

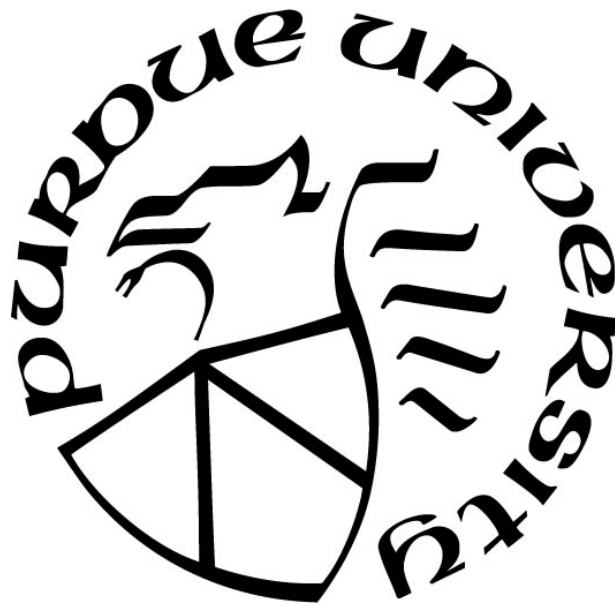
**RESTING-STATE NEURAL CIRCUIT CORRELATES OF
NEGATIVE URGENCY: A COMPARISON BETWEEN TOBACCO
USERS AND NON-TOBACCO USERS**

by
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ABSTRACT

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Title: Resting-state Neural Circuit Correlates of Negative Urgency: A Comparison
Between Tobacco Users and Non-tobacco Users

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Negative urgency, defined as a tendency to act rashly under extreme negative emotion, is strongly associated with tobacco use. Despite the robust cross-sectional and experimental evidence linking negative urgency and tobacco use, neural correlates of negative urgency in tobacco use have not been studied. The purpose of the current study was to 1) identify neural circuits that differ between tobacco users and non-tobacco users and 2) explore the relationship between resting-state seed-based functional connectivity (rsFC) and negative urgency, both in the overall group and between tobacco users and non-tobacco users. Using negative urgency-related brain regions as seed regions (voxel-level $p = .005$, cluster-level $\alpha < .05$), compared to non-tobacco users ($n = 21$; mean age = 36.57, 62% female, 76% white), tobacco users ($n = 22$; mean age = 37.50, 64% female, 77% white) had stronger rsFC strengths in the right amygdala – left medial orbitofrontal cortex/ventromedial prefrontal cortex circuit and the right nucleus accumbens – right temporoparietal junction circuit. Additionally, rsFC in the bilateral temporal pole – left supramarginal gyrus circuits was positively correlated with negative urgency (Left temporal pole: $r = .55$, $p < .001$; Right temporal pole: $r = .51$, $p < .001$). The current study extends previous neuroimaging findings, which have mainly focused on how negative urgency is related to brain responses in localized, segregated brain regions, by examining the network-level interactions between different brain regions. This study provides prime preliminary data for future neuroimaging studies of negative urgency by providing potential target networks that would aid the development of novel intervention strategies for negative urgency-based maladaptive behaviors.

INTRODUCTION

Negative Urgency, defined as the tendency to act rashly under extreme negative emotion (Cyders & Smith, 2007; Whiteside & Lynam, 2001), is related to various tobacco use behaviors and patterns across both cross-sectional and laboratory-based studies (Billieux, Van der Linden, & Ceschi, 2007; Doran, Cook, McChargue, Myers, & Spring, 2008; Doran, Cook, McChargue, & Spring, 2009; Lee, Peters, Adams, Milich, & Lynam, 2015). Although well documented to be a robust risk factor, the neural mechanisms underlying how negative urgency influences tobacco use are not yet well understood. Understanding the neural mechanisms that contribute to tobacco use can lead to the identification of novel prevention and intervention targets that can increase efficacy of tobacco use cessation approaches, which are often characterized by limited effectiveness (Piasecki, 2006). The current study examined the neural circuitry of negative urgency in tobacco use by comparing resting-state functional connectivity (rsFC) in tobacco users and non-tobacco users and by examining the relationship between such connectivity patterns and negative urgency.

Negative Urgency

Negative urgency is one of the personality traits from the UPPS-P model of impulsive behavior, a multidimensional model of impulsivity widely used to study various maladaptive behaviors (Cyders et al., 2007; Whiteside & Lynam, 2001). The multidimensional model of impulsivity consists of five traits: negative urgency, lack of premeditation (a tendency to act without thinking), lack of perseveration (an inability to

stay focused on a task that may be boring or difficult), sensation seeking (a tendency to seek out novel and exciting experiences), and positive urgency (a tendency to act rashly in response to extreme positive emotion). Among them, negative urgency is the personality trait that has been most extensively studied and linked to various maladaptive behaviors, including tobacco use (e.g., Billieux et al., 2007; Doran et al., 2008, 2009; Lee et al., 2015), problematic alcohol use (e.g., Coskunpinar, Dir, & Cyders, 2013), risky sexual behaviors (e.g., Settles et al., 2012), and drug use (e.g., Settles et al., 2012). Therefore, negative urgency is proposed as a transdiagnostic endophenotype for problematic levels of risk taking behaviors (Cyders, Coskunpinar, & VanderVeen, 2016).

Existing neuroimaging studies have primarily focused on neural correlates of negative urgency implicated in other healthy and at-risk populations, such as cocaine users with and without personality disorders (Albein-Urios et al., 2012; Albein-Urios, Martinez-Gonzalez, et al., 2013; Albein-Urios, Verdejo-Román, et al., 2013; Contreras-Rodríguez et al., 2015; Moreno-López et al., 2012), patients with schizophrenia (Hoptman, Antonius, Mauro, Parker, & Javitt, 2014), and individuals across the alcohol use spectrum (Cyders et al., 2014, 2015; Zhu, Cortes, Mathur, Tomasi, & Momenan, 2015). Most of this previous work has focused on brain correlates using segregated brain regions and has failed to consider interactions and connectivity between whole brain networks, which is necessary for the design of more effective pharmacological or physiological treatment design (e.g., Opitz, Fox, Craddock, Colcombe, & Milham, 2015). So far, only three studies have examined negative urgency as related to neural connectivity (Contreras-Rodríguez et al., 2015; Hoptman et al., 2014; Zhu et al., 2015). These studies examined negative urgency with respect to connectivity patterns identified

using brain regions related to general self-control or connectivity pattern differences between their study groups. No study has attempted to examine neural connectivity of negative urgency-related brain regions that have frequently appeared in neuroimaging studies.

This study is one of the early attempts to document neural connectivity related to negative urgency and the first to examine the negative urgency-related rsFC across tobacco users and non-tobacco users. My model assumes that negative urgency contributes to tobacco use (as one candidate condition of maladaptive behavior). Identifying the neural mechanisms underlying how negative urgency influences tobacco use would further build on the idea that negative urgency is a common transdiagnostic endophenotype for a range of risk taking behaviors. However, it is important to note that due to the cross-sectional nature of the data used in my study, the neural mechanisms of negative urgency could also be a product of tobacco use. Identifying neural mechanisms underlying negative urgency could lead to the development of novel interventions that directly modify these circuits via pharmacological interventions or transcranial magnetic stimulation (TMS) approaches. Additionally, identification of these circuits would provide an innovative, objective biomarker of treatment response that can be used as a platform to test the effectiveness of negative urgency-based interventions. These goals are not possible without first documenting the neural connectivity underlying negative urgency. Given that negative urgency is a risk factor for a wide range of clinical disorders and problems (Cyders et al., 2016), the findings from this study have a strong potential for high clinical impact across various problematic risk-taking disorders and populations, which have significant public health relevance.

Relationship between negative urgency and tobacco use

Tobacco use is a maladaptive behavior that increases health risks. Tobacco users have higher mortality rates and incur greater health care costs compared to non-tobacco users, due to higher rates of tobacco use-related diseases, including lung cancer, chronic obstructive pulmonary disease, and cardiovascular disease (Barendregt, Bonneux, & van der Maas, 1997; Bjartveit & Tverdal, 2005; Thun et al., 2013). In addition to serious health risks, tobacco use is highly prevalent and addictive compared to other drugs (Kandel, Chen, Warner, Kessler, & Grant, 1997). Despite high societal costs associated with tobacco use, a wide range of tobacco use cessation efforts, including psychosocial treatments, pharmacotherapy, and self-guided quit attempts, have been unsuccessful in initial quitting and continued abstinence (Piasecki, 2006). This warrants the identification of new prime targets that can aid the development and objective testing of novel tobacco use cessation interventions.

Across studies, there is a robust positive relationship between negative urgency and tobacco use. For example, negative urgency is significantly associated with tobacco craving, specifically an anticipated relief from negative affect, in both cross-sectional and tobacco cue exposure paradigms (Billieux et al., 2007; Doran et al., 2009). Negative urgency is also uniquely associated with daily tobacco use (compared to intermittent tobacco use and non-tobacco use) in young adults (Lee et al., 2015). Tobacco users with high negative urgency have higher negative affective states in response to tobacco cue exposure (Doran et al., 2008), which could increase a likelihood of subsequent tobacco use. These findings suggest that negative urgency is a critical target to consider when developing effective tobacco use cessation intervention approaches; however, no

treatments currently exist to improve this maladaptive behavior by modifying negative urgency.

Brain Correlates of Negative Urgency

Despite the need to understand how negative urgency relates to brain differences underlying tobacco use, the neural circuitry of negative urgency in general, and specifically in tobacco use, is not yet well understood. Existing neuroimaging work has employed various methods in their investigation of negative urgency in the human brain, including 1) brain structure, 2) changes in blood-oxygen-level-dependent (BOLD) signals during tasks, and 3) neural connectivity in a resting brain (i.e., a state of the brain when subjects are not engaged in any tasks). I review this literature in each of these areas next.

Evidence of negative urgency from brain structure

Measures of grey matter, such as its volume, thickness, and density, have been used to study various psychopathological conditions, addictive behaviors, and cognitive functions across different populations (e.g., Brody et al., 2004; Gogtay & Thompson, 2010; Gur et al., 1999). Many studies have examined the relationship between negative urgency and regional grey matter measures. In healthy participants, a negative relationship was found between negative urgency and grey matter volume in the left ventral striatum/nucleus accumbens (VS/NAcc; Muhlert & Lawrence, 2015), which is a part of the reward pathway in the brain implicated in addictive behaviors, specifically in tobacco dependence (Brody, 2006). Smaller left VS/NAcc grey matter volume was

related to greater lifetime tobacco use, which suggests negative urgency as a predisposing factor for tobacco use via a volumetric feature of the VS/NAcc (Das, Cherbuin, Anstey, Sachdev, & Eastaer, 2011). This study also found that higher negative urgency was related to lower regional grey matter volume in the dorsomedial prefrontal cortex (dmPFC) and right temporal pole, which are regions thought to be implicated in emotion regulation (Muhlert & Lawrence, 2015). Similarly, another study found a negative correlation between negative urgency and right middle temporal pole grey matter density across individuals with comorbid cocaine dependence and personality disorders, individuals with cocaine dependence only, and non-drug using controls (Albein-Urios, Martinez-Gonzalez, et al., 2013). Although the study did not find group-specific effects of negative urgency, increases in right middle temporal pole volume was negatively related with lower negative urgency scores: The non drug-using group had the greatest grey matter volume in the right middle temporal pole and the lowest negative urgency scores, followed by the cocaine dependence group and the comorbid group (Albein-Urios, Martinez-Gonzalez, et al., 2013). Although its function is unclear, the temporal pole is located in between the amygdala and the orbitofrontal cortex (OFC) and anatomically interconnects these regions, which are linked to emotional processing (Olson, Plotzker, & Ezzyat, 2007). Olson et al. (2007) theorized the function of the right temporal pole is to link perceptual inputs with visceral emotional responses, which suggests this region may be related to negative urgency.

In contrast, individuals with cocaine dependence and the controls show differential relationships between regional grey matter volume and negative urgency (Moreno-López et al., 2012). The right sub-gyral/Broadmann Area 8 (BA8) grey matter

volume was positively correlated with negative urgency in cocaine users, but it was negatively correlated with negative urgency in controls (although grey matter volume in this region was higher in controls than in the cocaine users). The right sub-gyral BA 8 is related to uncertainty (Volz, Schubotz, & Von Cramon, 2005). This may mean that having greater grey matter volume in this region is important to trigger extreme negative emotions in those who may have difficulties identifying their own emotions (e.g., drug users), thereby increasing the activation of the sub-gyral BA 8 in cocaine users, but not in controls. Further, greater cortical thickness (a measure of grey matter that estimates a shortest distance between a grey matter/white matter boundary and a grey matter/cerebrospinal fluid boundary) of the right frontal pole and the right medial OFC (mOFC) was negatively associated with lower negative urgency in a spectrum of patients with schizophrenia, who generally exhibit poor affect regulation and impulsive behaviors (Hoptman et al., 2014). The frontal pole is proposed to synthesize different information to generate goals and goal-related processes and link these processes to specific outcomes to improve future choices (Tsujiimoto, Genovesio, & Wise, 2011). The mOFC is related to an evaluation of rewarding stimuli (Kringelbach & Rolls, 2004). Therefore, reduced cortical thickness in the right frontal pole and the right mOFC as a function of elevated negative urgency may be related to maladaptive evaluative processes due to extreme negative affect.

Evidence of negative urgency during task-based activation

Blood-oxygen-level-dependent (BOLD) signals are indirect measures of neural activation in the human brain collected via functional magnetic resonance imaging

(fMRI). In a study by Cyders et al. (2014, 2015), social drinkers completed six fMRI scans of combined olfactory and visual stimuli. Each scan had emotional visual stimuli (i.e., neutral, negative, and positive) to induce mood. Three types of olfactory stimuli (i.e., alcohol, appetitive control, and sham) were intermittently given to subjects in each mood condition. Negative urgency was significantly related to increased BOLD signals in the bilateral ventromedial and medial prefrontal cortex (vmPFC, mPFC respectively) when social drinkers received the alcohol odors as compared to the appetitive control and sham odors (Cyders et al., 2014). Negative urgency mediated the relationship between the bilateral vmPFC activation and subjective craving and problematic alcohol use, suggesting that increased alcohol cue salience in the prefrontal cortex might underlie the relationship between negative urgency and both craving and use. Negative urgency was also related to hyperactivity in the left amygdala and the right lateral OFC in response to negative mood images (Cyders et al., 2015). Notably, negative urgency also mediated the relationship between the limbic and OFC BOLD responses to negative emotional stimuli and risk taking (Cyders et al., 2015). Given these regions are related to negative emotion processing (Phan, Wager, Taylor, & Liberzon, 2002), these findings suggest that affective hyperarousal might underlie negative urgency's influence on risk-taking.

A few studies have examined the role of negative urgency in response inhibition. Response inhibition refers to the suppression of pre-potent motor response based on the context of the task. For example, the typical task, such as the Go/No-Go task, instructs participants to push a button when a letter "X" (the "Go" trial) appears on the screen while withhold a button press when a letter "Y" (the "No-Go" trial) appears on the screen.

