug related thoughts. Individuals with SUD exhibit varying degrees of attentional bias towards drug related cues. One theory to account for individual differences in attentional bias is individuals who may have generally reduced cognitive flexibility may be more susceptible to attentional bias (Field & Cox, 2008). This raises the question of whether individuals with SUD only experience reduced cognitive flexibility when drug cues are present and automatic constraints are high or more generally when automatic constraints are low. To answer our second question, we used attentional bias as a predictor of alpha power during the classic Stroop trials and in addition, the same participants completed a probabilistic reversal learning task (PRL). The PRL task presents participants with two stimuli with differing probabilities of reward. After several trials of choosing the more rewarding stimulus, the reward probabilities reverse. When a reversal occurs in the task, participants must flexibility shift their mode of thinking in order to adapt to the new task contingencies. Previous studies reveal an association between attentional bias and impaired performance on PRL tasks (Ersche et al., 2011; Izquierdo & Jentsch, 2012; Kanen et al., 2019; Lesage et al., 2017; Moreno-Lopez et al., 2014). In addition, PRL task performance is demonstrated to increase activity in nodes of the

frontoparietal control network (Cools et al., 2002; Dickstein et al., 2010; Hornak et al., 2004; Yaple & Yu, 2019). Because attentional bias is associated with decreased cognitive flexibility, we expected to see that participants with greater attentional bias would exhibit higher alpha power in left frontal and parietal electrodes when attempting to shift their mode of thinking.

3.2 Materials and Methods

3.2.1 Subjects

A total of 28 nicotine dependent smokers were recruited for this study through McLean Hospital. Four participants were excluded from final analyses. One participant voluntarily opted out of the study after the first task and the other three were excluded to due technical difficulties with the EEG recordings. Data from the remaining 24 (10 female; Fagerstrom test of nicotine dependence, *m*=5) participants were used for analysis. Participants were between 18-45 years old (*m*=32) and met the DSM-IV criteria for nicotine dependence. Before participating, it was confirmed that participants were not experiencing a current serious medical illness, pregnant, dependent on alcohol or drugs other than nicotine, diagnosed with major depressive disorder in the previous 6 months, or diagnosed with a current or lifetime psychotic disorder. Eligible participants were then given informed consent in line with the IRB of McLean Hospital. All participants completed a Stroop task followed by a probabilistic reversal learning task and were compensated with a flat rate of $50 for their time.

3.2.2 Stroop Task

The Stroop task was presented using PsychoPy (Open Science Tools Ltd., Nottingham, England). Stimuli were presented in six different blocks consisting of 152 experimental trials each (912 experimental trials total). The order in which the blocks were presented was counterbalanced across participants. Each block contained either classic (congruent and incongruent) or emotional (drug or neutral) stimuli (Fig. 3.1). The classic Stroop task presents stimuli on a computer screen that are the names of colors in different colored fonts. The colors

used in this task were red, green, and blue. The font color could either be congruent (e.g., the word green in green color font) or incongruent (e.g., the word green in red color font) with word meaning. The emotional Stroop stimuli consisted of English words that had a meaning either related to smoking (drug; e.g., cigarette) or not related to smoking (neutral; e.g., dog) in different colored fonts. The emotional stimuli were also presented in blue, green, or red font color. Each font color was assigned a button on a keyboard and participants were instructed to press the button corresponding to the font color of the words presented on the computer screen as quickly and accurately as possible and to ignore the meaning of the word. Participants practiced responding to font color on random strings of letters for forty-eight trials before beginning the experimental trials in which behavioral and EEG data were collected. After the practice trials were complete, the participants completed the experimental trials in the blocked format. Each block began with a 250 ms fixation cross followed by stimulus presentation. The stimulus remained onscreen for 150 ms during which time the participant pressed a button corresponding to the font color. An intertrial interval between 1850-1950 ms separated stimulus presentation from performance feedback. After the inter-trial interval, participants were presented with a smiling face if they indicated the correct response or a frowning face if they made an incorrect response or did not submit a response. Another inter-trial interval between 900-1100 ms followed feedback presentation. During the experimental trials, PsychoPy collected data on accuracy and reaction time for each trial type to be later analyzed. An attentional bias score (Williams et al., 1996) was calculated for each participant by subtracting the average reaction time for accurate neutral trials from the average reaction time for accurate smoking trials (attention bias score = accurate drug trials RT – accurate neutral trials RT).

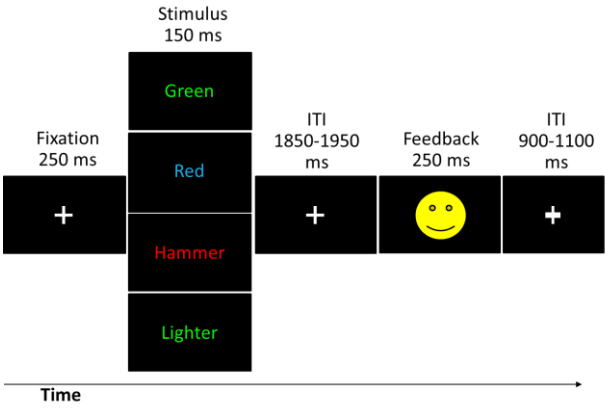


Figure 3.1. Stroop study procedure. Participants are presented with one of four different types of stimuli in the center of the computer screen. Stimulus types from top to bottom are congruent, incongruent, neutral, and drug. The participant's goal is to respond as quickly and accurately as possible to the font color of the stimulus and ignore word meaning. After a response is entered, feedback on accuracy is presented.

3.2.2.1 Stroop Behavior Analysis

An alpha level of .05 was used for all behavioral comparisons. Accuracy and reaction time values were extracted from PsychoPy and analyzed in SPSS. Behavioral performance was compared using paired samples t-tests for within subjects comparisons. One paired samples t-test was used to compare average accuracy during congruent trials to average accuracy during incongruent trials. An additional paired samples t-test was used to compare the average reaction time during congruent trials to the average reaction time during incongruent trials. Similar paired samples t-tests were used to analyze average accuracy and reaction time between the drug and neutral trials.

3.2.2.2 Stroop EEG Data Acquisition

EEG data was collected using a 96-channel Geodesic Sensor Net system (Electrical Geodesic, Inc. OR). Data were sampled at a rate of 250Hz with a bandwidth of .01-100Hz. Electrode impedances were kept below 50 kΩ.

3.2.2.3 Stroop EEG Data Analysis

EEG data were processed using the MATLAB (Mathworks, Natick, MA) plug-in EEGLAB (Delorme & Makeig, 2004). For each participant's data, the EEGLAB tool for automatic channel rejection was used to identify any channels with kurtosis greater than five standard deviations from that channel's mean. Identified channels were not completely removed from processing but were excluded during re-referencing to the average EEG signal. An average of 7 channels (SD= 2) were excluded from re-referencing for each participant. First, the EEG data were filtered between 1-100 Hz followed by re-referencing to the average EEG signal. After re-referencing, the EEG data were segmented into epochs in which the zero time point was locked with stimulus presentation and the end points of the epoch were one second prior to the stimulus onset and two seconds after stimulus onset. Each epoch was visually inspected for any non-blink related changes in voltage greater than 75 microvolts. If an epoch contained a change in voltage exceeding 75 microvolts, the epoch was manually removed from the data and excluded from further processing. Upon completion of epoch rejection, ICA was used to separate the data into independent components. Epochs for the resulting independent components were visually inspected for noise characterized by large uniform changes in voltage. An average of 603 epochs (SD=14) in total were rejected for each participant and an average of 309 trials were left for EEG analysis. Upon completion of the independent component epoch rejection, infomax ICA was run again. The EEGLAB plug-in function ICLabel (Pion-Tonachini et al., 2019) was used on the processed data for each participant to identify artifact components (e.g., muscle activity, channel noise, heartbeat, etc…). Identified artifact components were excluded from further analysis and data were converted back into sensor space. An average of 40 components (SD=10) were excluded for each participant. All oscillatory analyses were done using channel data in sensor space.