The “Go” trials and “No-Go” trials are balanced such that the button press becomes more automatic and difficult to suppress.

Healthy participants completed a reward-modulated Go/No-Go task, in which two types of the “No-Go” trials were presented that differed by color (Wilbertz et al., 2014). One color was related to a potential reward upon successful inhibition, and another color was not related to a potential reward. Higher negative urgency was associated with weaker activation in the right inferior frontal gyrus (IFG)/anterior insula (aI) during response inhibition. Further, negative urgency moderated the relationship between feedback signals (i.e., BOLD signal changes from successful response inhibition and unsuccessful response inhibition) from the VS/NAcc and response inhibition, such that individuals with low or medium negative urgency were able to use the feedback signals from the VS/NAcc, but those with high negative urgency were not able to use such feedback. Another study compared healthy young adults with high and low negative urgency using an emotional Go/No-Go task, in which “Go” and “No-Go” signals were overlapped with emotional visual stimuli such as positive, neutral, and negative images (Chester et al., 2016). In the negative affect condition, the high negative urgency group showed greater activation in the bilateral anterior insula (aI), dorsal striatum, and ventrolateral PFC (VLPFC) during response inhibition. Among these regions, only the right aI mediated the relationship between negative urgency and alcohol consumption, such that higher negative urgency was associated with greater right aI activation, which in turn was associated with greater alcohol consumption. In the high negative urgency group, response inhibition accuracy during the negative affect condition was positively correlated with activations in inhibitory regions of the prefrontal cortex (PFC), such as

the dorsal anterior cingulate cortex (dACC), dorsolateral prefrontal cortex (DLPFC), aI, and VLPFC. In sum, these findings suggest that negative urgency is associated with weaker neural activations in brain regions involved in self-control and that these regions are hyper-activated to exert effortful control under negative affect.

A few other neuroimaging studies used a cognitive re-appraisal task to examine the involvement of negative urgency in emotion regulation. The cognitive re-appraisal task consists of three tasks that ask participants to passively observe neutral pictures, to actively maintain emotions induced by negative visual stimuli, and to suppress the emotions induced by negative visual stimuli using cognitive re-appraisal techniques. In a study that compared cocaine users and controls, right DLPFC activation was positively correlated with negative urgency during the conscious maintenance of negative emotion compared to the observed condition in the whole sample of cocaine users and controls (Albein-Urios et al., 2012). Negative urgency was more strongly related to the functional connectivity (i.e., the temporal correlation of BOLD responses in two regions) between the right DLPFC and the right insula/OFC during the negative emotion maintenance in cocaine users than in the controls. However, negative urgency was negatively related to the functional connectivity between the right IFG and amygdala in the re-appraisal of negative emotion in controls and unrelated in cocaine users. Finally, during the re-appraisal of negative emotion, cocaine users with personality disorders had a positive relationship between negative urgency and amygdala activation, whereas cocaine users without comorbidity and controls did not (Albein-Urios, Verdejo-Román, et al., 2013). This evidence suggests reduced “top-down” control of self-control-related brain regions (i.e., excessive recruitment of prefrontal regions during negative affect maintenance;

maintaining the negative affective state depicted as an extra effort for exerting self-control because individuals with high negative urgency are likely to act rashly to diminish negative affect) and maladaptive “bottom-up” influence of impulsivity-related brain regions (i.e., abnormal amygdala activity during the re-appraisal of negative affect) as a function of negative urgency (Bechara, 2005).

Evidence of negative urgency from resting-state neural circuits

Resting-state fMRI data is collected while a human participant is in an fMRI scanner and not performing any task. Subjects are usually asked to stay awake for approximately five to ten minutes with eyes either closed or opened, while not engaging in any motor, language, or cognitive tasks. Resting-state imaging data measures low frequency (< 0.1 Hz), spontaneous fluctuation of BOLD signals in the resting brain (Biswal, Yetkin, Haughton, & Hyde, 1995). An analysis of resting-state functional connectivity (rsFC) measures synchronous activations between spatially distant regions in the brain that occurs in an absence of distinct stimulus presentation (Lee, Smyser, & Shimony, 2013).

In patients with schizophrenia, negative urgency was related to reduced rsFC between the left lateral OFC and left middle frontal gyrus, the left mOFC and left superior frontal gyrus/rostral anterior cingulate cortex (rACC), and the left rACC and left superior/medial frontal gyrus (Hoptman et al., 2014). In cocaine dependent individuals, negative urgency was positively associated with higher rsFC between the OFC and subgenual anterior cingulate cortex (sgACC), and with negative correlations between the right caudate and occipital cortex (Contreras-Rodríguez et al., 2015). Individuals with

alcohol dependence showed a negative correlation between negative urgency and rsFC in the amygdala-striatum network, thought to be an “impulsive system” (Zhu, Cortes, Mathur, Tomasi, & Momenan, 2015). Also, negative urgency was negatively correlated with rsFC couplings between 1) reflective systems (i.e., OFC network and left executive control network), 2) the reflective system (i.e., OFC network) and anterior default mode network (DMN), and 3) the reflective system (i.e., OFC network) and posterior DMN. The converging evidence from the resting-state neuroimaging studies highlights the OFC in connection with other brain regions. The OFC could be the key region: when its connection to other regions is impaired, it could promote impulsive action in response to unusually high negative affect, given its involvement in emotion- and value-based learning (Schoenbaum, Roesch, & Stalnaker, 2006).

Converging evidence for neural correlates of negative urgency

In sum, recent evidence demonstrates the relationship between negative urgency and brain regions involved in emotion processing (i.e., aI, amygdala, temporal pole, DMPFC, and VMPFC), specifically that of negative affect and self-control (i.e., lateral OFC, mOFC, sgACC, rACC, dACC, IFG, frontal pole, DLPFC, and VLPFC). It provides converging evidence that neural representations for the core components of negative urgency, a tendency to *act rashly* (i.e., lack of or diminished self-control) under *extreme negative emotion*, are indeed implicated in the human brain and are related to the personality trait of negative urgency. Thus, previous work provides feasibility for studying resting-state neural correlates of negative urgency in the current study.

Most existing neuroimaging work has focused on identifying and localizing specific brain regions involved in negative urgency, which does not take into account the important effect of interactions between different brain regions. Additionally, the handful of imaging studies that have studied network-level neural correlates of negative urgency examined brain regions focused on self-control, a related but broader construct, or brain regions that initially differ between two groups without taking into account negative urgency levels. In this light, the current study is novel because it investigated resting-state network-level neural circuits of negative urgency by focusing on negative urgency-related brain regions identified in previous literature. This provides an understanding of patterns in which spatially distinct brain regions work with each other in the behavioral expression of negative urgency as maladaptive behaviors that pose health risks, such as tobacco use.

Tobacco use as a candidate condition to study the neural basis of negative urgency

Despite growing evidence for the neural basis of negative urgency, as well as cross-sectional and experimental evidence for its role in tobacco use, the neural correlates of negative urgency among tobacco users have not yet been explored. Exploring neural evidence for negative urgency in this population is particularly worthwhile because stress (i.e., negative affect) has been linked to tobacco use. Extended from cross-sectional and experimental evidence supporting the association between stress and tobacco use, Todd (2004) employed a naturalistic research design that measured stress and tobacco use behaviors in participants' daily living and found a positive relationship between stress

and tobacco use. More importantly, recent evidence points to a partially mediating role of impulsivity in the relationship between lifetime stress and tobacco use (Ansell, Gu, Tuit, & Sinha, 2012).

Due to the strong involvement of negative affect in tobacco use, several studies explored the efficacy of incorporating mood management in tobacco use cessation programs, but results are inconsistent. Some studies found similar abstinence rates between the standard treatments and those combined with mood management (Brown et al., 2001; Hall et al., 1996), while other studies found favorable abstinence rates for the treatments combined with mood management over the standard treatments (Muñoz, Marín, Posner, & Pérez-Stable, 1997; Patten, Martin, Myders, Calfas, & Williams, 1998). Coupled with limited effectiveness in a wide range of tobacco use cessation strategies (Piasecki, 2006), these mixed results beg for the investigation of the neural basis of negative urgency. Although many studies identified the brain regions involved in negative urgency, this line of research is still in its infancy and needs further investigation, particularly in network-level neural circuits that are specific to negative urgency and impact tobacco use. The identification of negative urgency-related neural circuits can lead to direct modification of these circuits via pharmacological interventions or TMS approaches (Opitz et al., 2015). Additionally, the identification of such circuits can provide a novel, objective biomarker for objectively testing treatment response. Thus, this study conducted resting-state functional connectivity analysis to identify resting-state neural circuits involved in negative urgency across tobacco users and non-tobacco users.

Resting-State Functional Connectivity (rsFC) in Studying Neural Basis of Negative Urgency in Tobacco Use

The majority of existing studies documenting neural correlates of negative urgency among diverse populations have examined anatomical and task-related fMRI and studies that examined negative urgency-related rsFC are limited in scope. To this end, rsFC analysis can augment recent neuroimaging findings of negative urgency beyond anatomically-connected patterns (Buckner, 2010). Specifically, Buckner (2010) asserted that rsFC combines influences of anatomically-connected patterns and synaptic modifications derived by an individual's prior experiences, and that this could provide meaningful information about individual differences in brain circuit function. Negative urgency is a stable personality trait independent of frequency and intensity of emotional states (Cyders & Coskunpinar, 2010) and describes how an individual experiences and behaves under emotionally charged circumstances. Given recent findings suggesting individual differences in grey matter patterns and changes in regional BOLD signals during cognitive tasks as underlying negative urgency, it is reasonable to speculate that negative urgency, which can shape an individual's experiences, could be driven by individual differences in resting brain function.

rsFC measures a temporal correlation of different brain regions using low frequency, spontaneous fluctuations of BOLD signals in a resting brain, and previous literature has demonstrated a temporal correlation of BOLD signals among brain regions that are functionally-related (Biswal, Kylen, & Hyde, 1997; Biswal et al., 1995). This means that BOLD signals in brain regions located in distinct locations concurrently activate during cognitive performance and synchronically fluctuate in the resting brain.

Identifying resting brain circuits related to negative urgency would explain a baseline pattern of these circuits before engaging in any actions and provide novel insights to their patterns of activation during a task. Further, it would provide a more system-level approach in examining negative urgency-related resting brain circuits related to maladaptive behaviors that increase health risks, especially tobacco use.

rsFC: A seed-based correlation analysis

This study employed seed-based correlation analysis, which is one of the methods to study rsFC (Cole, Smith, & Beckmann, 2010). This method requires an *a priori* region called a seed region typically derived from the evidence in previous literature. The time series data is extracted from the seed region and is used as a regressor in a correlational analysis or general linear model analysis. Then, the whole-brain, voxel-wise functional connectivity map is produced, representing regions that are functionally connected (or temporally correlated) with the seed region. I conducted the seed-based correlation analyses because there is evidence for the brain correlates of negative urgency with a few segregated regions more frequently appeared as significant regions in negative urgency than others, as previously discussed. Examining the connectivity between these brain regions and other regions was the reasonable next step into the identification of the brain network-level correlates of negative urgency.

This study used five negative urgency-related brain regions found in the previous literature as seed regions to identify neural circuits related to negative urgency in tobacco users and non-tobacco users. I selected the five most frequently appearing brain regions related to negative urgency in the existing literature (based on the empirical findings

discussed in the previous sections; see *Appendix A3* for locations of brain regions). Of those, the amygdala and the temporal pole were selected as primary seed regions. The amygdala is related to negative emotion processing (Phan et al., 2002) and thought to be a key region in negative urgency (Cyders et al., 2014; Cyders & Smith, 2008). The temporal pole is a relatively under-studied brain region, which anatomically interconnects the amygdala and the OFC, the two key regions in negative urgency (Cyders et al., 2014; Cyders & Smith, 2008) and is theorized to modulate emotions in response to emotional perceptual stimuli (Olson et al., 2007); thus, a potential role of the temporal pole in negative urgency is worth investigating. Three additional exploratory seed regions included the anterior insula, due to its role in tobacco addiction (Naqvi, Rudrauf, Damasio, & Bechara, 2007), and the DLPFC and the VS/NAcc, as drug addiction is characterized by the imbalance between regions involved in executive function (e.g., DLPFC) and reward processing (e.g., VS/NAcc; Volkow, Wang, Fowler, Tomasi, & Telang, 2011).

Current Study

The purpose of the present study was to 1) identify neural circuits using seed regions (i.e., bilateral amygdala, bilateral temporal pole, bilateral anterior insula, bilateral DLPFC, and bilateral VS/NAcc) found in previous studies to be related to negative urgency that differ between tobacco users and non-tobacco users; and 2) explore the relationship between rsFC strength and negative urgency, both in the overall group and between tobacco users and non-tobacco users.

Hypothesis 1: The rsFC pattern from negative urgency-related seed regions will be different between tobacco users and non-tobacco users.

Hypothesis 2: The rsFC patterns will be related to negative urgency in the overall group.

Exploratory Hypothesis 3: The relationship between rsFC patterns and negative urgency will differ across tobacco users and non-tobacco users.

METHODS

Design

This study utilized a publicly available neuroimaging data set collected by the Nathan Kline Institute (NKI)-Rockland Project (Rockland data; Nooner et al., 2012). The aim of the project was to enable a developmentally focused investigation of psychopathology across the lifespan ranging from 6 to 85 years old. The community sample was from Rockland County in New York. They completed various tasks, fMRI scans, physiological measures, and psychological assessments (see *Appendix A1* for details). The goal of this open source neuroimaging data was to enable “open neuroscience, with the goal of prospective, pre-publication sharing of all collected data (Nooner et al., 2012).” The project aimed to recruit 1000 participants over a 4-year period starting in March 2012 and the participants are representative of Rockland County, NY based on age, sex, ethnicity, and socioeconomic status. The demographics of Rockland County, NY closely match U.S. demographic distributions; thereby reducing potential sampling biases and maximizing representativeness (see *Appendix A2*). Over-representation of any portion of the community was avoided with zip code based recruitment, and proportions of demographic variables such as age, sex, and ethnicity were balanced across the recruitment period. The current study used a subset of eligible samples to test the study hypotheses.

Participants

Of the 905 participants who participated in the NKI-Rockland Project (last data access on June 16, 2016), this study initially included participants 1) between the ages of 18 – 65 (to account for age-related brain changes) and 2) who had available MPRAGE anatomical and resting-state functional scans, resulting in an initial sample of $n = 441$ (See *Appendix B1*). Then, participants were excluded from the study based on the following criteria: 1) non-right handedness ($n = 38$; to control for functional lateralization), 2) positive drug screening except marijuana (benzodiazepines, cocaine, methadone, phencyclidine, barbiturates, opiates, and amphetamines) result on the scan day ($n = 16$; to avoid drug effects on brain function; e.g., Denier et al., 2013; Li et al., 2000), 3) history of medical or neurological diagnosis that is not suitable for fMRI scan (i.e., HIV, seizure disorders, history of head trauma with loss of consciousness, or neurological disorders such as epilepsy/stroke, Alzheimer’s Disease, Huntington’s Disease, meningitis, multiple sclerosis, and Parkinson’s Disease) because the exclusion criteria during the Rockland project data collection was minimal ($n = 20$), 4) fMRI scans with significant incidental findings ($n = 2$), and 5) missing MPRAGE anatomical or resting-state functional scans because some individuals have only one scan type, not both ($n = 11$). Positive marijuana results were not excluded because of high occurrence of tobacco and marijuana co-use among the U.S. population and an increasing rate of co-use due to the recent marijuana legalization (Richter et al., 2004; Schauer, Berg, Kegler, Donovan, & Windle, 2015). Given tobacco and marijuana co-use, I chose not to exclude individuals with positive marijuana testing because it would hamper identifying a large

enough sample to conduct analysis and sampling tobacco use-only sample would limit the generalizability of study findings to the general tobacco users.

These exclusions resulted in a sample of $n = 354$. I identified 39 tobacco users within this sample. Participants were further excluded if they 6) had missing self-report drug use data ($n = 6$), 7) reported using marijuana more than once per week ($n = 33$; 8 tobacco users), and 8) reported using other drugs (except tobacco and alcohol) more than once per month ($n = 6$; 1 tobacco user). Then, I selected two groups of tobacco users and non-tobacco users matched on age, gender, ethnicity, and DSM diagnosis. Tobacco users had to be daily tobacco users (i.e., at least once per day) and be free of current dependence/abuse on other substances except tobacco, which resulted in 25 tobacco users from the remaining sample. Non-tobacco users had to be free of current substance dependence/abuse including tobacco, endorsed no history of lifetime tobacco use, and were matched with tobacco users for age, gender, race/ethnicity, and any DSM-IV-TR diagnosis while again excluding individuals with severe mental illnesses. Both tobacco users and non-tobacco users were excluded if they were diagnosed with severe mental illnesses (i.e., schizophrenia, obsessive-compulsive disorder, post-traumatic stress disorder, and bipolar disorders; 5 tobacco users), as assessed by Structured Clinical Interview for DSM-IV-TR Axis I Disorders – Non-Patient Edition (SCID-I/NP; First, Spitzer, Gibbon, & Williams, 2002). I used a serial process to match tobacco users and non-tobacco users. I first started matching based on age, then gender, and then race/ethnicity. If demographic profiles roughly matched between a tobacco user and a non-tobacco user, I matched the two based on the DSM-IV diagnosis. I did not have access to other data at the time of matching (e.g., negative urgency, fMRI data). During

the data analysis, three tobacco users and five non-tobacco users were dropped because of excessive head motion and imaging data processing error.

The final sample included in the study was 22 tobacco users (mean age = 37.50, $SD = 13.21$) and 21 age-, gender-, ethnicity- and DSM diagnosis-matched non-tobacco users (mean age = 36.57, $SD = 13.78$; see *Appendix B1*). Of these individuals, four tobacco users and one non-tobacco user had a positive marijuana drug test, and three tobacco users and two non-tobacco users had missing drug test data.

Age, gender, and race were matched between tobacco users and non-tobacco users because these demographic variables have been associated with differing levels of tobacco use (Kandel et al., 1997; see *Appendix B2*). Additionally, lifetime history of DSM psychiatric disorder diagnosis, while excluding individuals with severe mental illnesses, was matched to control for potential confounding effects. Other sample characteristics include DSM substance abuse/dependence diagnosis, past year regular alcohol use (i.e., once per month or more during the past year), and past year marijuana use (i.e., once or more during the past year). Participants were matched based on the DSM diagnosis itself, and not specific to whether the diagnosis is current or past.

Measures

Tobacco Use

The Comprehensive Addiction Severity Index for Adolescent's (CASI-A) Alcohol and Other Drugs (AOD) subscale (Meyers, McLellan, Jaeger, & Pettinati, 1995) was used to characterize tobacco users and non-tobacco users. The CASI-A AOD

subscale was administered to participants who were 13 – 85 years old in the NKI-Rockland sample. The questionnaire was originally developed as an interview-based structured instrument, but it was administered as a self-report questionnaire. This study used the tobacco use-related items, which include “Have you ever used Tobacco?” “Age when first used,” “In the past year, what was your typical pattern of use?” and “How long have you used?” Individuals were classified as tobacco users if they were daily tobacco users in the past year (i.e., Responded “Once per day” or more frequent tobacco use to the item “In the past year, what was your typical pattern of use?”). Individuals were classified as non-tobacco users if they endorsed no lifetime history of tobacco use (i.e., Responded “No” to the item “Have you ever used Tobacco?”). Tobacco users’ age of first tobacco use, years of tobacco use, and past 6-month frequency of tobacco use per day were also included. Nicotine dependence was measured using the Fagerström Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991). The internal consistency estimate of FTND for the tobacco users in this study was low ($\alpha = .61$).

Negative urgency

The UPPS-P Impulsive Behavior Scale – Revised (UPPS-P; Lynam, Smith, Whiteside, & Cyders, 2006) is a 59-item self-report scale that measures five sub-facets of trait impulsivity: negative urgency, lack of premeditation, lack of perseverance, sensation seeking, and positive urgency. Responses range from 1 (agree strongly) to 4 (disagree strongly). The Negative Urgency subscale items include “Sometimes when I feel bad, I can’t seem to stop what I am doing even though it is making me feel worse” and “When I

am upset I often act without thinking.” The negative urgency subscale has shown strong internal consistency (Cronbach’s $\alpha > .75$) among adult smokers recruited from the community (Doran et al., 2008, 2009). The present study used the 12-item from the negative urgency subscale. The internal consistency estimate of negative urgency in the current sample was excellent ($\alpha = .90$).

fMRI data

The fMRI data were collected from a 3.0T SIEMENS MAGNETOM TrioTrim scanner at the NKI. The T1-weighted anatomical image was acquired for each subject using the magnetization-prepared rapid gradient echo (MPRAGE) sequence (repetition time (TR)/echo time (TE) = 1900/2.52ms, Flip Angle (FA) = 9°, slice thickness = 1.0mm, Field of View (FOV) = 250mm, 176 slices, voxel size = 1.0 x 1.0 x 1.0 mm, 256 x 246 matrix). The 5-minute resting-state image was acquired for each subject using an echo-planar imaging (EPI) sequence (TR/TE = 2500/30ms, FA = 80°, FOV = 216mm, slice thickness = 3.0mm, voxel size = 3.0 x 3.0 x 3.0 mm, 38 interleaved slices, transversal orientation, 72 x 72 matrix).

Data Analysis

Questionnaires

Between-group t-tests were conducted to assess any group differences in age and negative urgency. Chi-squared tests were conducted to test goodness of fit in gender, race, psychiatric disorder diagnosis, substance abuse/dependence diagnosis, past year regular

alcohol use, and past year marijuana use. Negative urgency item scores were first reverse-scored as necessary, and the mean scores were calculated so that the higher mean scores indicated higher negative urgency, with a range from 1 to 4. The normal distribution of negative urgency was supported (skewness = .28; kurtosis = -.80). FTND scores were summed to produce total scores ranging from 0 to 10. The normal distribution of FTND was supported (skewness = .17; kurtosis = -1.26).

Correlational analyses examined any initial relationship between age and negative urgency in the whole sample, and age of first tobacco use, frequency of tobacco use per day in the past 6-months, length of tobacco use, FTND total scores, and negative urgency among tobacco users. Simple regression analyses examined the effect of gender (male = 0, female = 1), race (white = 0, non-white = 1), psychiatric disorder diagnosis (absence = 0, presence = 1), substance abuse/dependence diagnosis (absence = 0, presence = 1), past year regular alcohol use (absence = 0, presence = 1), and past year marijuana use (absence = 0, presence = 1) on negative urgency in the whole sample. The alcohol and marijuana use variables in the simple regression analyses were dummy coded as the original response scales for each variable were categorical in nature (e.g., 0 = no use, 1 = 1-10 times per year, 2 = once a month, 3 = binge use only, 4 = once per month, 5 = two or more times per month, 6 = once per week, 7 = two or more times per week, 8 = once per day, 9 = more than once per day). The presence of past year regular alcohol use was defined as once per month or more. The presence of past year marijuana use was defined as once per year or more.

Preprocessing of fMRI data

Standard preprocessing steps were employed to prepare imaging data for subsequent analyses examining study hypotheses. The imaging data was analyzed using neuroimaging analysis software called the Analysis of Functional NeuroImages (AFNI Version 16.2.18; Cox, 1996) and FreeSurfer (Version 5.2.0; <https://surfer.nmr.mgh.harvard.edu>). Unless otherwise indicated, each processing step was conducted using AFNI.

Of the 120 time series volumes collected for resting-state functional data, the first five volumes were removed to ensure the steadiness of magnetization of remaining volumes (Jo, Saad, Simmons, Milbury, & Cox, 2010) and the remaining 115 volumes of resting-state functional data were concatenated to create a four-dimensional time series dataset for each subject. Then, the resting-state functional dataset was slice-time corrected and “de-spiked” to truncate time-series outliers (Jo et al., 2013). The skull was stripped from the anatomical image, and this image was aligned to resting-state functional data using the third volume of functional data as a base volume. Visual inspection of outputs for functional and structural alignment did not reveal any deviations. Each resting-state functional volume was registered to the base volume and spatially transformed.

Next, the anatomical data were segmented into whole brain, white matter, grey matter, and the four large ventricles using the FreeSurfer. Quality control was performed on the segmentation outputs produced. No deviations were observed when visually inspecting grey and white matter boundaries. The AFNI function called ANATICOR (Jo et al., 2010) is a method to remove potential noise artifacts using anatomically modeled

signals by calculating signals emanating from white matter and cerebrospinal fluid. A regression analysis was conducted to model and remove the impact of potential noise. Six motion parameters, six motion derivative parameters, and non-grey matter signals (i.e., from white matter and four large ventricles) were regressed out as nuisance signals (i.e., noises) or regressors of no interest. Global signal (i.e., an average signal of entire brain) was not included as a regressor because regressing out global signal can dramatically change interregional correlations and subsequently the resulting interpretation of the functional connectivity (Saad et al., 2012). Following the recommendations by Jo et al. (2010), the data were smoothed with a 6mm full-width half-maximum (FWHM) kernel to reduce noise after nuisance signals have been regressed out. Bandpass filtering retained frequencies between 0.01 Hz and 0.08 Hz (Satterthwaite et al., 2013).

In addition, time points with excessive head motion were censored out using the following two exclusion criteria: 1) more than average change of 0.3mm in head movement from one volume of the data to the next volume, with additional removal of time points before and after the excessive head movement; and 2) more than 10% of voxels across the brain were outliers at a specific time point. Individuals were excluded when more than 30% of time series data were excluded due to failing to meet the two criteria (two tobacco users and three non-tobacco users). One tobacco user and two non-tobacco users were further excluded due to preprocessing error. The head movement parameters were not significantly different between tobacco users and non-tobacco users. All preprocessing steps were done in the original space of each subject's brain. The alignment of final anatomical and functional data was visually inspected and no deviations were found. The voxel was resized to 2.0 x 2.0 x 2.0mm.

rsFC analysis: Seed-based functional connectivity analyses

Seed generations. Automatic anatomical parcellation developed by Destrieux, Fischl, Dale, & Halgren (2010) was used to parcellate and localize cortical and subcortical brain regions in each participant's brain using the FreeSurfer. Ten seed regions (five on each side of the brain) were identified (see *Appendix B3*; Destrieux et al., 2010). The anterior insula seed regions combined four parcellations based on a previous study that focused on the anterior insula (Churchwell & Yurgelun-Todd, 2013).

Seed-based functional connectivity analyses. The following seed-based functional connectivity analyses were conducted for each seed region separately, totaling ten analyses (consisting of four primary analyses and six exploratory analyses). First, anatomical seeds were resampled to the resolution of the functional time series. Next, the censored time points were excluded from the whole-brain based resting-state functional data. Third, a mean functional time series was calculated from all voxels in each seed region. This averaged time series in the seed region was correlated with the time series across the rest of brain. The visual inspection of each functional connectivity map produced from all seed regions did not show any deviations (i.e., brain regions that are supposed to be correlated were highly correlated. For example, correlations between the average time series from a seed region and each voxel within the seed region itself was high.). This functional connectivity map was then z-transformed to have a standardized value across participants. Finally, the functional connectivity map was warped into the standard Talairach space.

Hypothesis Testing

The functional connectivity maps from each seed region were examined separately using respective statistical tests in AFNI. All statistical tests used a voxel-wise threshold $p < .005$ and a cluster-wise threshold to correct for false positive rate (family wise error rate) at $\alpha < .05$ using a Monte Carlo approach to simulate random cluster distributions given estimated smoothness between voxels. Scatter plots with regression lines by group were produced to visualize the relationship between mean rsFC strength and negative urgency. Also, the correlations between mean rsFC strength and both negative urgency and tobacco use-related variables (e.g., age of first use, past 6-month frequency of tobacco use per day, length of use, and FTND scores) were examined.

Hypothesis 1: The rsFC pattern from each negative urgency-related seed region will be different between tobacco users and non-tobacco users. To test hypothesis 1, the participants' functional connectivity maps were entered to examine group differences between tobacco users and non-tobacco users using between-group t-tests.

Hypothesis 2: The rsFC patterns will be related to negative urgency in the overall group. To test hypothesis 2, correlational analyses between the participants' functional connectivity maps and negative urgency across the entire sample were completed.

Exploratory Hypothesis 3: The relationship between rsFC and negative urgency will differ across tobacco users and non-tobacco users. To test exploratory hypothesis 3, whole-brain functional connectivity maps of estimated slope differences in the relationship between negative urgency and connectivity were compared between tobacco users and non-tobacco users.

RESULTS

Descriptive Statistics

I conducted the descriptive analyses using SPSS version 24.0 (IBM Corp., 2016). Tobacco users and non-tobacco users did not differ on any study variables (negative urgency, $t(41) = .69, p = .49$; age, $t(41) = .22, p = .82$; gender, $\chi^2(1) = .01, p = .91$; race, $\chi^2(3) = 2.01, p = .57$; psychiatric disorder diagnosis, $\chi^2(1) = .21, p = .65$; substance abuse/dependence diagnosis, $\chi^2(1) = 3.15, p = .08$; past year regular alcohol use, $\chi^2(1) = .22, p = .64$; and past year marijuana use, $\chi^2(1) = .34, p = .56$; see *Appendix B2*).

Negative urgency was not significantly related to age, gender, race, psychiatric diagnosis, substance abuse/dependence diagnosis, past year regular alcohol use, or past year marijuana use (see *Appendix C1*) in the whole sample. However, there were trends toward positive relationships with medium effect size between negative urgency and substance abuse/dependence diagnosis in tobacco users ($r = .44, p = .10$) and race and past year regular alcohol use in non-tobacco users ($r = .55, p = .07$; $r = .48, p = .07$ respectively). In tobacco users, negative urgency was not significantly related with age of first tobacco use ($r = -.13, p = .57$), frequency of tobacco use per day in the past 6 months ($r = -.04, p = .86$), length of tobacco use ($r = .03, p = .91$), and FTND scores ($r = -.19, p = .40$).