Three regions of interest (ROIs) were used for oscillatory analyses, a left frontal region located over dlPFC including electrodes 11, 12, 18, and 19 (Fig. 3.2a), a posterior parietal region including electrodes 44, 45, 46, 51, 52, and 53 (Fig. 3.2b), and a midfrontal region located over the ACC including electrodes 2, 8, 9, and 67 (Fig. 3.2c). A time-frequency decomposition was performed on the cleaned EEG data using a modified Morlet wavelet in 25 ms steps for 30 log-spaced frequencies between 4 and 50 Hz with 2 cycles at 4 Hz and 5 cycles at 50 Hz. Average alpha power (8-13 Hz) values and average alpha inter-trial coherence (ITC) values between 400-800 ms post-cue during drug and neutral trials were extracted from EEGLAB for each participant to be further analyzed in SPSS. ITC is a measure of phase synchrony across trials. The closer the ITC value is to 1, the greater the degree of phase coherence across trials. The time window of 400-800 ms post-cue was selected based on alpha effects observed in previous Stroop EEG studies (Ergen et al., 2014; Hanslmayr et al., 2008; Popov et al., 2019; Tafuro et al., 2019). Separate averages were calculated for the left frontal, mid-frontal, and posterior parietal regions of interest during each trial type.

A. B. C.

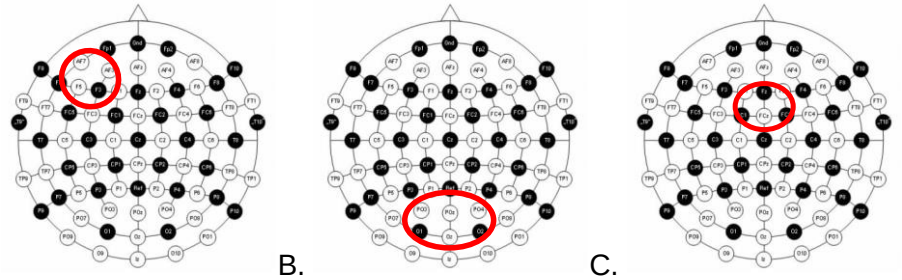


Figure 3.2. Electrode regions of interest. Pictured is a diagram of the layout of electrodes for the 96 channel Geodesic sensor net system. The triangle at the top of the image represents the front of the head. The red circles highlight the electrodes used in our EEG analyses. A.) left frontal ROI. B.) Parietal ROI. C.) Midfrontal ROI.

Each participant's behavioral reaction time data were used to calculate an attentional bias score (average accurate reaction time Drug – average accurate reaction time Neutral;

Williams et al., 1996). As cue reactivity is associated with greater activity in midfrontal regions, but reduced cognitive flexibility, one of our hypotheses was that attentional bias score would be negatively correlated with alpha power in the midfrontal ROI and positively correlated with alpha power in the left frontal and parietal ROIs during drug trials, but there would be no significant correlation during neutral trials in all regions of interest. Severity of smoking behavior may also impact task performance; therefore, we also included pack year (number of cigarettes smoked per day x number of years smoking) as a predictor of alpha power in our analyses to account for variance attributable to smoking behavior severity (Janes et al., 2010a, b; 2015). To address the relationship between attentional bias and alpha power during the task, we performed linear regression analyses with attentional bias score, pack year, and their interaction term predicting average alpha power between 400-800 ms post cue during drug trials and average alpha power between 400-800 ms post cue during neutral trials for each ROI. Additionally, we hypothesized that attentional bias score would be negatively correlated with alpha ITC in the midfrontal ROI and positively correlated with alpha ITC in the left frontal and parietal ROIs, but there would be no significant correlation during neutral trials. Linear regression analyses with the same predictor variables were used to predict average alpha ITC between 400-800 ms post-cue during drug trials and average alpha ITC between 400-800 ms post-cue during neutral trials. An alpha level of .05 was used to determine significance for all regression analyses.

3.2.3 Probabilistic Reversal Learning Task

Stimuli for the probabilistic reversal learning task were presented using PsychoPy. Participants were presented with two different colored circles (red and blue) on the left and right side of a computer screen and were asked to select one of the circles with a corresponding button press (Fig. 3.3). One of the circles yielded a positive outcome 80% of the time while choosing the other circle yielded a negative outcome 80% of the time. A positive outcome resulted in a gain of 5 cents of fictional money, while a negative outcome resulted in no fictional

money earned. Participants were instructed that the goal of the task was to collect as much fictional money as possible. If the participant selected the circle with the 80% chance of a positive outcome for 8 consecutive trials, then the reward contingencies reversed so that the circle that previously yielded a positive outcome 80% of the time then yielded a negative outcome 80% of the time and vice versa. This pattern continued until a total of 300 trials was reached. Before starting the experimental trials, participants completed 10 practice trials to ensure they understood the goal of the task.

Each trial began with a fixation cross in the center of the computer screen that lasted between 500-1000 ms followed by presentation of the stimuli. Stimuli remained onscreen for 2000 ms or until a response was entered. If a response was entered, a black border appeared around the designated stimulus for 400 ms. A break between 400-600 ms separated the disappearance of the stimuli and response feedback. Positive feedback and negative feedback were associated with either a 700 Hz tone or a 1000 Hz tone, which was counterbalanced between participants. The tone sounded for 200 ms. Additionally, the sound of a coin drop followed the positive feedback tone and lasted 1200 ms. The coin drop sound was meant to imitate the rewarding effects of food reward in animal studies. If the participant did not designate a response within the response window, the feedback was a 300 Hz tone paired with visual presentation of “No response!”

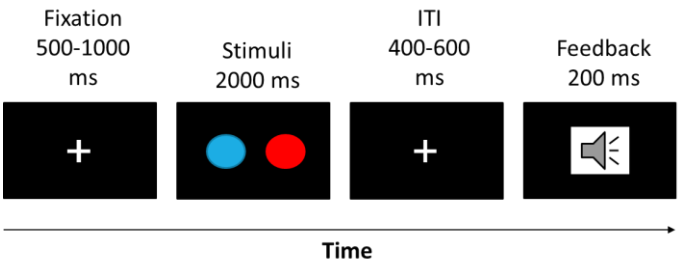


Figure 3.3. Probabilistic reversal learning task procedure. Participants are presented with two stimuli and are instructed to select one. After an intertrial interval, participants are given either positive or negative feedback accompanied by different tones on their choice.

3.2.3.1 Probabilistic Reversal Learning EEG Data Acquisition

The same participants that completed the Stroop task also completed the PRL task using the same data acquisition parameters (See “Stroop EEG Data Acquisition”).

3.2.3.2 Probabilistic Reversal Learning EEG Data Analysis

EEG data processing followed the same steps as those outlined in “Stroop EEG Data Analysis”. An average of 6 channels (SD= 3) were excluded from re-referencing for each participant. An average of 57 epochs (SD=32) in total were rejected for each participant. An average of 41 components (SD=11) were excluded for each participant. Average alpha power and average alpha ITC values post-cue during trials that followed a negative outcome and the participant shifted their response (lose/shift) were extracted from EEGLAB for each participant to be further analyzed in SPSS. Separate averages were calculated for the left frontal, mid-frontal, and posterior parietal regions of interest. Our hypothesis was that individuals that exhibit greater attentional bias would exhibit higher alpha power and lower alpha ITC during lose/shift trials. To answer this question, we performed regression analyses with attentional bias score, pack year, and their interaction term as predictors of average alpha power post-cue during lose/shift trials and average alpha ITC post-cue during lose/shift trials. An alpha level of .05 was used to determine significance.