Hypothesis Testing

I set significance testing for all analyses at a voxel-wise threshold of $p = .005$ and cluster-wise threshold (to correct for family-wise error) at $\alpha < .05$. Overall, there were four significant rsFC circuits and two trend rsFC circuits (see *Appendix C2*). I conducted all rsFC analyses with and without the participants diagnosed with psychiatric disorders (study exclusion criteria have excluded individuals with severe mental illnesses), and with and without participants with missing or positive drug tests for marijuana. Results were unchanged. Because the presence of psychiatric disorders and missing or positive marijuana drug test did not affect the rsFC results, I only report the results of analyses using the whole sample.

Hypothesis 1: The rsFC pattern from negative urgency-related seed regions will be different between tobacco users and non-tobacco users

Amygdala. There was significantly stronger rsFC strength between the right amygdala and left mOFC/vmPFC in tobacco users than non-tobacco users (See *Appendix C3*). There were no significant relationships between negative urgency and the right amygdala – left mOFC/vmPFC rsFC strength in either group (tobacco users: $r = .07, p = .77$; non-tobacco users: $r = .15, p = .52$; see *Appendix C4*). Among tobacco users, there was a trend toward a negative relationship with medium effect size in past 6-month frequency of tobacco use ($r = -.43, p = .07$; see *Appendix C15*). All other tobacco use-related variables were not significantly related to the mean rsFC strength ($r_s = -.18 - .02, p_s = .43 - .93$). There were no group differences in left amygdala connectivity.

Temporal pole. There were no group differences in bilateral temporal pole connectivity.

Anterior Insula. There were no group differences in bilateral anterior insula connectivity.

DLPFC. There were no group differences in bilateral DLPFC connectivity.

NAcc. There was significantly stronger rsFC strength between the right NAcc and the right temporoparietal junction (TPJ) in tobacco users than non-tobacco users (See *Appendix C5*). There were no significant correlations between negative urgency and right NAcc – right TPJ rsFC strength (tobacco users: $r = .05, p = .84$; non-tobacco users: $r = .06, p = .81$; see *Appendix C6*). Among tobacco users, there was a trend toward a negative relationship with medium effect size in FTND total scores ($r = -.42, p = .06$; see *Appendix C15*). Other tobacco use-related variables were not significantly related to the mean rsFC strengths ($r_s = -.13 - .03; p_s = .64 - .91$).

There was a trend toward greater rsFC strength between the right NAcc and the left precuneus in tobacco users than in non-tobacco users; this effect met voxel level significance ($p < .005$), but not cluster level significance ($\alpha = .06$; see *Appendix C7*). There were no significant correlations between negative urgency and right NAcc – left precuneus rsFC strength (tobacco users: $r = -.28, p = .21$; non-tobacco users: $r = .29, p = .21$; see *Appendix C8*). Among tobacco users, the mean rsFC strength was not significantly related with any tobacco use-related variables ($r_s = -.18 - .13, p_s = .28 - .59$; see *Appendix C15*). There were no group differences in left NAcc connectivity.

Hypothesis 2: The rsFC patterns will be related to negative urgency in the overall group

Amygdala. Negative urgency was not significantly correlated with any rsFC patterns from the bilateral amygdala in the overall group.

Temporal pole. Negative urgency was significantly and positively associated with rsFC strength between the right temporal pole and the left supramarginal gyrus (see *Appendices C9 and C10*) in the overall group ($r = .51, p < .001$). This relationship continued in both groups regardless of smoking status (tobacco users, $r = .49, p = .02$; non-tobacco users, $r = .52, p = .02$). Among tobacco users, there was a significant negative relationship in FTND total scores ($r = -.48; p = .03$; see *Appendix C15*). The mean rsFC strength was not significantly related with other tobacco use-related variables ($r_s = -.30 - .17; p_s = .21 - .84$; see *Appendix C15*).

Negative urgency was significantly and positively associated with rsFC strength between the left temporal pole and the left supramarginal gyrus (see *Appendices C11 and C12*) in the overall group ($r = .55, p < .001$). Again, this relationship continued in both groups regardless of smoking status (tobacco users, $r = .62, p = .002$; non-tobacco users, $r = .48, p = .03$). Among tobacco users, the mean rsFC strength was not significantly correlated with any tobacco use-related variables ($r_s = -.24 - .25, p_s = .29 - .93$; see *Appendix C15*).

Anterior Insula. Negative urgency was not significantly correlated with any rsFC patterns from the bilateral anterior insula in the overall group.

DLPFC. Negative urgency was not significantly correlated with any rsFC patterns from the bilateral DLPFC in the overall group.

NAcc. Negative urgency was not significantly correlated with any rsFC patterns from the bilateral NAcc in overall group.

Exploratory Hypothesis 3: The relationship between rsFC patterns and negative urgency will differ across tobacco users and non-tobacco users

Amygdala. There were no differences in the relationship between bilateral amygdala rsFC strength and negative urgency across groups.

Temporal pole. There were no differences in the relationship between bilateral temporal pole rsFC strength and negative urgency across groups.

Anterior Insula. There were no differences in the relationship between bilateral anterior insula rsFC strength and negative urgency across groups.

DLPFC. There were no differences in the relationship between bilateral DLPFC rsFC strength and negative urgency across groups.

NAcc. There were no differences in the relationship between right NAcc rsFC strength and negative urgency across groups. There was a trend in group difference in the relationship between left NAcc - right DLPFC rsFC strength and negative urgency that met voxel level significance ($p < .005$), but not cluster level significance ($\alpha = .09$; see *Appendix C13*). Tobacco users had a significant negative relationship between negative urgency and left NAcc – right DLPFC rsFC strength ($r = -.69, p < .001$; see *Appendix C14*), but there was no relationship in non-tobacco users ($r = .35, p = .12$). Among tobacco users, the mean rsFC strength was not significantly related to any tobacco use-related variables ($rs = -.30 - .09, ps = .20 - .71$; see *Appendix C15*).

DISCUSSION

The goal of the present study was to identify neural correlates of negative urgency among tobacco users and non-tobacco users using brain seed regions that were previously reported as related to negative urgency. There were four significant rsFC circuits: 1) right amygdala – left mOFC/vmPFC, 2) right NAcc – right TPJ, 3) right temporal pole – left supramarginal gyrus, and 4) left temporal pole – left supramarginal gyrus. There were two trend rsFC circuits: right NAcc – left precuneus and left NAcc – right DLPFC.

Tobacco users had significantly stronger rsFC strength than non-tobacco users in the right amygdala – left mOFC/vmPFC circuit and the right NAcc – right TPJ circuit. These findings suggest that the resting brains of tobacco users have stronger connectivity between brain regions that might reflect hypersensitivity to tobacco use-related cues (e.g., right amygdala for negative emotions, right NAcc for tobacco cues). Specifically, the balance between bottom-up processing in the right amygdala and top-down processing in the mOFC/vmPFC may be disrupted. The right NAcc may functionally work with the right TPJ, which orients attention to salient stimuli that are behaviorally relevant, in this case, tobacco use-related cues.

In the overall group, and in each subgroup, there were positive significant correlations between negative urgency and rsFC strength in the right temporal pole – left supramarginal gyrus circuit and the left temporal pole – left supramarginal gyrus circuit. Negative urgency is directly related to the functional connectivity between the bilateral temporal pole – left supramarginal gyrus, further supporting the potential significance of the temporal pole in negative urgency, as this region activates in response to personally

relevant emotional stimuli. Although the role of the supramarginal gyrus is not well known other than its involvement in language processing, several studies have reported evidence suggesting a potential involvement of the supramarginal gyrus in cognitive control. This suggests that this circuit may be involved in the modulation of negative emotional stimuli with respect to negative urgency.

Because tobacco users and non-tobacco users were not different on any measured variables, such as age, gender, race, presence of lifetime psychiatric and substance abuse/dependence diagnoses, past year regular alcohol use, and past year marijuana use, this suggests that the current findings are not likely due to any demographic differences. Additionally, because negative urgency was not significantly related to these demographic variables (although a few variables show trend effects, such as substance abuse/dependence diagnosis in tobacco users and race and past year regular alcohol use in non-tobacco users), it is unlikely that findings related to negative urgency can be better explained by confounding factors. However, in contrast to previous findings (Lee et al., 2015; Spillane, Smith, & Kahler, 2010), negative urgency did not differ between tobacco users and non-tobacco users and was not related to any smoking variables, which leaves some question to sample generalizability. However, the patterns of relationship between negative urgency and rsFC circuits found here are still noteworthy as these *a priori* seed regions were selected because of their relationship to negative urgency evidenced in the previous literature. Given the limited amount of research on network-level neural correlates of negative urgency, the current results provide preliminary, but novel and meaningful, evidence that extends previous research findings from region-specific correlates of negative urgency.

Hypothesis Interpretation

Hypothesis 1: The rsFC pattern from negative urgency-related seed regions will be different between tobacco users and non-tobacco users

Significant circuit 1: Right Amygdala – Left mOFC/vmPFC circuit. The study results indicated that tobacco users demonstrated stronger right amygdala – left mOFC/vmPFC rsFC strength at rest than non-tobacco users, although the rsFC strength was unrelated to negative urgency in both groups. The amygdala - mOFC/vmPFC circuit has been theorized to play a central role in negative urgency (Cyders & Smith, 2008; Smith & Cyders, 2016), representing bottom-up processing (Bechara, 2005). Increased bottom-up processing of the impulsive system from the amygdala in response to emotional stimuli can override the top-down processing of the reflective system from ventromedial frontal cortical region, including the mOFC/vmPFC. However, it is also possible there could be depleted top-down processing from the mOFC/vmPFC inappropriately regulating the normal bottom-up processing from the amygdala. The tobacco users in this study showed increased connectivity strength between the right amygdala and left mOFC/vmPFC relative to non-tobacco users, suggesting that the circuit might be wired to readily react to emotionally charged stimuli, despite the lack of a statistically significant relationship with negative urgency.

These findings are supported by other work. Drug users, including those using tobacco, show greater neural activity in the bilateral amygdala during the presentation of drug stimuli, relative to non-drug stimuli (Childress et al., 1999; Franklin et al., 2007). Further, tobacco users show reduced cortical thickness of the left mOFC, which is also

correlated with increased lifetime exposure to tobacco use (Kühn, Schubert, & Gallinat, 2010). A recent data-driven meta-analysis highlighted the co-activation of the amygdala and the mOFC/vmPFC, suggesting the role of the mOFC/vmPFC to incorporate signals that arise in response to emotional stimuli from subcortical regions like the amygdala to the cortical area (de la Vega, Chang, Banich, Wager, & Yarkoni, 2016). A recent proposal suggests that the role of the mOFC/vmPFC is to determine appropriate behavioral responses to emotional stimuli through the generation of affective meaning (Roy, Shohamy, & Wager, 2012). Given this evidence, the more readily wired right amygdala – left mOFC/vmPFC circuit in tobacco users may indicate that tobacco use is related to hypersensitive amygdala activation overriding the activity in the mOFC/vmPFC to generate appropriate behavioral response to negative emotional stimuli or, in contrast, related to reduced ability of the mOFC/vmPFC to appropriately guide behavioral response from normal amygdala activity in response to negative emotional stimuli.

Importantly, negative urgency was unrelated to connectivity in this circuit in the current study. Of course, this finding might reflect the true state of nature; however, alternative methodological considerations likely better explain these null results. First, the two groups were closely matched in substance use-related variables that typically show robust relationships with negative urgency (e.g., Coskunpinar et al., 2013; Settles et al., 2012) and the tobacco users showed low severity of nicotine dependence in general. Second, substance abuse/dependence diagnosis in tobacco users and past year alcohol use in non-tobacco users trended with negative urgency, which might have confounded the present findings. Further, there were no expected differences between the groups in

negative urgency. Finally, a significant relationship between the circuit connectivity and negative urgency may only exist during the task active-state. Previous task-based studies showed higher amygdala activation in response to negative emotional stimuli and higher vmPFC activation in response to alcohol olfactory cue among social drinkers were related to higher negative urgency (Cyders et al., 2014, 2015). Therefore, the task-based studies may reflect the relationship between the circuit and negative urgency more clearly, as task-based fMRI would mimic the states of rash action under negative emotions.

Significant circuit 2: Right NAcc – Right TPJ circuit. The study results indicated that tobacco users demonstrated stronger right NAcc – right TPJ connectivity strength at rest than non-tobacco users. The NAcc activates in response to or in anticipation of reward-related cues (including drug cues) after learning the cue – reward association (Kühn & Gallinat, 2011; Schultz, Dayan, & Montague, 1997; Volkow et al., 2011). The right TPJ is a part of the right hemisphere-lateralized ventral frontoparietal attentional network, which orients attention to behaviorally-relevant visual stimuli that are salient and terminates the ongoing cognitive processing (Corbetta & Shulman, 2002). Further, the right TPJ is involved in the detection of visual stimuli with low predictability in its spatial orientation, suggesting bottom-up stimulus-driven attentional control (Hahn, Ross, & Stein, 2006) and responses in the right TPJ to behaviorally-relevant visual stimuli can prompt an appropriate behavioral response (Geng & Mangun, 2011). The stronger connectivity in the right NAcc – right TPJ circuit among tobacco users may indicate hypersensitivity towards salient visual tobacco cues that induce tobacco use. The already-heightened right NAcc – right TPJ circuit among tobacco users may become highly

reactive upon the detection of unpredictable, but behaviorally-relevant, tobacco-related cues, leading these individuals to use tobacco.

The TPJ is also a part of dorsal medial subsystem in the default mode network, which shows greater activity during the resting-state than task active-state (Andrews-Hanna, Smallwood, & Spreng, 2014; Raichle et al., 2001). The default mode network is anti-correlated with brain regions that are commonly active during the cognitively demanding tasks (Fox et al., 2005). During the resting state, brain regions that are task active tend to deactivate while brain regions in the default mode network tend to activate, and vice versa during the cognitive tasks. One interesting point to note in the current result is that the tobacco users showed greater rsFC between right NAcc, which is commonly active upon the receipt of external environmental stimuli, and right TPJ, which shows increased activity during the resting state. This hyperconnectivity between the two regions that are supposed to be anticorrelated is consistent with the proposal indicating reduced anticorrelations between such regions with patients with psychopathology, which can disrupt appropriate switching between networks according to a presented state (Whitfield-gabrieli & Ford, 2012). This further suggests that the heightened right NAcc – right TPJ circuit is readily wired to react to the behaviorally relevant tobacco cues in the external environment among tobacco users.