3.3 Results

3.3.1. Stroop Behavior Results

Behavioral performance was compared using paired samples t-tests for within subjects comparisons. Average accuracy and reaction time values were extracted from PsychoPy. Means and standard deviations are listed in Table 3.1. A total of four paired samples t-tests

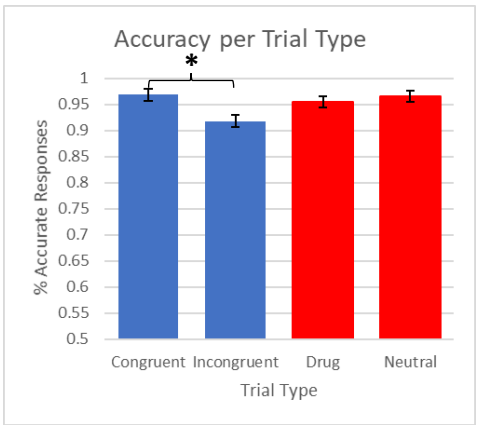
were run for accuracy and reaction time with an alpha level of .05. For accuracy, the comparison of average accuracy during congruent trials to average accuracy during incongruent trials was significant ($t(24)=4.42$, $p<.001$, Fig. 3.4a). Participants demonstrate more accurate responses during congruent trials ($m=.97$) than incongruent trials($m=.92$). The comparison of average accuracy during drug trials to neutral trials failed to reach significance. For reaction time, the comparison of average reaction time during accurate congruent trials to accurate incongruent trials was significant ($t(24)=-6.07$, $p<.001$, Fig. 3.4b). Participants respond faster during congruent trials ($m=.75$ ms) than incongruent trials ($m=.83$ ms). The comparison of average reaction time during accurate drug trials to accurate neutral trials was also significant ($t(24)=2.10$, $p=.045$, Fig. 3.4b). Participants respond faster during neutral trials ($m=.75$ ms) than drug trials ($m=.76$ ms).

Table 3.1.
Means and Standard Deviations of Stroop Behavior Variables

Variables	**Mean**	**SD**
Average Percent Accurate Congruent Trials	.97	.03
Average Percent Accurate Incongruent Trials	.92	.07
Average Percent Accurate Neutral Trials	.97	.03
Average Percent Accurate Drug Trials	.95	.04
Average Reaction Time Accurate Congruent Trials	.75	.09
Average Reaction Time Accurate Incongruent Trials	.83	.13
Average Reaction Time Accurate Neutral Trials	.75	.07
Average Reaction Time Accurate Drug Trials	.76	.07

Notes. Reaction times are reported in milliseconds.

A.



B.

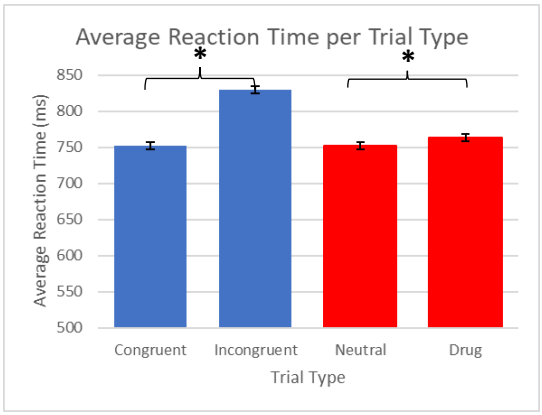


Figure 3.4. Stroop Behavior Results. For both graphs the horizontal access labels the different trial types during the Stroop task. Blue bars compare congruent to incongruent trials. Red bars compare drug to neutral trials. Lines with asterisks denote a significant difference at the .05 level between two trial types. A.) The bars represent average proportion of accurate responses during different trial types. B.) The bars represent the average reaction time in milliseconds during accurate responses for different trial types.

3.3.2 EEG Results

Drug attentional bias score, pack year, and the interaction of drug attentional bias score and pack year were used as predictor variables in standard linear regressions with average alpha power in decibels (dB) and average alpha ITC as the dependent variables. The part correlation squared (sr^2), beta (b), standard error of beta (SEb), and standardized beta value are reported for any individual predictor variables that uniquely account for a significant proportion of variance in the dependent variable. Means and standard deviations for each variable can be found in Table 3.2. The variables included in the models had no outliers, impossible scores, or missing scores. All quantitative variables were normally distributed, and pairs of quantitative variables had a normal bivariate distribution, no evidence of heteroscedasticity, and there were no bivariate outliers. An alpha level of .05 was used to determine significance.

Table 3.2.
Means and Standard Deviations of EEG Variables

Variables	**Mean**	**SD**
Attentional Bias Score	.01	.03
Pack Year	9.04	6.39
Left Frontal Drug Alpha	.81	1.92
Left Frontal Drug ITC	.10	.02
Left Frontal Neutral Alpha	.63	1.94
Left Frontal Neutral ITC	.10	.01
Left Frontal Lose/Shift Alpha	.07	.88
Left Frontal Lose/Shift ITC	.13	.03
Midfrontal Drug Alpha	.22	1.34
Midfrontal Drug ITC	.10	.01
Midfrontal Neutral Alpha	.17	1.47
Midfrontal Neutral ITC	.10	.01
Midfrontal Lose/Shift Alpha	.06	.86
Midfrontal Lose/Shift ITC	.13	.02
Parietal Drug Alpha	.88	1.28
Parietal Drug ITC	.10	.01
Parietal Neutral Alpha	.91	1.24
Parietal Neutral ITC	.10	.01
Parietal Lose/Shift Alpha	.14	1.08
Parietal Lose/Shift ITC	.13	.03

Notes: Intertrial coherence (ITC)

3.3.2.1 Stroop EEG results

Standard linear regressions were used to examine whether attentional bias, pack year, and their interactions predict average alpha power between 400-800 ms post-cue during drug and neutral trials in left frontal, midfrontal, and parietal located electrodes with a total of six

independent linear regressions. Zero order correlations between variables can be found in Table 3.3. The overall regression model was not significant for any of the models and most of the predictor variables also did not yield significant results (Table A1-5). However, attentional bias score alone uniquely accounts for 20.25% of the variance in average alpha power between 400-800 ms post-cue during drug trials in the left frontal ROI when accounting for variance attributed to all other variables in the model (sr^2=.2025, *b*=34.78, *SEb*=14.67, *standardized beta*= .467; *t*(24)=2.37, *p*=.028; Fig. 3.5; Table 3.4.). For each one-second change in attentional bias score, average alpha power increases by 34.78 dB. Because there is a significant relationship between drug related attentional bias and alpha power in left frontal regions, we performed a mirror analysis using non-drug attentional bias score (average accurate reaction time incongruent – average accurate reaction time congruent) as a predictor of alpha power during incongruent trials. The analysis did not reveal any significant relationships (Table A6).

Table 3.3
Zero order correlations of variables for Stroop Alpha Power Regressions

	AB	PY	Interaction of AB and PY	LF D	LF N	MF D	MF N	P D	P N
AB	-	-.20	-.12	.39	.29	.33	.21	.20	.25
PY	-.20	-	-.20	.04	.00	-.11	-.07	-.08	-.21
Interaction of AB and PY	-.12	-.20	-	.25	.26	.15	.16	.20	.22
LF D	.39	.04	.25	-	-	-	-	-	-
LF N	.29	.00	.26	-	-	-	-	-	-
MF D	.33	-.11	.15	-	-	-	-	-	-
MF N	.21	-.07	.16	-	-	-	-	-	-
P D	.20	-.08	.20	-	-	-	-	-	-
P N	.25	-.21	.22	-	-	-	-	-	-

Notes: Attentional bias (AB), Pack year (PY), left frontal (LF), drug (D), neutral (N), midfrontal (MF), parietal (P).