Trend circuit: Right NAcc – Left Precuneus circuit. The study results showed a trend to stronger right NAcc and left precuneus connectivity strength in tobacco users than non-tobacco users. Positive functional connectivity between the NAcc and precuneus was previously seen in a small sample of healthy controls (Di Martino et al., 2008) and later replicated in a large sample of healthy controls (Choi, Yeo, & Buckner,

2012), which suggests the trend effect in the current study may be due to the small sample size. The precuneus is a core node of the default mode network (Raichle et al., 2001). Its activity is inversely related to prefrontal brain regions (e.g., ventrolateral PFC and DLPFC) that are more active during task active-state (Greicius, Krasnow, Reiss, & Menon, 2003). The precuneus is involved in monitoring of external stimuli (Gusnard & Raichle, 2001), and drug-addicted individuals show hyper-sensitivity toward self-relevant external stimuli, such as drug-related cues (Dewitt, Ketcherside, McQueeny, Dunlop, & Filbey, 2015). This is consistent with recent findings that show smoking cue-induced reactivity in the precuneus among heavy drinking daily smokers (Courtney, Ghahremani, London, & Ray, 2014). Stronger right NAcc – left precuneus couplings in tobacco users in this study suggests (though it did not reach statistical significance likely due to the small sample size) that this circuit might be hypersensitive in monitoring and detection of external tobacco-related cues during resting state. Because of the imbalance between the NAcc and prefrontal regions in the addicted brain (Volkow et al., 2011), the detection of tobacco cues would likely trigger tobacco use among tobacco users.

Although not reaching significance, a medium effect was detected in the relationship between negative urgency and right NAcc – left precuneus rsFC strength, such that negative urgency was negatively related to rsFC strength in tobacco users and positively related to rsFC strength in non-tobacco users. How the specific pattern in tobacco users relates to tobacco use is hard to interpret as negative urgency and rsFC strength were not significantly related to any tobacco use-related variables and as negative urgency did not differ between groups. Future work should seek to study this in a larger, more properly powered study.

Hypothesis 2: The rsFC patterns will be related to negative urgency in the overall group

Significant circuits 3 & 4: Bilateral Temporal Pole – Left Supramarginal Gyrus circuits. The study results showed positive relationships between the bilateral temporal pole – left supramarginal gyrus rsFC strength and negative urgency in the overall group, as well as in each group. Consistent with the current findings, a recent study that examined temporal pole connectivity to other brain regions demonstrated the functional connection between the temporal pole and the supramarginal gyrus (Pascual et al., 2015). The temporal pole anatomically and functionally interconnects the two key regions in negative urgency: the OFC and the amygdala (Fan et al., 2014; Olson et al., 2007; Pascual et al., 2015). A recent proposal suggests that the temporal pole is involved in socio-emotional processing, suggesting that the temporal pole modulates visceral emotional responses cued from extreme emotional stimuli and serves as a memory storage for perception and emotion associations formed from personal experiences (Olson et al., 2007). For example, visual drug cue is associated with heightened temporal pole activity among detoxified cocaine users (Childress et al., 1999) who show temporal pole activation in response to emotionally salient cue relevant to personal experiences. Given the past evidence and current findings, the temporal pole may serve as a crucial brain region for negative urgency.

The function of the supramarginal gyrus has not acquired enough accumulating science other than its involvement in language processing (e.g., Stoeckel, Gough, Watkins, & Devlin, 2009). However, some interesting findings exist in this research that inform the current study results. Supramarginal gyrus activation is related to heightened

craving in response to tobacco-related cues among tobacco users (Brody et al., 2007) and is greater during reflective, deliberative choices among healthy participants (Christakou, Brammer, & Rubia, 2011), suggesting the potential involvement of the supramarginal gyrus in cognitive control. Consistently, greater supramarginal gyrus activation is observed during response inhibition, and this activation predicted higher later drug use among adolescent high frequency drug users (Mahmood et al., 2013). Drug users, who have diminished cognitive control, may need to exert effortful control via supramarginal gyrus hyperactivation to properly inhibit the prepotent response than non-drug users, and this hyperactivation may be a marker for future drug use. Conversely, the suppression of supramarginal gyrus activation is observed during the impulsive choices among adolescent substance users (Stanger et al., 2013), as this region may not be required to exert impulsive behaviors. Further, greater supramarginal gyrus activation during successful reappraisal of negative emotions is related to greater decrease in negative emotion (Ochsner, Bunge, Gross, & Gabrieli, 2002). However, although these previous studies report the supramarginal gyrus as one of the significantly activated regions, they do not fully recognize or discuss supramarginal gyrus involvement or they considered its activation as “atypical.” However, a general trend seems to converge into the potential, but preliminary, function of the supramarginal gyrus in cognitive control, which is depleted in substance users, as exhibited by heightened recruitment of the region during tasks involving cognitive control and reduced recruitment during the impulsive decision-making. However, the literature in this area is underdeveloped, making this interpretation a conjecture, and requires a task-based fMRI study focused on the relationship between cognitive control and the supramarginal gyrus.

The bilateral temporal pole – left supramarginal gyrus circuit findings in this study suggest that these circuits might be involved in modulation of response to emotional stimuli with respect to negative urgency. Also, the potential involvement of these circuits in negative urgency is further supported by the findings that negative urgency did not differ across groups and that the relationship between negative urgency and the circuit strengths were similar regardless of the tobacco use status. While the bilateral temporal poles process emotional responses to external stimuli relevant to one's personal experience, the left supramarginal gyrus modulates the emotional responses and guides subsequent behaviors to be less risky. Specifically, the right temporal pole – left supramarginal gyrus circuit is especially important because of the lateralized function of right temporal pole in emotion regulation and as a storage for personal episodic memories (Olson et al., 2007), as well as its involvement in negative emotion processing and high arousal emotions (Beauregard, Lévesque, & Bourgouin, 2001; Blair, Morris, Frith, Perrett, & Dolan, 1999). Interestingly, reduced right temporal pole GMV is associated with greater difficulty identifying feelings (Grabe et al., 2014) and higher negative urgency (Albein-Urios, Martinez-Gonzalez, et al., 2013; Muhlert & Lawrence, 2015). Further, greater task activation in the right temporal pole during negative affective state is related to more effective negative emotion regulation (Mathiak et al., 2011). Given this evidence, the right temporal pole – left supramarginal gyrus circuit may be an important circuit to target negative urgency-related maladaptive behaviors like tobacco use.

Exploratory Hypothesis 3: The relationship between rsFC patterns and negative urgency will differ across tobacco users and non-tobacco users

Trend circuit: Left NAcc – Right DLPFC circuit. The study results showed a trend toward differing relationships between negative urgency and the left NAcc – right DLPFC rsFC strength, such that there was a negative relationship between negative urgency and the rsFC strength in tobacco users, but no relationship (although a medium effect size) in non-tobacco users. In tobacco users, negative urgency may be involved in tobacco use given weaker rsFC strength between the left NAcc and right DLPFC, although the tobacco use-related variables did not reveal any relationship with the rsFC strength. The medium effect between negative urgency and rsFC strength between the left NAcc and right DLPFC in tobacco users, although it did not reach significance, might suggest that the strength of the circuit may be a protective factor to a tobacco user. Drug addiction is characterized by an imbalance between reward-related regions like the NAcc and cognitive control-related regions like the DLPFC, in which brain regions involved in cognitive control are disrupted and overridden by reward related-regions (Goldstein & Volkow, 2012; Volkow et al., 2011). In tobacco users, the disrupted cognitive control may be characterized by smaller DLPFC GMV and lower DLPFC GM density, relative to non-tobacco users (Brody et al., 2004; Zhang et al., 2011). While the NAcc does not show any anatomical differences between tobacco users and non-tobacco users, right DLPFC cortical thickness is negatively associated with tobacco dependence (Li et al., 2015). Further, right DLPFC cerebral blood flow activity during tobacco cue condition is negatively correlated with lifetime tobacco use and right DLPFC GM density is positively correlated with tobacco cue related cerebral blood flow activity in right

DLPFC (Zhang et al., 2011), further supporting disruption in brain regions related to cognitive control in tobacco use. The current finding suggests that the interactive effect of negative urgency and tobacco use status is involved in the left NAcc – right DLPFC rsFC strength. However, this interpretation should be taken critically as the circuit strength was not related to any tobacco use-related variables in tobacco users.

Discussion of null findings

Despite novel findings in the current study, there are several potential reasons for null findings. First, the null findings may be related to the nature of data in the NKI-Rockland project. Having missing data was not uncommon among the measures of my interest, and I excluded participants if they had missing data on key variables (i.e., self-reported drug use data especially tobacco use), but did not exclude participants for missing the variables describing the participant characteristics (e.g., age of first tobacco use, frequency of tobacco use per day in the past 6 months, years of tobacco use, FTND scores). I conducted the analysis only including the subset of participants with data on the variables of interest, which reduced a statistical power. Additionally, the null findings in the relationships among negative urgency, rsFC strengths, and demographics and other substance use variables could be partially attributed to the limited variability among several variables. For example, past year alcohol and marijuana use frequencies were collected in a Likert scale format, but using categorical frequency (e.g., 0 = no use, 1 = 1-10 times per year, 2 = once a month, 3 = binge use only, 4 = once per month, 5 = two or more times per month, 6 = once per week, 7 = two or more times per week, 8 = once per day, 9 = more than once per day), so the frequency of alcohol and marijuana use was

dummy-coded (absence = 0, presence = 1) based on the study operationalization.

Similarly, the history of substance use and psychiatric disorder was assessed with DSM diagnosis, which limited variability in disease severity. Therefore, it is likely that these variables have significant relationships with negative urgency or rsFC strengths when the variables can be assessed with continuous measures.

Second, the groups did not differ in their levels of negative urgency, unlike previous studies reporting higher negative urgency in tobacco users (Lee et al., 2015; Spillane, Smith, & Kahler, 2010). A high proportion of the current sample is not purely tobacco users or non-tobacco users, as most endorse past DSM-IV diagnosis for psychiatric disorders, substance abuse/dependence, or alcohol and marijuana use. However, this study did not exclude for history of DSM-IV diagnosis or alcohol and marijuana use because of their high lifetime prevalence in the U.S. population (Kessler et al., 2005). Comparing tobacco users and non-tobacco users without any history of such disorders or drug use would not be ecologically valid and such groups would be unlikely to represent a general population limiting the generalizability of study findings. Given that the prevalence of other substance use-related variables and that these variables were matched between groups, having similar levels of negative urgency between groups is not completely unsurprising. Additionally, an examination of group differences in negative urgency between tobacco users and non-tobacco users in the sample $n = 354$, which only includes samples suitable for fMRI analysis, showed that tobacco users ($n = 39$) have significantly higher negative urgency compared to non-tobacco users ($n = 156$; $t(52.37) = -2.21, p = .32$) consistent with previous reports. Therefore, this suggests that the included sample might indeed be a unique sample due to selection and matching process.

However, having similar levels of negative urgency between groups may provide a better picture on how tobacco use status contributes to the rsFC patterns without the confound of negative urgency. Having differing levels of negative urgency would easily lead to the assumption of differing patterns of rsFC patterns. However, because the levels of negative urgency were similar between groups in the present study, the study provided meaningful information as to how tobacco use relates to rsFC patterns while “controlling” for the level of negative urgency.

Third, this study did not exclude participants with missing a drug test (three tobacco users and two non-tobacco users) or who tested positive for recent THC/marijuana use (four tobacco users and one non-tobacco users), and those with lifetime DSM diagnosis (while excluding severe mental illnesses). This decision was made because of high co-occurrence of tobacco and marijuana use in the U.S. population (Richter et al., 2004) and recent marijuana legalization that escalated the rate of the co-use (Schauer et al., 2015). Excluding those with lifetime DSM diagnosis would limit the ecological validity of the study findings due to high prevalence of psychopathologies in the U.S. population (Kessler et al., 2005). Further, additional rsFC analyses that excluded participants without a drug test and with a positive drug test or those with lifetime DSM diagnosis show a similar pattern of findings, suggesting that the study results were not driven by missing or positive drug test results nor by lifetime DSM diagnosis.

Fourth, the current study includes samples with age ranging 19 – 63. The age range includes the age with ongoing cortical development (i.e., early 20’s; Gogtay et al., 2004), which presents potential connectivity differences between the younger age group (i.e., ongoing cortical development) and the older age group (i.e., relatively matured

brain), which might confound the current findings. However, human brains constantly go through changes as a function of normal aging. For example, GM density shows non-linear changes (Sowell et al., 2003) and resting-state networks show differing levels of recruitment (Mowinckel, Espeseth, & Westlye, 2012) as a function of normal aging. These suggest that human brains continuously change as a part of normal aging, and this was controlled by matching the age between the groups.

Fifth, small sample size ($n = 22$ in tobacco users; $n = 21$ in non-tobacco users) limited the power to detect effects, specifically for exploratory Hypothesis 3, which examined the relationship patterns between mean rsFC strength and negative urgency within each group. In the sample size of $n = 354$ that met inclusion/exclusion criteria for fMRI data suitable for analysis, 39 daily tobacco users were identified. After imposing further inclusion/exclusion criteria to ensure consistency in sample characteristics, 25 tobacco users remained. This process was undertaken to ensure the internal validity by ensuring similar characteristics among tobacco users at the expense of reduced power (i.e., increasing the chance of Type II error) and weakened external validity. Although studies examining adequate sample size for fMRI studies suggests the sample size in this study is adequate to detect power (Desmond & Glover, 2002; Mumford & Nichols, 2008), the study findings should be considered in light of the sample size and selection process as it can affect power and generalizability.

Finally, several large effect sizes (despite non-significance) between rsFC strengths and tobacco-use related variables showed unexpected, but consistent, patterns of relationship. The right amygdala – left mOFC/vmPFC and right NAcc – right TPJ circuits were stronger in tobacco users compared to non-tobacco users, and the stronger

couplings in these regions were related to lower past 6-month tobacco use frequency and lower nicotine dependence, respectively. Also, the right temporal pole – left supramarginal gyrus circuit was positively related to negative urgency in tobacco users, and the stronger coupling in these regions was related to lower nicotine dependence and lower past 6-month tobacco use frequency. This relationship is unexpected because the positive relationships between circuit strengths and the tobacco use variables were expected given the patterns of rsFC findings. Although mainly non-significant, questions remain with the interpretability of these results considering the large effect sizes. For example, the FTND scores among tobacco users had a restricted variability in nicotine dependence severity (i.e., the low-to-moderate range of nicotine dependence), with a majority indicating low nicotine dependence. The past 6-month tobacco use frequency had 3 missing data (approximately 15% of data missing), further reducing power. Therefore, these relationships warrant further examination with larger sample size that provides greater statistical power and variability.

Future directions

The current study provides preliminary evidence for the future investigation of network-level neural correlates of negative urgency in tobacco users and non-tobacco users. This study extended previous neuroimaging findings, which have mainly focused on how negative urgency is related to brain responses in localized, segregated brain regions, by examining the network-level interactions between brain systems. Therefore, I outline some of the future implications of the present study.

First, similar analyses can be conducted using other types of drug users, which would lead to the development of a more transdiagnostic approach to understanding negative urgency's contributions on substance use. This approach would provide converging neural networks for negative urgency, guiding the identification of focal biomarkers across different types of problematic substance use.

Second, current findings could serve as prime preliminary data to examine these patterns in a larger study integrating Diffusion Tensor Imaging (DTI; an imaging technique that maps white matter tracts) and task-based fMRI studies of tobacco use and negative urgency. DTI can examine white matter integrity and whether white matter integrity influences the connection between two brain regions in the tobacco use-related or negative urgency-related rsFC circuits. The task-based investigation would augment the current findings by showing how these rsFC patterns change (e.g., maintain, strengthen, or weaken) during the task active state in comparison to resting-state, and better explain the behavioral manifestations (e.g., task performance) of these circuits in relation to tobacco use and negative urgency.