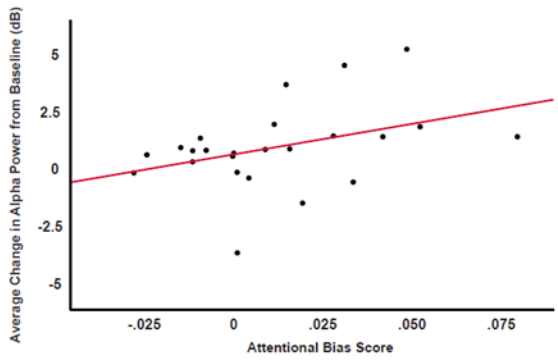


Figure 3.5. Attentional Bias Score Predicting Average Change in Alpha Power in Left Frontal Electrodes During Drug Trials. Each dot represents the average change in alpha power (in decibels) 400-800 ms post-cue during drug trials for each participant included in the analysis. The red line is the line of best fit for the data to demonstrate the positive relationship between attentional bias and average change in alpha power. Attentional bias score was calculated by subtracting the average reaction time during accurate drug trials from the average reaction time during neutral trials.

Table 3.4
Results from left frontal alpha drug trial regression

Variables	**b**	**SEb**	**Standardized beta**	**Sr^2**	**p value**
Attentional Bias Score	34.78*	14.67*	.48*	.2025*	.028*
Pack Year	.06	.06	.20	.04	.318
Interaction of Attentional Bias and Pack Year	5.13	2.89	.35	.11	.09

Notes: An asterisk denotes significance at the .05 level. beta (b), standard error of beta (SEb). Sr^2 is the unique variance explained by a predictor variable.

Standard linear regressions were also used to examine whether attentional bias, pack year, and their interactions predict average alpha ITC between 400-800 ms post-cue during drug and neutral trials in left frontal, midfrontal, and parietal located electrodes with a total of six

independent linear regressions. Zero order correlations between variables can be found in Table 3.5. The overall regression model was not significant for any of the models and there were no predictor variables that accounted for a significant unique proportion of variance (Table A7-12).

Table 3.5
Zero order correlations of variables for Stroop Alpha ITC Regressions

	AB	PY	Interaction of AB and PY	LF D	LF N	MF D	MF N	P D	P N
AB	-	-.20	-.12	.01	.27	-.02	.01	.16	.17
PY	-.20	-	-.20	.06	-.27	-.19	-.02	-.03	-.32
Interaction of AB and PY	-.12	-.20	-	.25	-.31	.15	-.28	.26	-.04
LF D	.01	.06	.25	-	-	-	-	-	-
LF N	.27	-.27	-.31	-	-	-	-	-	-
MF D	-.02	-.19	.15	-	-	-	-	-	-
MF N	.01	-.02	-.28	-	-	-	-	-	-
P D	.16	-.03	.26	-	-	-	-	-	-
P N	.17	-.32	-.04	-	-	-	-	-	-

Notes: Attentional bias (AB), Pack year (PY), left frontal (LF), drug (D), neutral (N), midfrontal (MF), parietal (P).

3.3.2.2 Probabilistic Reversal Learning EEG Results

Standard linear regressions were used to examine whether attentional bias, pack year, and their interactions predict average alpha power post-cue during lose/shift trials in left frontal, midfrontal, and parietal located electrodes with a total of three independent linear regressions. Zero order correlations between variables can be found in Table 3.6. The overall regression model was not significant for any of the models and there were no predictor variables that accounted for a significant unique proportion of variance (Table A13-15).

Table 3.6
Zero order correlations of variables for PRL Lose/Shift Alpha Power Regressions

	AB	PY	Interaction of AB and PY	LF	MF	P
AB	-	-.2	-.12	.01	-.05	-.01
PY	-.2	-	-.20	-.29	-.23	-.25

Interaction of AB and PY	-.12	-.20	-	-.03	.04	.01
LF	.01	-.29	-.03	-	-	-
MF	-.05	-.23	.04	-	-	-
P	-.01	-.25	.01	-	-	-
Notes: Attentional bias (AB), Pack year (PY), left frontal (LF), midfrontal (MF), parietal (P).						

Standard linear regressions were also used to examine whether attentional bias, pack year, and their interactions predict average alpha ITC post-cue during lose/shift trials in left frontal, midfrontal, and parietal located electrodes with a total of three independent linear regressions. Zero order correlations between variables can be found in Table 3.6. The overall regression model was not significant for any of the models and there were no predictor variables that accounted for a significant unique proportion of variance (Table A16-18).

Table 3.7
Zero order correlations of variables for PRL Lose/Shift Alpha ITC Regressions

	AB	PY	Interaction of AB and PY	LF	MF	P
AB	-	-.2	-.12	-.05	-.11	-.10
PY	-.2	-	-.20	-.05	-.09	-.03
Interaction of AB and PY	-.12	-.20	-	.34	.34	.24
LF	-.05	-.05	.34	-	-	-
MF	-.11	-.09	.34	-	-	-
P	-.10	-.03	.24	-	-	-
Notes: Attentional bias (AB), Pack year (PY), left frontal (LF), midfrontal (MF), parietal (P).						

3.4 Discussion

Attentional bias towards drug cues may create a state of temporary reduced cognitive flexibility accompanied by higher alpha power in left frontal brain regions. Our behavioral results reveal that nicotine dependent smokers exhibit lower accuracy and slower reaction time during incongruent trials compared to congruent trials (Fig 3.4a). Additionally, when comparing reaction time between drug and neutral trials, reaction time is slower for drug trials (Fig. 3.4b). Linear regression analyses of attentional bias score predicting average alpha power between 400-

800ms post-cue revealed a significant effect in a left frontal ROI with greater attentional bias predicting higher alpha power during drug trials (Fig. 3.5). No significant associations were revealed for other regions of interest or alpha ITC. We also examined attentional bias score as a predictor of average alpha power and ITC post-cue during lose/shift trials in a probabilistic reversal learning task, but no significant associations were revealed. Together our results suggest that attentional bias towards drug cues may create a state of reduced cognitive flexibility when drug cues are present, but cognitive flexibility may not be impacted in the absence of drug cues.

Higher alpha power when drug cues are present may contribute to the mental "stickiness" associated with attentional bias towards drug cues. Behaviorally, we demonstrate that nicotine dependent smokers experience attentional bias towards drug cues as revealed through a slower reaction time during the Stroop task when words had a drug related meaning (Fig 3.4b). Previous studies suggest the slowing in reaction time during drug trials is likely attributable to semantic processing of the word meaning and the salience of the word meaning due to its association with the substance of abuse (Dias et al., 2015; Janes et al., 2010b; Kang et al., 2012; Luijten et al., 2011; Zhang et al., 2018). Drug cues can be highly salient for individuals with substance use disorder, therefore the cues hijack attention, which may increase difficulty in shifting attention away from the cues. Our oscillatory results support this notion. We observe that greater attentional bias is associated with higher alpha power in left frontal located electrodes when drug cues are present (Fig. 3.5). Higher alpha power is associated with reduced activity in an underlying population of neurons (Hanslmayr et al., 2011; Laufs et al., 2003a; Moosmann et al., 2003; Mantini et al., 2007), suggesting left frontal regions may be less active during drug trials for individuals that experience attentional bias. Our left frontal ROI is located above left dlPFC. The dlPFC may be important for identifying information that is goal/task relevant (Badre & Nee, 2018; Braver, 2012; Crone et al., 2005; Kok, 1999; Liu, et al.,

2003; Marek & Dosenback, 2018; Miller & Cohen, 2001; Praamstra et al., 2005). Reduced activity near this region when drug cues are present may suggest that dlPFC may not be updating information about task relevant stimuli. Additionally, a lowering of alpha power may be important for shifting from one mode of thinking to another (Cooper et al., 2016; Cunillera et al., 2012; Foxe et al., 2014; Phillips et al., 2014; Thut et al., 2006; Wolff et al., 2017; Worden et al., 2000). Therefore, higher alpha power in individuals that experience greater attentional bias suggests it may be more difficult to shift attention away from drug cues back to the task at hand.