Finally, in the long term, the incorporation of additional neuroimaging techniques would strengthen and refine this study's findings and lead to the identification of biomarkers as potential treatment targets to improve maladaptive behaviors manifested by negative urgency, especially for psychosocial treatment resistant patients. This can also lead to the development of novel interventions that directly modify these circuits via pharmacological interventions or TMS approaches and the identification of a novel, objective biomarker of treatment response that can be used as a platform to test the effectiveness of negative urgency-based interventions. Specifically, TMS has been

examined across various psychopathologies including depression and schizophrenia and have shown its effectiveness as a therapeutic tool (Slotema, Blom, Hoek, & Sommer, 2010). The current TMS approach targets a single cortical region (e.g., DLPFC) to intervene on psychopathologies. The key brain regions in negative urgency are subcortical (e.g., amygdala), medial (e.g., mOFC/vmPFC) or inferior (e.g., temporal pole), which are located in areas that are difficult to directly target using TMS. However, recent evidence suggests that stimulating a single cortical region could also stimulate associated functional networks, thereby providing potential to indirectly target negative urgency-related brain regions (Opitz et al., 2015).

Limitations

In addition to potential reasons for null findings, I outline other study limitations. First, self-selection bias poses concern as participants chose to participate in the study by responding to the advertisement in the community. However, as described in the earlier section, the research team took every measure to reduce bias (i.e., strategic recruitment based on zip code, balancing key demographics across the recruitment period; Nooner et al., 2012). Second, there is a limitation of generalizability of the study findings. Females were oversampled in each sub-sample and the majority of the participants were white, which limits the generalizability of current findings to other populations. However, gender or race did not have any relationships with negative urgency in overall samples and within each group suggesting unlikely effects of gender or race on the key variable. Third, unlike many studies that focus on cigarette smokers, the present study sample is comprised of tobacco users, which may include users of various tobacco products.

However, given that most tobacco users in the current study consumed their tobacco products by smoking ($n = 19$; orally, $n = 1$; missing data, $n = 2$) and tobacco products contain nicotine, the variation in tobacco products across tobacco users would be unlikely to have significant confounding effects. Fourth, resting-state functional connectivity analysis that I used in this study examines the temporal correlation between two brain regions or the synchronous fluctuation of resting-state BOLD signals in two brain regions over time. This means that directionality of influence from one brain region to another cannot be examined or established. Finally, the way I matched non-tobacco users to tobacco users may have induced unforeseen sampling bias in sample selection, as the matching process was completed by manually matching non-tobacco users with tobacco users, primarily using demographics such as age, gender, and race, and then matching them on DSM diagnosis.

Conclusion

The present study investigated the network level neural correlates of negative urgency between tobacco users and non-tobacco users using negative urgency-related brain regions identified in previous literature as seed regions. The seed-based rsFC analyses identified evidence for the network-level neural correlates of negative urgency in tobacco users and non-tobacco users. First, compared to non-tobacco users, tobacco users show higher rsFC strengths in the right amygdala – left mOFC/vmPFC and the right NAcc – right TPJ circuits. Most importantly, negative urgency was positively correlated with rsFC strength in the bilateral temporal pole – left supramarginal gyrus circuits. The study findings provide prime preliminary evidence for network-level neural correlates of

negative urgency that can be leveraged and targeted in future research and treatment target development.

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APPENDIX A: STUDY INFORMATION

Table A1. NKI-Rockland Project: List of measures

General Information:

- Demographic Questionnaire
- Edinburg Handedness Questionnaire
- Hollingshead Four-Factor Index of Socioeconomic Status
- Medical History Questionnaire
- Medical Conditions
- Medication Form
- PhenX
- Sex Role Identity Scale
- Sexual History
- Sexual Orientation Scale

Physical Measures:

- Actigraphy
- Bike Test
- Blood Collection: chemistry profile, lipid profile, thyroid profile, CBC with differential, lead level, genetics, pregnancy test
- Urine Sample (drug test)
- Height/Weight
- Hip/Waist Measurements
- Ishihara's Test for Color Deficiency
- Grip Strength
- The Grooved Pegboard Test
- MRI Mock Scan
- MRI Scan
- MRI Incidental Finding Report
- Tanner Staging
- Vital Signs

Cognitive Tasks:

- Attention Network Test
- Penn's Computerized Neurocognitive Battery
- Delis-Kaplan Executive Functioning System
- Wechsler Abbreviated Scale of Intelligence
- Wechsler Individual Achievement Test – Second Edition Abbreviated
- Digit Span (Forward and Backward)
- Rey Auditory Verbal Learning Test

Table A1 continued

 Diagnostic Assessments:

- Adult ADHD Clinical Diagnostic Scale
 - Kiddie Schedule for Affective Disorders and Schizophrenia
 - Structured Clinical Interview for DSM-IV – Non-Patient Edition
-

Behavioral Measures:

- The High-Functioning Autism Spectrum Screening Questionnaire
- Behavioral Assessment System for Children, 2nd Edition – Parent Rating Scale
- The Behavioral Indicator of Resiliency to Distress
- Yale-Brown Obsessive Compulsive Scale
- Conners Adult ADHD Rating Scale – Self Report, Short Version
- The Child Behavior Checklist – Parent Report Form, Youth Self-Report, Adult Self-Report, Older Adult Self Report
- The Children’s Behavior Questionnaire (Very Short Form)
- The Early Adolescent Temperament Questionnaire (Revised) Parent Report
- Adult Temperament Questionnaire
- The Children’s Depression Inventory 2
- Beck Depression Inventory
- Geriatric Depression Scale
- The Comprehensive Addiction Severity Index for Adolescents
- The Children’s Eating Behavior Questionnaire
- Tanner Three-Factor Eating
- The Cognitive Failures Questionnaire
- The Cambridge-Hopkins Restless Legs Syndrome (Version 2)
- The Conners ADHD Rating Scale 3 – Parent Short Form, Youth Short Form
- The Domain-Specific Risk-Taking Scale
- Dot Probe
- Eating Disorder Examination Questionnaire
- Fagerstrom Test for Nicotine Dependence
- Modified Fagerstrom Tolerance Questionnaire – Adolescents
- Inventory of Callous-Unemotional Traits – Parent Version, Youth Self-Report
- International Physical Activity Questionnaire
- Interpersonal Reactivity Index
- Multidimensional Anxiety Scale for Children
- MRI Mind Wandering Questionnaire
- NEO Five Factor Inventory
- NIDA Quick Screen V1.01
- The 21-Item Peters et al. Delusions Inventory
- Pittsburgh Sleep Quality Index
- Positive and Negative Affect Schedule – Short Form
- Repetitive Behaviors Scale – Revised

Table A1 continued

-
- Satisfaction Survey (Adult, Child)
 - Social Networking Questionnaire
 - Social Responsiveness Scale
 - State Trait Anxiety Inventory
 - Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behavior Scale
 - Trauma Symptom Checklist for Adults & Children
 - UCLA PTSD Reaction Index – Parent & Youth
 - UPPS-P Impulsive Behavior Scale
 - Yale Global Tic Severity Scale
 - Youth Risk Behavior Surveillance System – MS & HS
 - Affect Intensity Measure
 - Ruminative Response Scale
 - Rapid Visual Information Processing Assessment
 - Penn State Worry Questionnaire
 - Preservative Thinking Questionnaire
 - Emotional Regulation Questionnaire
 - Short Imaginal Process Inventory
 - Meditation Questionnaire
-

Table A2. 2010 United States census data: Rockland county versus United States (Table 1 from Nooner et al. (2012))

| People facts (Census, 2010) | Rockland County | USA |
|--|------------------------|-------------|
| Population | 311,687 | 308,745,538 |
| Persons under 5 years old | 7.6% | 6.5% |
| Persons under 18 years old | 28.1% | 24.0% |
| Persons 65 years old and over | 13.4% | 13.0% |
| Female persons, percent, 2010 | 51.0% | 50.8% |
| White | 73.2% | 72.4% |
| Black or African American | 11.9% | 12.6% |
| American Indiana/Alaska Native | 0.3% | 0.9% |
| Asian | 6.2% | 4.8% |
| Native Hawaiian or other Pacific Islander | 0.0% | 0.2% |
| Two or more races reported | 2.5% | 2.9% |
| Hispanic or Latino | 15.7% | 16.3% |
| White, non-Hispanic | 65.3% | 63.7% |
| Foreign born, 2006-2010 | 22.1% | 12.7% |
| Language other than English spoken at home | 35.6% | 20.1% |
| High school graduates | 87.9% | 85.0% |
| Bachelor's degree or higher | 40.7% | 27.9% |
| Persons per household, 2006-2010 | 3.02 | 2.59 |
| Median household income, 2006-2010 | \$82,534 | \$51,914 |
| Per capita money income, 2006-2010 | \$34,304 | \$27,334 |
| Persons below poverty level | 11.3% | 13.8% |

This figure contains 2010 census data for Rockland County in the State of New York as well as for the United States of America (USA). The purpose of this figure is to demonstrate the census composition of Rockland County is similar to that of the USA as a whole. Therefore, data from this discovery science project based in Rockland Count is likely to generalize to the USA.

Figure A3. Locations of brain regions

(Images derived from <http://www.columbia.edu/itc/hs/medical/neuroanatomy/neuroanat/>)

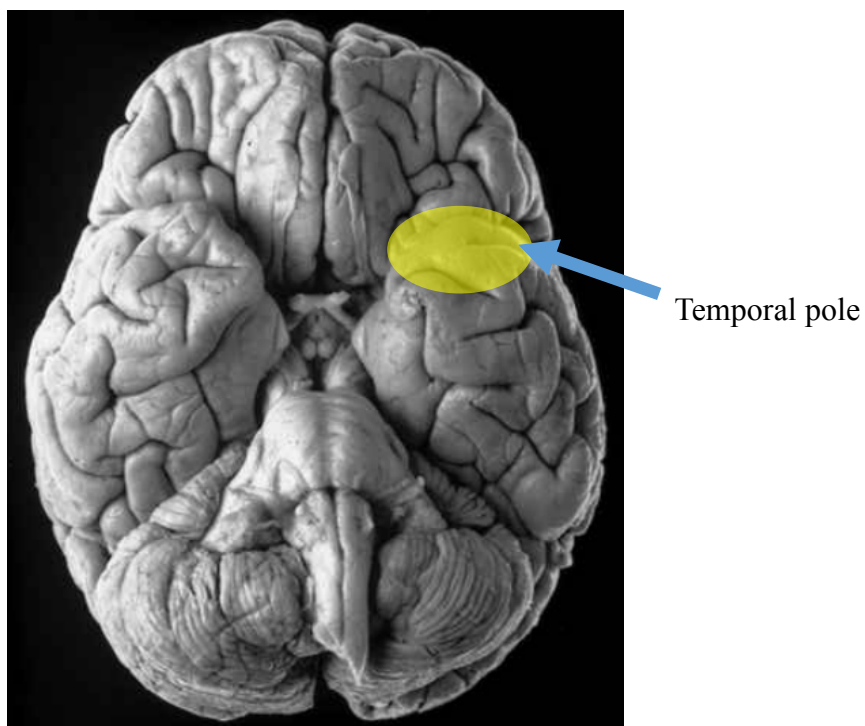
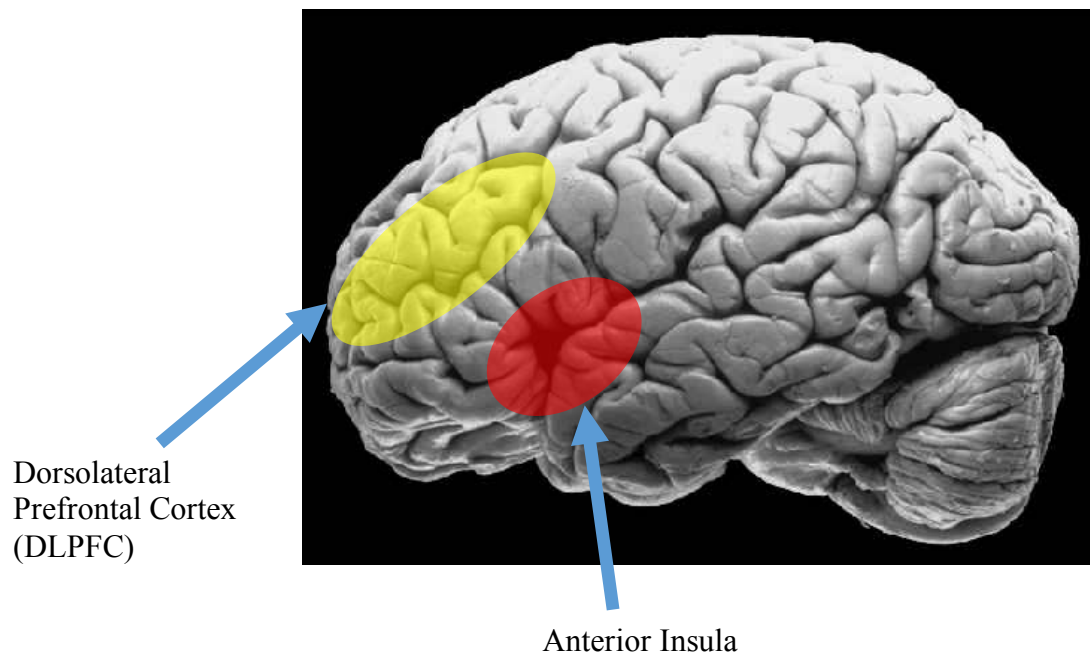
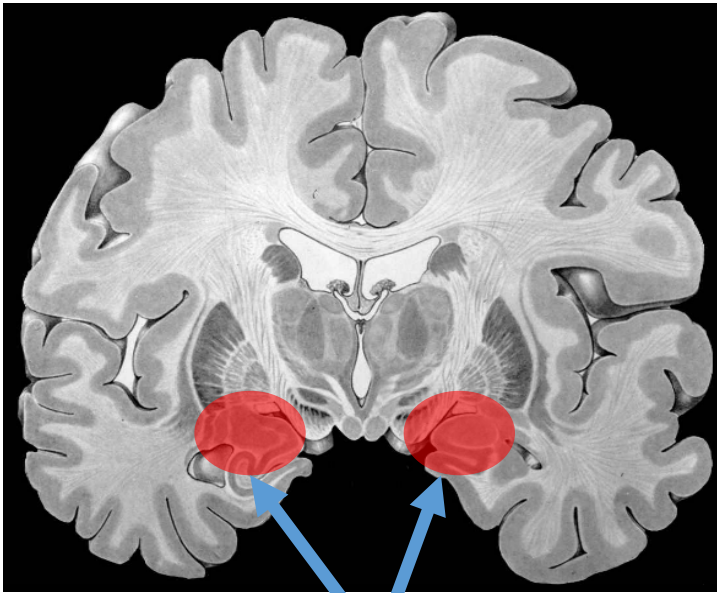
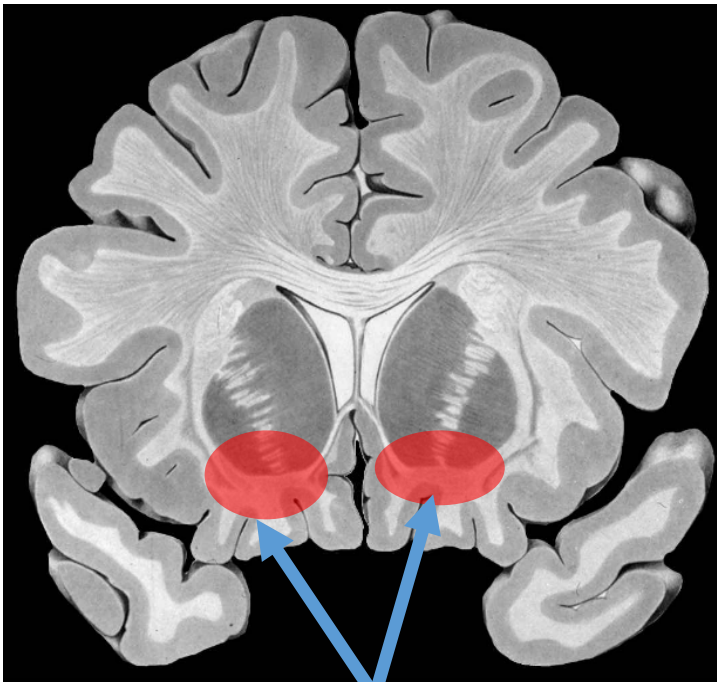