Cognitive flexibility may only be negatively impacted for individuals that display attentional bias when automatic constraints are high. Probabilistic reversal learning requires participants to flexibly shift from one mode of thinking to another based on feedback on their task performance. Some theorists suggest that individual differences in attentional bias may be due to more general differences in cognitive control ability (Field & Cox, 2008). If individuals that experience greater attentional bias experience a general reduction in cognitive flexibility, we would expect that alpha oscillatory activity would be similarly altered as observed during the Stroop task when drug stimuli are present. However, no significant associations between attentional bias and average alpha power post-cue during the trials in which the participants shifted their mode of thinking were revealed. A possible difference between the emotional Stroop task and the PRL task is that in the emotional Stroop task drug cues are present, which due to the saliency of drug cues is expected to increase automatic constraints on thought, whereas drug cues are not present in the PRL task and automatic constraints would likely be low. The stimuli used in the PRL task are not inherently salient and because reward contingencies shift between the two stimuli, it is unlikely that one stimulus would become more salient than the other. A difference in automatic constraints may explain why there is a significant relationship between attentional bias and alpha power in left frontal regions during the emotional Stroop task, but not during the PRL task. To further support this notion, we

performed an additional analysis with the Stroop data to assess any relationship between general (non-drug related) attentional bias and alpha power during incongruent trials. We did not find a significant relationship between non-drug attention bias and alpha power in left frontal located electrodes during incongruent trials. Incongruent trials are similar to lose/shift trials in the PRL task because attention must be shifted to processing font color and there are no drug stimuli present, therefore automatic constraints are likely low. Together these findings suggest that alterations in alpha power may be tied to an increase in automatic constraints prompted by drug cues, which may increase difficulty in shifting attention away from drug related thoughts.

Reduced cognitive flexibility associated with attentional bias may make drug abstinence more difficult. Not all individuals with SUD demonstrate an attentional bias towards drug related stimuli, but those that do tend to be less successful in attempts to abstain from a substance of abuse (Janes et al., 2010a, b; Waters et al., 2003). Studies of cue reactivity demonstrate that drug cues can be highly salient, which is also linked to greater attentional bias (Dias et al., 2015; Janes et al., 2010b; Kang et al., 2012; Luijten et al., 2011; Zhang et al., 2018). Our results suggest that drug cues capture attention and may increase difficulty in shifting attention away from drug cues. Together these results suggest that when an individual experiences attentional bias, their attention is directed towards drug related stimuli and it may be difficult to shift their attention away, which may make abstinence from drug use more challenging (Janes et al., 2010a, b; Waters et al., 2003). Identifying a role for alpha oscillations in attentional bias may provide new avenues for drug abstinence programs. Behavioral interventions such as mindfulness meditation and neurofeedback training are shown to alter alpha oscillations (Gruzelier, 2014; Kerr et al., 2013). Therefore, interventions such as these may be able to help individuals that experience attentional bias to disengage from drug cues and shift their attention more flexibly and boost their drug abstinence success.

3.4.1 Conclusions

Greater attentional bias to drug related cues is associated with higher alpha power in left frontal located electrodes. This suggests that neural resources to shift attention away from drug related thoughts are not being deployed as effectively with increasing attentional bias. However, when drug cues are not present, the relationship between attentional bias and alpha power during shifting is not present. As such, alpha oscillatory power dynamics may only be altered during tasks that require flexibility when salient distracting stimuli are present.

CHAPTER 4: Summary and Discussion

4.1 Summary of Results

4.1.1 Restatement of original hypothesis

In a series of studies using two different populations that experience reduced cognitive flexibility, we sought to determine the role of alpha oscillations in such difficulties as a possible unifying factor. Chapter 2 summarizes a study using a group of participants comprised of neurotypical young adults who completed the RRS-R to assess trait levels of rumination followed by collection of EEG data during quiet wakefulness. We expected to see that higher trait rumination would be predictive of higher resting state alpha power in left frontal and parietal located electrodes. Chapter 3 summarizes a study using a group of participants comprised of long-term nicotine smokers who completed an emotional Stroop task and a probabilistic reversal learning task while EEG was recorded. In the emotional Stroop task, we expected to see that accuracy would be lower and reaction time would be slower during incongruent trials and drug trials compared to congruent trials and neutral trials respectively. An attentional bias score was calculated from reaction time data for each participant in order to account for individual differences in attentional bias. The attentional bias score was used as a predictor of alpha power and phase coherence across drug and neutral trials during the Stroop task. We expected to see that attentional bias would have a negative correlation with alpha power near midfrontal located electrodes and a positive correlation with alpha power near left frontal and parietal located electrodes during drug trials, but there would be no significant correlations during neutral trials. In addition, we expected to see that attentional bias would be positively correlated with alpha ITC during drug trials, but there would be no significant correlation during neutral trials for all regions of interest. In the probabilistic reversal learning task, we expected to see a positive correlation between attentional bias score and alpha power during lose/shift trials and a negative correlation between attentional bias score and alpha ITC in all regions of interest. Together, these studies help demonstrate that cognitive inflexibility in multiple forms may be traced back to altered alpha power dynamics.

4.1.2 Summary of Trait Rumination is Associated with Higher Alpha Oscillatory Power During Resting State

Chapter 2 examined the relationship between trait tendency to ruminate and resting state alpha power in left frontal and posterior parietal located electrodes. Individuals higher in trait rumination exhibit higher alpha power at rest near left frontal located electrodes. Elevated resting state alpha oscillatory power may underlie cognitive inflexibility associated with high trait rumination. Behavioral studies of trait rumination demonstrate that individuals high in trait rumination (high ruminators) exhibit impaired performance on tasks that require cognitive flexibility (Altamirano et al., 2010; Davis, & Nolen-Hoeksema, 2000; Whitmer & Banich, 2007; Yee lo et al., 2012). A difference in behavior suggests there may be underlying differences in neural functioning in high ruminators. Previous studies show hypoactivation of dorsolateral prefrontal cortex is associated with rumination (Ferdek et al., 2016; Nejad et al., 2013; Putnam & McSweeney, 2008). Higher alpha power is associated with decreased activity in an underlying population of neurons (Hanslmayr, et al., 2011; Laufs et al., 2003a; Moosmann et al., 2003; Mantini et al., 2007), therefore alpha power is expected to be high over areas that exhibit reduced activity. Activation of frontal and parietal brain regions, particularly dlPFC and posterior parietal cortex which make up the frontoparietal control network, are demonstrated to be important for the performance of tasks that utilize cognitive flexibility (Barbey et al., 2013; Berry et al., 2017; Caeyenberghs, et al., 2014; Cole et al., 2013; Dosenbach et al., 2006; Hopfinger et al., 2000; Liu et al., 2003; Mecklinger et al., 1999; Meyer et al., 1998, Monsell, 2003; Panikratova et al., 2020; Rogers, et al., 1998; Sadaghiani et al., 2019; Smith et al., 2010). In the frontoparietal control network, dlPFC is thought to be important for identifying a task set and modulating activity of parietal brain regions to orient attention in line with current task goals (Badre & Nee, 2018; Braver, 2012; Kok, 1999; Liu, et al., 2003; Marek & Dosenback, 2018; Miller & Cohen, 2001; Praamstra et al., 2005). Therefore, dampened activity in nodes of the frontoparietal control network in high ruminators at rest may suggest frontal brain regions may

not be effectively identifying task relevant information, which may underlie difficulties with cognitive flexibility these individuals experience. Without updated information about task goals from dlPFC, parietal cortex may orient attention towards whatever the most salient stimulus is (Chica et al., 2013; Constantinidis, 2006; Gottlieb, 2007; Nardo et al., 2011). For individuals high in trait rumination, negative self-focused thoughts may be most salient (Kaiser et al., 2018; Nolen-Hoeksema et al., 2008). In addition to an association with reduced neural activity, higher alpha power is also associated with internally directed attention (Adrian & Matthews, 1934; Bai et al., 2016; Klimesch, 2012; Knyazev et al., 2011; Laufs et al., 2003a, b; Lopez da Silva, 1991). Therefore, high ruminators may have more of an internal focus of attention, which may set the stage for rumination to occur. Ruminative thoughts are high in automatic constraints (Christoff et al., 2016), which may make shifting attention away from ruminative thoughts more difficult. Higher alpha power at rest in nodes of the frontoparietal control network associated with rumination may impact alpha power dynamics during performance of tasks in which cognitive flexibility is needed. For example, individuals higher in trait rumination who are feeling more anxious experience difficulty remembering contextual details, which is accompanied by higher alpha power in parietal located electrodes (Forner-Phillips et al., 2020). Alpha power dynamics channeling neural resources may help bind information about an object and contextual details together (Klimesch, 2012; Minarik et al., 2018). Individuals higher in trait rumination may be more likely to ruminate during the task, which may hinder the binding of contextual information by disrupting the flow of neural resources in the brain. Alterations in alpha power dynamics for high ruminators suggest rumination may disrupt the normal distribution of neural resources and foster cognitive inflexibility.

4.1.3 Summary of Attentional Bias is Associated with Higher Alpha Oscillatory Power

Chapter 3 examined the relationship between attentional bias towards drug cues in a group of long-term nicotine smokers and alpha power during a Stroop task and a probabilistic

reversal learning task. Participants demonstrated a slowing in reaction time during trials with drug related words replicating previous studies and suggesting attentional bias towards drug cues. Greater attentional bias is associated with higher alpha power in left frontal located electrodes, but we did not find an association between attentional bias and alpha power when drug cues are not present and flexibility is required. A possible difference between the Stroop task and the PRL task is that drug cues in the Stroop task may increase automatic mental constraints, whereas automatic constraints are likely lower during the PRL task. These findings suggest that attentional bias towards drug cues may only negatively impact cognitive flexibility when automatic constraints are high.

Individuals with SUD that experience attentional bias towards drug cues demonstrate a similar cognitive inflexibility as rumination, which may be attributable to altered alpha oscillatory activity tied to strong automatic constraints as well. Attentional bias occurs when drug cues capture attention and it is difficult for the individual to shift their attention away from the drug cues (Dias et al., 2015; Janes et al., 2010b; Kang et al., 2012; Luijten et al., 2011; Zhang et al., 2018). The degree of salience attributed to a stimulus can be referred to in terms of automatic constraints with higher automatic constraints reflecting greater attention capture (Chirstoff et al., 2016). Alpha oscillatory power dynamics may channel neural resources in the brain in line with attentional demands (Bacigalupo & Luck, 2019; Doesburg et al., 2016; Foxe & Snyder, 2011; Haegens et al., 2011; Handel et al., 2011; Ikkai et al., 2016; Klimesch et al., 1998; Minarik et al., 2018; Moorselaar et al., 2018; Okazaki et al., 2015; Poch et al., 2017, 2018; Thut et al., 2006; van Diepen et al., 2016; Vollebregt et al., 2016; Worden et al., 2000). Therefore, when drug cues are present, alpha oscillations may be altered to direct neural resources towards processing information about the drug cues because the cues are highly salient. Increased neural resources directed towards processing highly salient stimuli may increase difficulty in attempts to direct attention away from the salient stimuli in order to pursue other goals when

those stimuli are present, thereby decreasing cognitive flexibility. A difference in automatic constraints associated with highly salient stimuli may explain why there is a relationship between attentional bias and alpha power during the Stroop task, but not during the PRL task. The stimuli used in the PRL task are not inherently salient and because reward contingencies shift between the two stimuli, it is unlikely that one stimulus would become more salient than the other. Together these results suggest that alterations in alpha power in left frontal regions may be tied to mental states characterized by high automatic constraints. In addition, the altered alpha power dynamics observed in this study are similar to those observed in high ruminators, which may suggest that drug related thoughts may be just as sticky as ruminative thoughts and that higher alpha power in left frontal regions may be a common underlying neural consequence.

4.2 Discussion

Cognitive flexibility is an important tool to help us adapt to our constantly changing environments. Reduced cognitive flexibility is associated with perseveration and “sticky” thoughts that capture attention and are difficult to shift attention away from. Gaining an understanding of the neural mechanisms that underlie cognitive flexibility and sticky thoughts can provide avenues for potential behavioral intervention to improve flexibility. In this dissertation we examine two populations that experience reduced cognitive flexibility and associated neural alterations. The main finding is that higher alpha power in left frontal located electrodes is associated with both higher trait rumination and greater attentional bias to drug cues. A commonality between high ruminators and individuals that experience attentional bias to drug cues is that both populations experience mental states that are high in automatic constraints. Alpha power dynamics are important for the distribution of neural resources in accordance with attentional demands (Bonnefond et al., 2017; Hanslmayr et al., 2016; Jensen & Mazaheri, 2010; Klimesch, 2012). Mental states high in automatic constraints may alter alpha

oscillatory power dynamics to bias neural resources towards processing highly salient stimuli, which in turn may make shifting attention away from salient thoughts more difficult. Cognitive inflexibility related to rumination is demonstrated to be tied primarily to negative self-focused thoughts, whereas cognitive inflexibility in individuals with SUD that exhibit attentional bias is tied to drug cues. On the surface, these two examples of cognitive inflexibility may seem quite different. However, in both cases there is a stimulus that is highly salient that is difficult to shift attention away from. For rumination, that stimulus is negative self-focused thoughts, whereas for attentional bias, the stimulus is a drug cue. From a cognitive perspective, these two modes of thinking have similar constraints suggesting a common underlying neural alteration. Both types of thoughts have strong automatic constraints (as both stimuli are highly salient; Christoff et al., 2016). Similar alterations of alpha oscillations in these two populations during states of high automatic constraints suggest that alpha oscillations may be the common underlying neural alteration underlying difficulty with cognitive flexibility. No significant relationship between attentional bias and alpha power during the PRL task or during incongruent trials in the Stroop task further suggests that high automatic constraints may be driving altered oscillatory activity as automatic constraints are low in both cases. Together these results suggest the distribution of neural resources is altered during mental states high in automatic constraints, particularly near left frontal located electrodes.

Both high ruminators and individuals with greater attentional bias towards drug cues exhibit altered alpha power near left frontal located electrodes suggesting activity of the frontoparietal control network may be negatively impacted by rumination and attentional bias to drug cues. Activity of frontal and parietal brain regions, particularly dlPFC and posterior parietal cortex which make up the frontoparietal control network, are demonstrated to be important for the performance of tasks that utilize cognitive flexibility and damage to these brain areas is linked to reduced cognitive flexibility (Barbey et al., 2013; Berry et al., 2017; Caeyenberghs, et