Figure A3. continued



Amygdala



Nucleus
Accumbens/Ventral
Striatum

APPENDIX B. STUDY DESCRIPTIONS

Figure B1. Sample selection flowchart

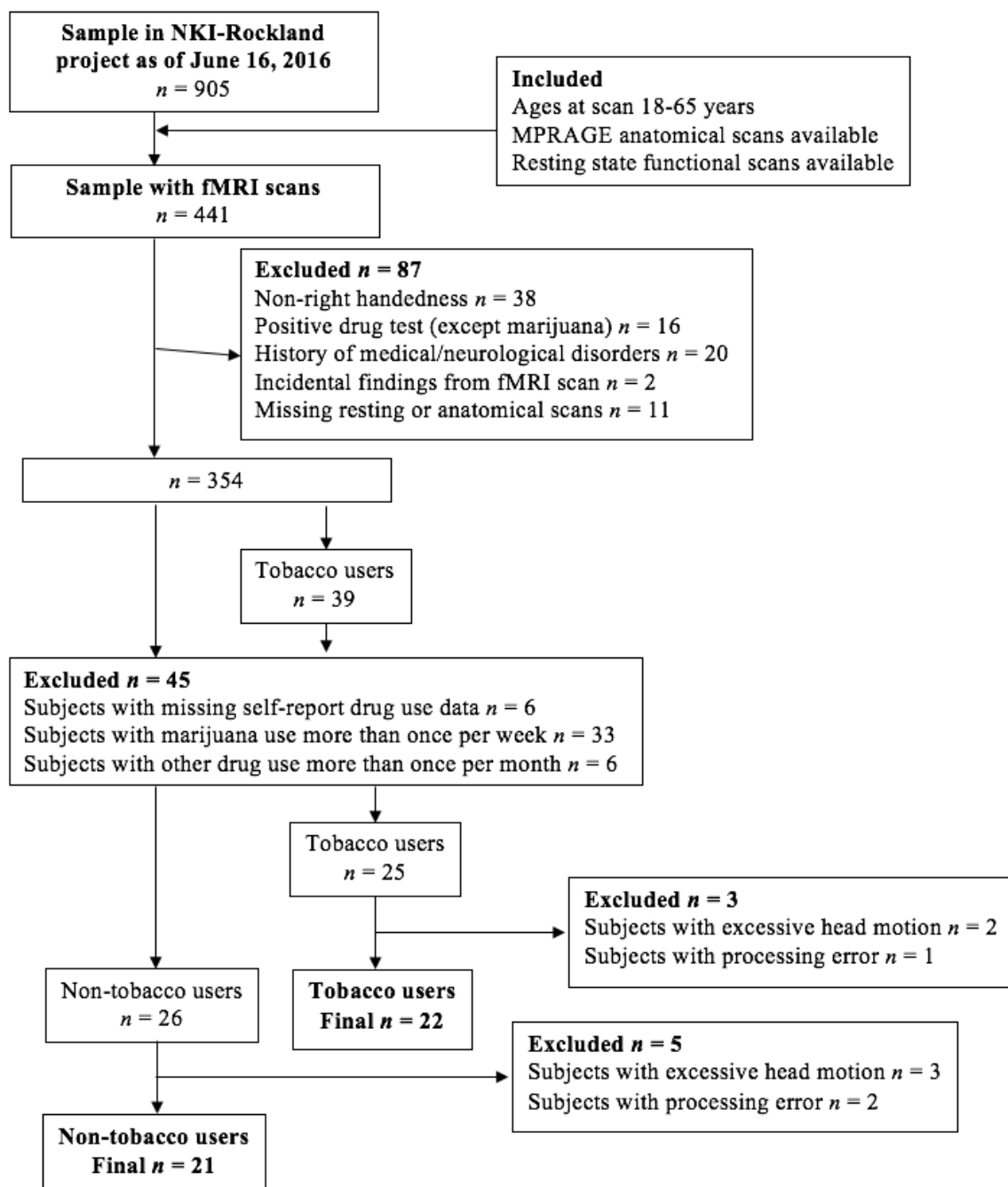


Table B2. Sample characteristics

| | Tobacco Users (<i>n</i> = 22) | Non-Tobacco Users (<i>n</i> = 21)* | <i>p</i> |
|---|--|---|-----------------|
| Age, mean (<i>SD</i>) | 37.50 (13.21) | 36.57 (13.78) | .82 |
| Gender, <i>n</i> | | | .91 |
| Female : Male | 14 : 8 | 13 : 8 | |
| Race, <i>n</i> (%) | | | .57 |
| White | 17 (77%) | 16 (76%) | |
| African American | 4 (18%) | 4 (19%) | |
| Other races | 1 (5%) | 1 (5%) | |
| Negative Urgency, mean (<i>SD</i>) | 1.94 (0.62) | 2.07 (0.59) | .49 |
| Psychiatric disorder diagnosis, <i>n</i>** | 4 | 5 | .65 |
| Major Depressive Disorder | 2 | 4 | |
| Panic Disorder w/o Agoraphobia | 1 | 1 | |
| Attention-Deficit/Hyperactivity Disorder | 1 | 1 | |
| Phobia | 1 | 0 | |
| Substance abuse/dependence diagnosis, <i>n</i>*** | 11 | 5 | .08 |
| Alcohol | 5 | 4 | |
| Cannabis | 10 | 2 | |
| Cocaine | 3 | 1 | |
| Sedative/Hypnotic/Anxiolytics | 0 | 1 | |
| Past year, <i>n</i> | | | |
| Regular alcohol use [^] | 11 | 9 | .64 |
| Marijuana use ^{^^} | 7 | 5 | .56 |
| Age of first tobacco use, mean (<i>SD</i>)[†] | 15.10 (2.36) | NA | |

Table B2. continued

| | | |
|---|--------------------------------|----|
| Frequency of tobacco use per day in the past 6-month, mean (SD)^{††} | 10.64 (7.15) | NA |
| Years of use, mean (SD)[†] | 19 Yrs 9 Mos (13 Yrs 2 Mos) | NA |
| FTND scores, mean (SD)^{†††} | 2.52 (2.11) | NA |

*Non-tobacco using controls did not endorse lifetime history of tobacco use.

**Diagnoses include both past and current diagnoses. One participant from each group was diagnosed with major depressive disorder and panic disorder without agoraphobia.

*** Diagnoses include both past and current diagnoses. Includes participants diagnosed with multiple substance abuse/dependence diagnoses.

^ Once per month or more during the past year

^^At least once or more per year during the past year

† Based on 20 tobacco users. Two tobacco users with missing data.

†† Based on 19 tobacco users. Three tobacco users with missing data.

††† Based on 21 tobacco users. One tobacco users with missing data.

Table B3. Seed regions: Nomenclature and index number used in FreeSurfer and corresponding cortical locations in anatomical parcellation in the Figure 1 (Destrieux et al., 2010)

| Seed regions | Nomenclature | Index Number in FreeSurfer | | Index Number in Destrieux et al. (2010) |
|-----------------|---|----------------------------|--------------|---|
| | | <i>Left</i> | <i>Right</i> | |
| Amygdala | Amygdala | 18 | 54 | - |
| Temporal Pole | Temporal pole | 11144 | 12144 | 43 |
| Anterior Insula | Anterior segment of the circular sulcus of the insula | 11148 | 12148 | 47 |
| | Superior segment of the circular sulcus of the insula | 11150 | 12150 | 49 |
| | Short insular gyri | 11118 | 12118 | 18 |
| | Long insular gyrus and central sulcus of the insula | 11117 | 12117 | 17 |
| NAcc | Accumbens area | 26 | 58 | - |
| DLPFC | Middle frontal gyrus | 11115 | 12115 | 15 |

Note. NAcc = Nucleus Accumbens; DLPFC = dorsolateral prefrontal cortex; Amygdala and NAcc do not have the Destrieux index number because these are subcortical structures and anatomical parcellation by Destrieux et al. (2010) is for cortical structure parcellation.

APPENDIX C. STUDY RESULTS

Table C1. Relationship among demographic variables, tobacco use variables and negative urgency

| | <i>All samples (n = 43)</i> | | | <i>Tobacco users (n = 22)</i> | | | <i>Non-tobacco users (n = 21)</i> | | |
|--|---------------------------------|----------|----------|-----------------------------------|----------|----------|---------------------------------------|----------|----------|
| | <i>r</i> | <i>B</i> | <i>p</i> | <i>r</i> | <i>B</i> | <i>p</i> | <i>r</i> | <i>B</i> | <i>p</i> |
| Age | -.10 | | .52 | -.09 | | .69 | -.11 | | .64 |
| Gender | | .13 | .51 | | -.01 | .96 | | .28 | .31 |
| Race | | .25 | .26 | | -.05 | .88 | | .55 | .07 |
| Psychiatric diagnosis | | .07 | .77 | | -.13 | .72 | | .22 | .49 |
| Substance abuse/dependence diagnosis | | .25 | .19 | | .44 | .10 | | .13 | .68 |
| Past year regular alcohol use | | .24 | .20 | | .03 | .27 | | .48 | .07 |
| Past year marijuana use | | .31 | .14 | | .19 | .51 | | .48 | .12 |
| Age of first tobacco use | | | | -.13 | | .57 | | | |
| Frequency of tobacco use per day in the past 6-month | | | | -.04 | | .86 | | | |
| Years of use | | | | .03 | | .91 | | | |
| FTND scores | | | | -.19 | | .40 | | | |

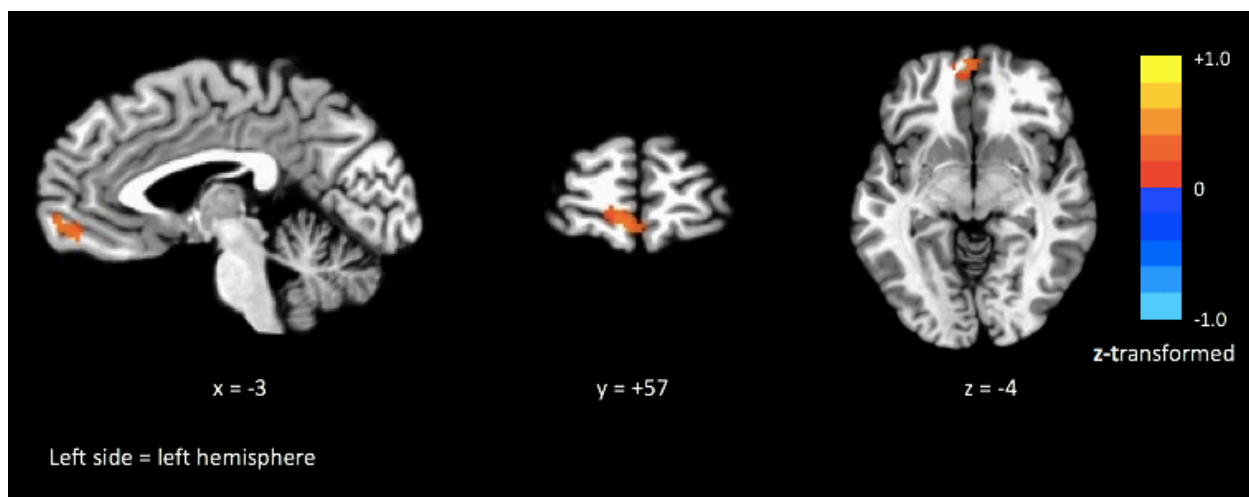
Note. *r* = Pearson's *r*; *B* = Unstandardized *B*; Correlational analyses examined the relationship between continuous variables and negative urgency. Simple regression analyses examined the relationship between dichotomous variables and negative urgency

Table C2. Significant and trend rsFC circuits in tobacco users and non-tobacco users

| Seed ROI | Cluster anatomical location | Cluster voxel size | Cluster level correction (α) | Primary peak location in Talairach space (x, y, z) | p-value | t-value | Mean rsFC (SD) | |
|--|-----------------------------|--------------------|---------------------------------------|--|---------|---------|----------------|-------------------|
| | | | | | | | Tobacco users | Non-tobacco users |
| <i>Group differences between tobacco users and non-tobacco users</i> | | | | | | | | |
| Right Amygdala | Left mOFC/vmPFC (BA10) | 121 | < .05 | -5, +57, -4 | < .005 | 2.97 | .34 (.24) | .10 (.10) |
| Right NAcc | Right TPJ (BA39) | 191 | < .05 | +51, -65, +20 | < .005 | 2.96 | .23 (.22) | .03 (.07) |
| Right NAcc | Left Precuneus | 103 | = .06 | -7, -57, +46 | < .005 | 2.96 | .20 (.16) | .03 (.12) |
| <i>Correlation between negative urgency and rsFC strength in overall group</i> | | | | | | | | |
| Right Temporal Pole | Left Supramarginal Gyrus | 124 | < .05 | -43, -51, +40 | < .005 | 2.97 | .12 (.18) | .16 (.21) |
| Left Temporal Pole | Left Supramarginal Gyrus | 372 | < .05 | -45, -53, +34 | < .005 | 2.97 | .21 (.32) | .19 (.20) |
| <i>Differences in correlations between negative urgency and rsFC strength between groups</i> | | | | | | | | |
| Left NAcc | Right DLPFC | 101 | = .09 | +29, +31, +42 | < .005 | 2.97 | .15 (.17) | .08 (.15) |