al., 2014; Cole et al., 2013; Dosenbach et al., 2006; Hopfinger et al., 2000; Liu et al., 2003; Mecklinger et al., 1999; Meyer et al., 1998, Monsell, 2003; Panikratova et al., 2020; Rogers, et al., 1998; Sadaghiani et al., 2019; Smith et al., 2010). In the frontoparietal control network, dlPFC is thought to be important for identifying a task set and modulating activity of parietal brain regions to orient attention in line with current task goals (Badre & Nee, 2018; Braver, 2012; Kok, 1999; Liu, et al., 2003; Marek & Dosenback, 2018; Miller & Cohen, 2001; Praamstra et al., 2005). Alpha power is higher near left frontal located electrodes for both high ruminators and individuals that exhibit a greater degree of attentional bias to drug cues. Higher alpha power is associated with reduced metabolic activity in an underlying group of neurons (Hanslmayr et al., 2011; Laufs et al., 2003a; Moosmann et al., 2003; Mantini et al., 2007). Therefore, dampened activity near left frontal electrodes may suggest frontal brain regions may not be effectively updating task-relevant information and modulating the activity of parietal regions, which may underlie difficulties with cognitive flexibility these individuals experience. Without updated information about task goals from dlPFC, parietal cortex may orient attention towards whatever the most salient stimulus is (Chica et al., 2013; Constantinidis, 2006; Gottlieb, 2007; Nardo et al., 2011). For individuals high in trait rumination, negative self-focused thoughts may be most salient (Kaiser et al., 2018; Nolen-Hoeksema et al., 2008) and for individuals that exhibit a greater degree of attentional bias towards drug cues, thoughts related to drug cues may be most salient (Chase et al., 2011; Courtney et al., 2016; Due et al., 2002; Engelmann et al, 2012; Huang et al., 2018; Janes et al., 2010b, 2015; Jasinska et al., 2014; Kang et al., 2012; McClernon et al., 2005, 2009; Schacht et al., 2013; Wang et al., 2020). Therefore, higher alpha power near left frontal regions may disrupt activity of the frontoparietal control network and contribute to difficulties shifting attention away from highly salient thoughts. However, higher alpha power is also associated with cognitive inhibition. Therefore as an alternative possibility, higher alpha power near left frontal regions could potentially reflect attempts to cognitively inhibit functioning of left dlPFC. If dlPFC identifies task relevant information, it is possible that when

stimuli are highly salient, the dlPFC may incorrectly identify the information as task relevant. In such case, cognitive inhibition of dlPFC may be necessary in order to disengage from thoughts related to the task-irrelevant salient stimulus and back to the task at hand. Future studies may be better able to determine the role of cognitive strategies related to rumination and attention bias.

4.3 Future Directions

Similar alterations of alpha power in two populations that experience mental states high in automatic constraints and reduced cognitive flexibility suggests alpha oscillations may be altered in other populations that struggle with cognitive flexibility and mental states strong in automatic constraints. For example, Kaiser et al. (2018) demonstrate that individuals with depression exhibit an attentional bias towards negative self-related material and that trait rumination is a mediating factor. In this dissertation we demonstrate higher left frontal alpha power related to trait rumination and attentional bias, which suggests alpha oscillatory power may be elevated in individuals with depression as well and contribute to difficulty disengaging from highly salient thoughts. Identification of altered alpha oscillations underlying difficulties with cognitive flexibility also opens the door for possible behavioral interventions that may improve cognitive flexibility and associated behavioral outcomes. For example, both mindfulness meditation and neurofeedback training are demonstrated to help individuals alter the functioning of their alpha oscillations (Gruzelier, 2014; Kerr et al., 2013). Such interventions may be able to help individuals who experience thoughts with strong automatic constraints alter alpha oscillatory activity and improve cognitive flexibility.

One of the limitations of the studies presented here is that we did not attempt to localize the source of the EEG signal and we did not assess connectivity between our regions of interest. Because we only observed significant alterations of alpha power in our left frontal ROI, utilizing methods to assess connectivity between regions may offer important information as to

how left frontal regions are communicating with other brain regions when cognitive flexibility is reduced, especially those in the frontoparietal and cingulo-opercular control networks. We would expect that connectivity between frontal regions and midfrontal and parietal regions may be lessened when an individual experiences reduced cognitive flexibility.

There are also more specific questions that arise from the experiments reported in chapters 2 & 3. In chapter 2 we revealed a relationship between trait rumination and alpha power at rest. However, participants were not questioned as to whether they engaged in state rumination during EEG recording, therefore any relationship between state rumination and alpha power is unclear. Nolen-Hoeksema & Morrow (1993) developed a rumination induction technique that may be utilized to explore whether state rumination alters alpha power dynamics. The rumination induction may also be used to explore whether reduced cognitive flexibility tied to state rumination may worsen task performance, such as in Forner-Phillips et al. (2020).

The results of the study summarized in chapter 3 offer several routes for future questions. First, because data collection was cut short due to the global pandemic, it would be useful to replicate the study reported here possibly with a task other than PRL that is low in automatic constraints and requires high deliberate constraints such as a task-switching task. Second, if changes in alpha power indeed only occur when highly salient stimuli such as drug cues are present, it may be useful to have participants complete a version of the PRL task that uses drug related stimuli as a reward and compare both their performance and changes in alpha power to the version of the PRL task that does not include drug related stimuli. Based on our current results we would expect to see that cognitive flexibility would be reduced in a drug cue version of the task and it would be accompanied by higher alpha power in left frontal brain regions.

4.4 Conclusion

The work presented in this dissertation supports a link between alpha oscillatory power dynamics and cognitive flexibility when attention is being captured by highly salient thoughts and stimuli. In two separate populations that experience reduced cognitive flexibility tied to mental states high in automatic constraints, higher alpha power is observed in left frontal located electrodes. Higher alpha power may disrupt the normal flow of neural resources in the brain and contribute to difficulties shifting attention away from highly salient thoughts and stimuli.

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Appendix A

University *of* New Hampshire

Research Integrity Services, Service Building
51 College Road, Durham, NH 03824-3585
Fax: 603-862-3564

25-Jan-2019

Ross, Robert S
Psychology, McConnell Hall
15 Academic Way
Durham, NH 03824

IRB #: 6938
Study: EEG Correlates of Rumination and Source Memory
Approval Expiration Date: 06-Jun-2019
Modification Approval Date: 16-Jan-2019
Modification: Changes per memo dated 8/14/18

The Institutional Review Board for the Protection of Human Subjects in Research (IRB) has reviewed and approved your modification to this study, as indicated above. Further changes in your study must be submitted to the IRB for review and approval prior to implementation.

Approval for this protocol expires on the date indicated above. At the end of the approval period you will be asked to submit a report with regard to the involvement of human subjects in this study. If your study is still active, you may request an extension of IRB approval.

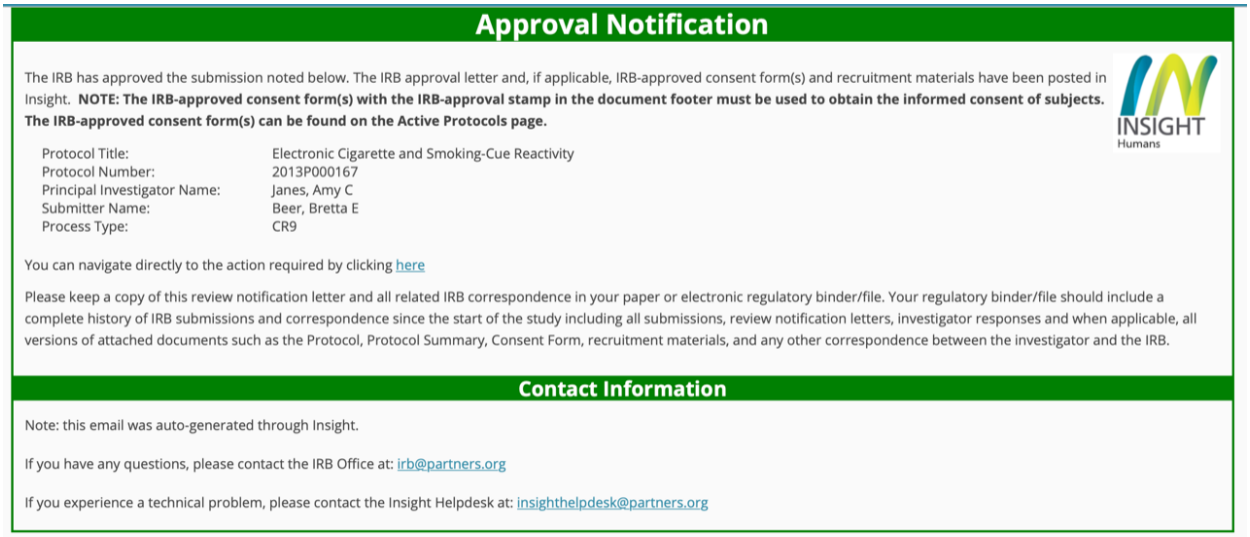
Researchers who conduct studies involving human subjects have responsibilities as outlined in the document, *Responsibilities of Directors of Research Studies Involving Human Subjects*. This document is available at http://unh.edu/research/irb-application-resources or from me.

Note: IRB approval is separate from UNH Purchasing approval of any proposed methods of paying study participants. Before making any payments to study participants, researchers should consult with their BSC or UNH Purchasing to ensure they are complying with institutional requirements. If such institutional requirements are not consistent with the confidentiality or anonymity assurances in the IRB-approved protocol and consent documents, the researcher may need to request a modification from the IRB.

If you have questions or concerns about your study or this approval, please feel free to contact Melissa McGee at 603-862-2005 or melissa.mcgee@unh.edu. Please refer to the IRB # above in all correspondence related to this study. The IRB wishes you success with your research.

For the IRB,

Julie F. Simpson
Director



Approval Notification

The IRB has approved the submission noted below. The IRB approval letter and, if applicable, IRB-approved consent form(s) and recruitment materials have been posted in Insight. **NOTE: The IRB-approved consent form(s) with the IRB-approval stamp in the document footer must be used to obtain the informed consent of subjects. The IRB-approved consent form(s) can be found on the Active Protocols page.**

INSIGHT Humans

Protocol Title:	Electronic Cigarette and Smoking-Cue Reactivity
Protocol Number:	2013P000167
Principal Investigator Name:	Janes, Amy C
Submitter Name:	Beer, Bretta E
Process Type:	CR9

You can navigate directly to the action required by clicking here

Please keep a copy of this review notification letter and all related IRB correspondence in your paper or electronic regulatory binder/file. Your regulatory binder/file should include a complete history of IRB submissions and correspondence since the start of the study including all submissions, review notification letters, investigator responses and when applicable, all versions of attached documents such as the Protocol, Protocol Summary, Consent Form, recruitment materials, and any other correspondence between the investigator and the IRB.

Contact Information

Note: this email was auto-generated through Insight.

If you have any questions, please contact the IRB Office at: irb@partners.org

If you experience a technical problem, please contact the Insight Helpdesk at: insighthelpdesk@partners.org

Table A1.
Results from left frontal alpha power neutral trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Attentional Bias Score	26.95	15.64	.36	.10
Pack Year	.04	.06	.14	.53
Interaction of Attentional Bias and Pack Year	4.93	3.08	.33	.13

Notes: beta (b), standard error of beta (SEb).

Table A2.

Results from midfrontal alpha power drug trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Attentional Bias Score	18.09	11.13	.35	.12
Pack Year	.00	.05	.00	.99
Interaction of Attentional Bias and Pack Year	1.92	2.19	.19	.39

Notes: beta (b), standard error of beta (SEb).

Table A3.
Results from midfrontal alpha power neutral trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Attentional Bias Score	13.63	12.69	.24	.30
Pack Year	.01	.05	.02	.93
Interaction of Attentional Bias and Pack Year	2.20	2.50	.20	.39

Notes: beta (b), standard error of beta (SEb).

Table A4.
Results from parietal alpha power drug trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Attentional Bias Score	11.62	10.91	.24	.30
Pack Year	.00	.05	.02	.94
Interaction of Attentional Bias and Pack Year	2.26	2.15	.23	.31

Notes: beta (b), standard error of beta (SEb).

Table A5.
Results from parietal alpha power neutral trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Attentional Bias Score	12.03	10.33	.25	.26
Pack Year	-.02	.04	-.11	.62
Interaction of Attentional Bias and Pack Year	2.17	2.04	.23	.30

Notes: beta (b), standard error of beta (SEb).

Table A6.

Results from left frontal alpha power incongruent trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Non-drug Attentional Bias Score	24.63	15.18	.34	.12
Pack Year	.02	.06	.07	.75
Interaction of Non-drug Attentional Bias and Pack Year	5.01	2.99	.35	.11

Notes: beta (b), standard error of beta (SEb).

Table A7.

Results from left frontal alpha inter-trial coherence drug trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Attentional Bias Score	.04	.15	.06	.78
Pack Year	.00	.00	.12	.54
Interaction of Attentional Bias and Pack Year	.04	.03	.28	.23

Notes: beta (b), standard error of beta (SEb).

Table A8.

Results from left frontal alpha inter-trial coherence neutral trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Attentional Bias Score	.07	.08	.16	.43
Pack Year	.00	.00	-.31	.14

Interaction of Attentional Bias and Pack Year	-.03	.02	-.36	.09
Notes: beta (b), standard error of beta (SEb).				

Table A9.
Results from midfrontal alpha inter-trial coherence drug trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Attentional Bias Score	-.02	.12	-.04	.87
Pack Year	.00	.00	-.17	.46
Interaction of Attentional Bias and Pack Year	.01	.02	.11	.63
Notes: beta (b), standard error of beta (SEb).				

Table A10.
Results from midfrontal alpha inter-trial coherence neutral trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Attentional Bias Score	-.01	.08	-.04	.87
Pack Year	.00	.00	-.08	.72
Interaction of Attentional Bias and Pack Year	-.02	.02	-.30	.19
Notes: beta (b), standard error of beta (SEb).				

Table A11.
Results from parietal alpha inter-trial coherence drug trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Attentional Bias Score	.11	.11	.21	.34
Pack Year	.00	.00	.07	.76

Interaction of Attentional Bias and Pack Year	.03	.02	.30	.18
Notes: beta (b), standard error of beta (SEb).				

Table A12.
Results from parietal alpha inter-trial coherence neutral trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Attentional Bias Score	.04	.09	.10	.65
Pack Year	.00	.00	-.32	.16
Interaction of Attentional Bias and Pack Year	.00	.02	-.09	.70
Notes: beta (b), standard error of beta (SEb).				

Table A13.
Results from left frontal alpha power lose/shift trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Attentional Bias Score	-2.38	7.49	-.07	.75
Pack Year	-.04	.03	-.32	.16
Interaction of Attentional Bias and Pack Year	-.67	1.48	-.10	.65
Notes: beta (b), standard error of beta (SEb).				

Table A14.
Results from midfrontal alpha power lose/shift trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Attentional Bias Score	-3.30	7.44	-.10	.66
Pack Year	-.03	.03	-.26	.27

Interaction of Attentional Bias and Pack Year	-.14	1.47	-.02	.92
Notes: beta (b), standard error of beta (SEb).				

Table A15.
Results from parietal alpha power lose/shift trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Attentional Bias Score	-2.97	9.35	-.07	.75
Pack Year	-.05	.04	-.28	.24
Interaction of Attentional Bias and Pack Year	-.42	1.84	-.05	.82
Notes: beta (b), standard error of beta (SEb).				

Table A16.
Results from left frontal alpha inter-trial coherence lose/shift trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Attentional Bias Score	-.01	.22	.00	.97
Pack Year	.00	.00	.01	.95
Interaction of Attentional Bias and Pack Year	.07	.04	.34	.14
Notes: beta (b), standard error of beta (SEb).				

Table A17.
Results from midfrontal alpha inter-trial coherence lose/shift trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Attentional Bias Score	-.07	.19	-.08	.72
Pack Year	.00	.00	-.04	.86

Interaction of Attentional Bias and Pack Year	.06	.04	.32	.16
Notes: beta (b), standard error of beta (SEb).				

Table A18.
Results from parietal alpha inter-trial coherence lose/shift trial regression

Variables	**b**	**SEb**	**Standardized beta**	**p value**
Attentional Bias Score	-.08	.23	.23	.74
Pack Year	.00	.00	.00	.99
Interaction of Attentional Bias and Pack Year	.05	.05	.23	.32
Notes: beta (b), standard error of beta (SEb).				