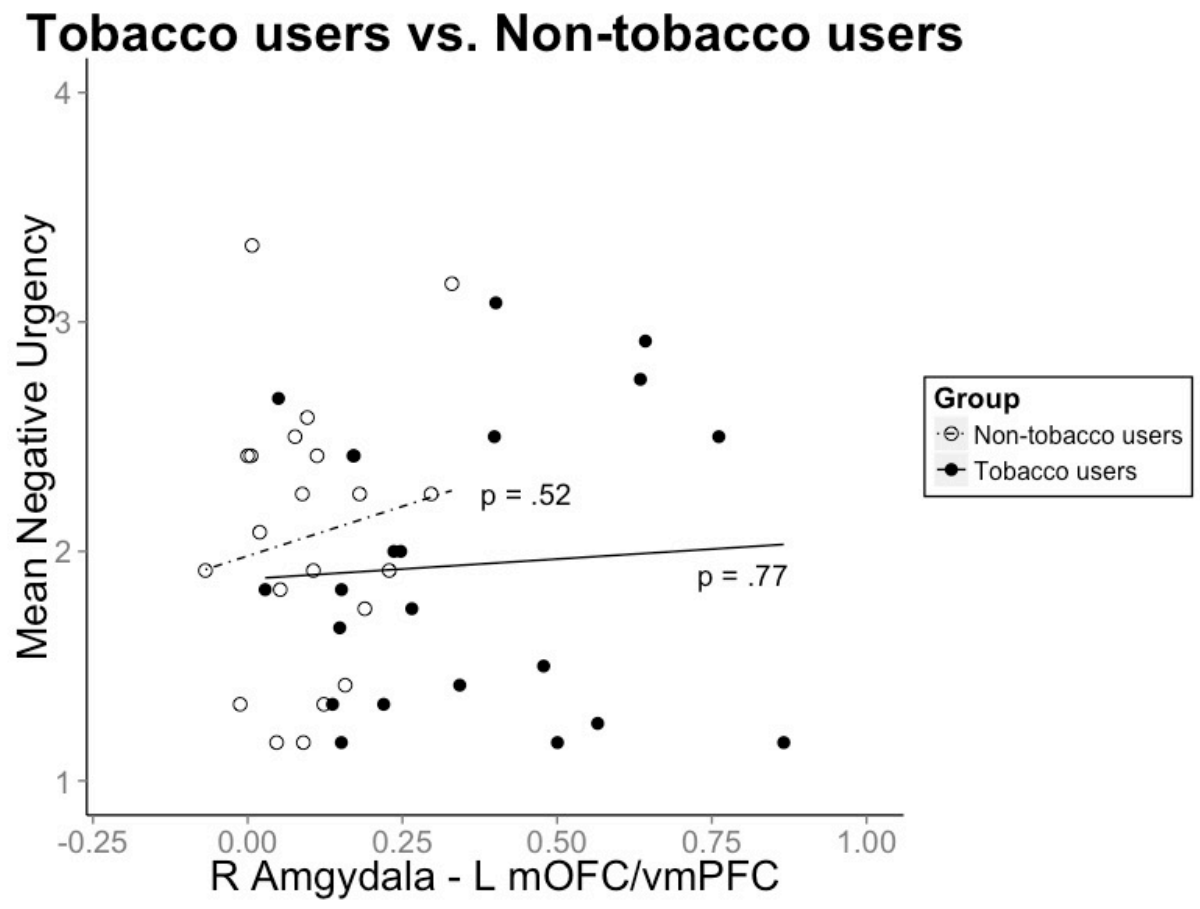
Note. Voxel level threshold $p < .005$; cluster level threshold $\alpha < .05$.

Figure C3. Significant group differences in rsFC strengths: Right Amygdala - Left mOFC/vmPFC



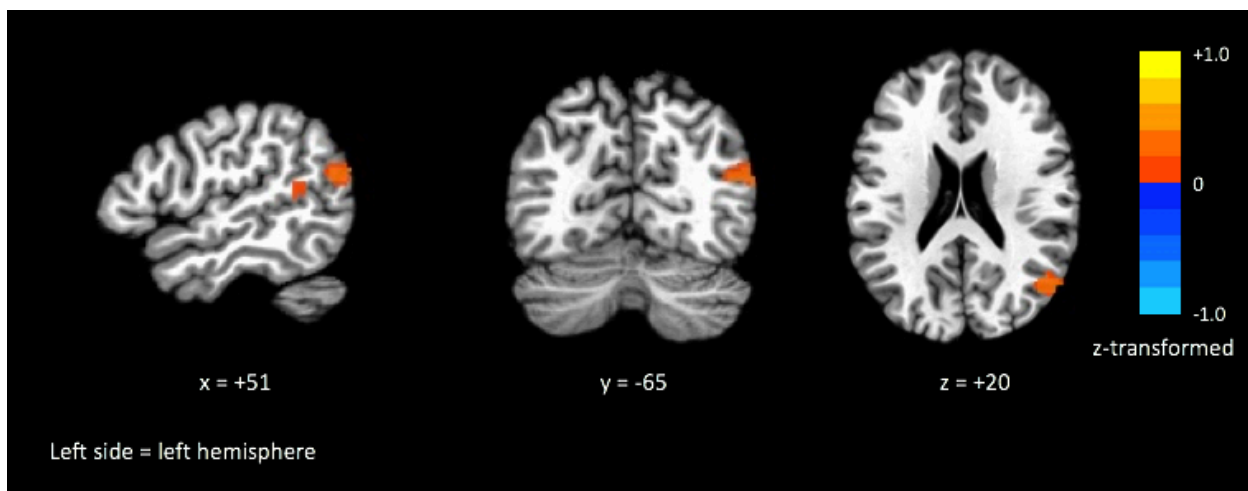
Note. mOFC/vmPFC = medial orbitofrontal cortex/ventromedial prefrontal cortex; Warm color indicates that the rsFC strength is stronger for tobacco users compared to non-tobacco users; voxel level threshold $p < .005$; cluster level threshold $\alpha < .05$.

Figure C4. Scatter plot: Right Amygdala – Left mOFC/vmPFC



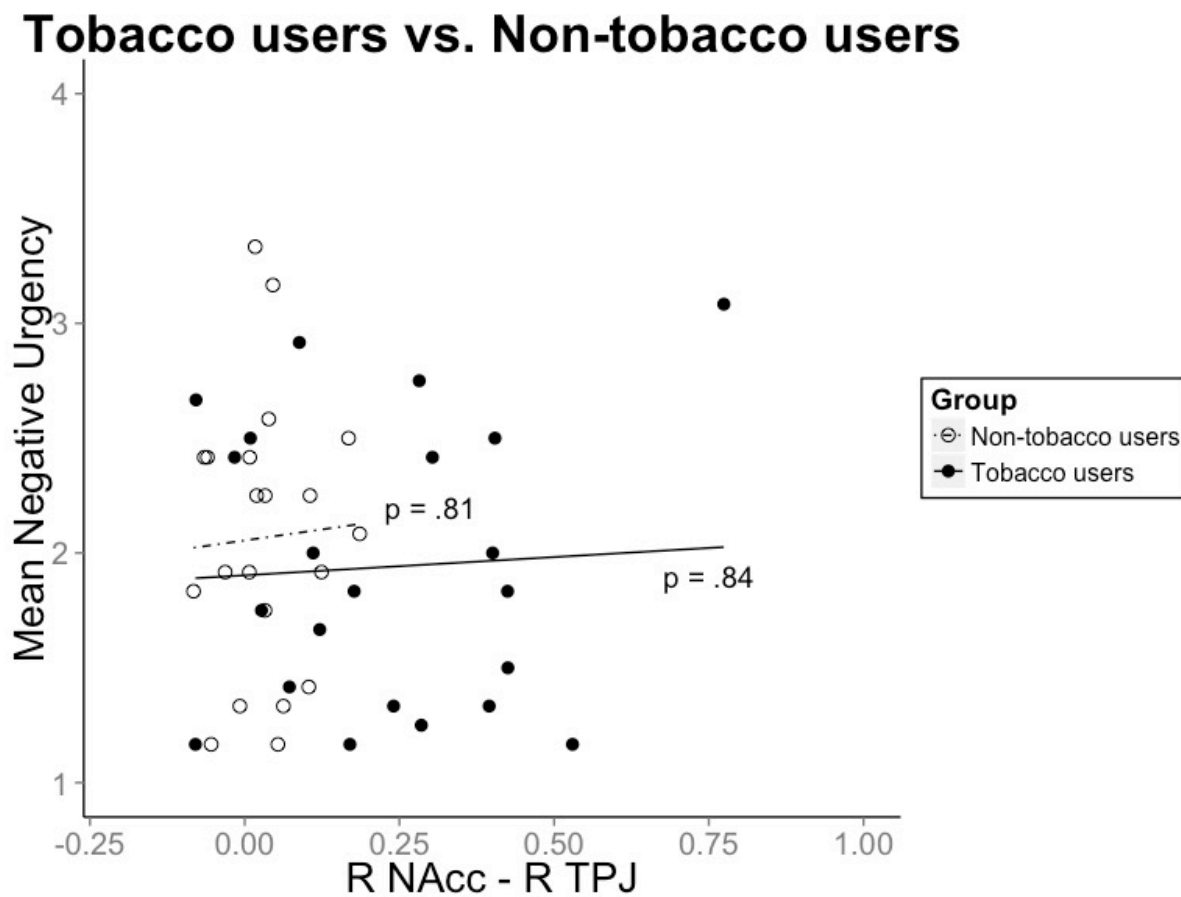
Note. mOFC/vmPFC = medial orbitofrontal cortex/ventromedial prefrontal cortex

Figure C5. Significant group differences in rsFC strength: Right NAcc – Right TPJ



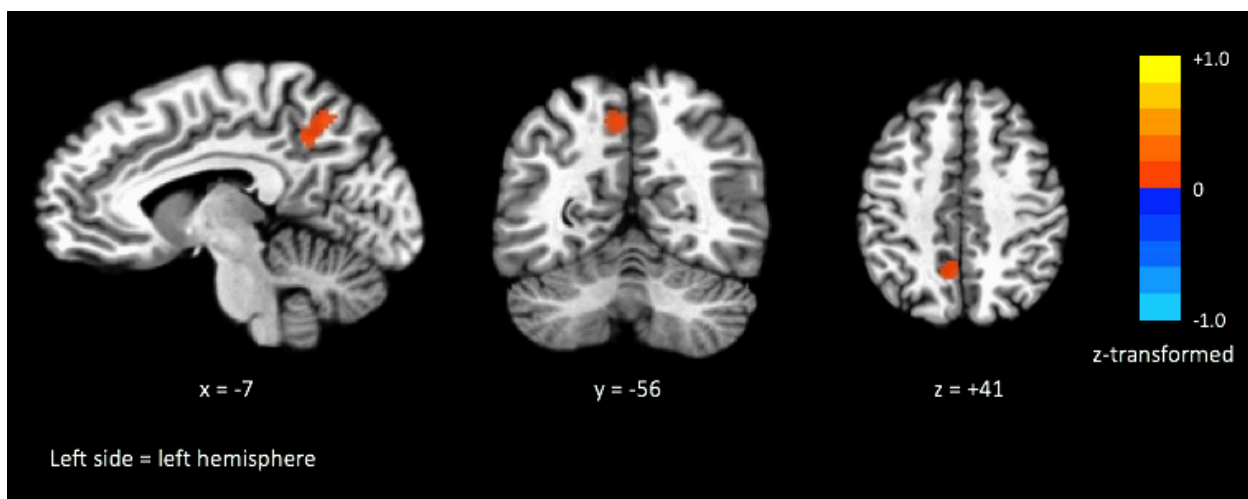
Note. NAcc = nucleus accumbens; TPJ = temporoparietal junction; Warm color indicates that the rsFC strength is stronger for tobacco users compared to non-tobacco users; voxel level threshold $p < .005$; cluster level threshold $\alpha < .05$.

Figure C6. Scatter plot: Right NAcc – Right TPJ



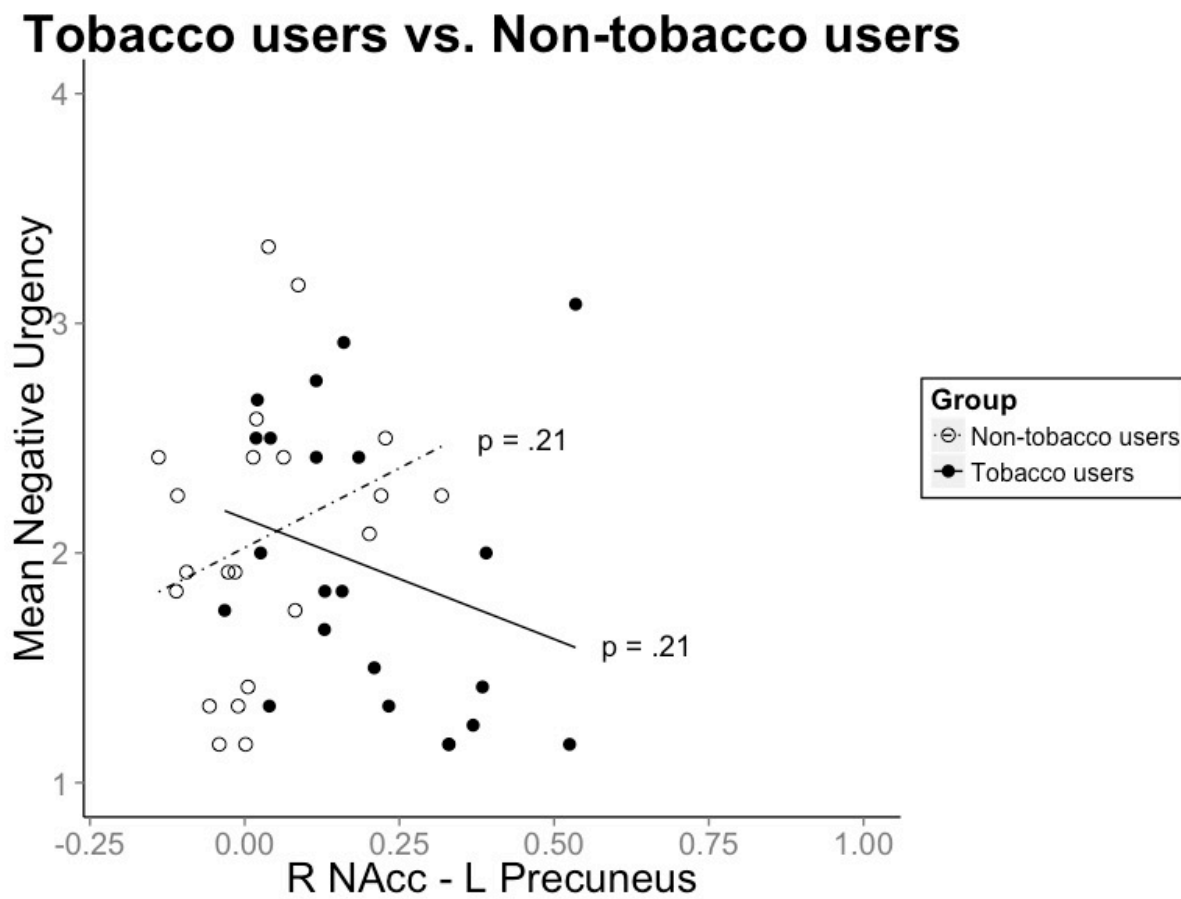
Note. NAcc = Nucleus Accumbens; TPJ = Temporoparietal junction

Figure C7. Trend group differences in rsFC strength: Right NAcc – Left Precuneus



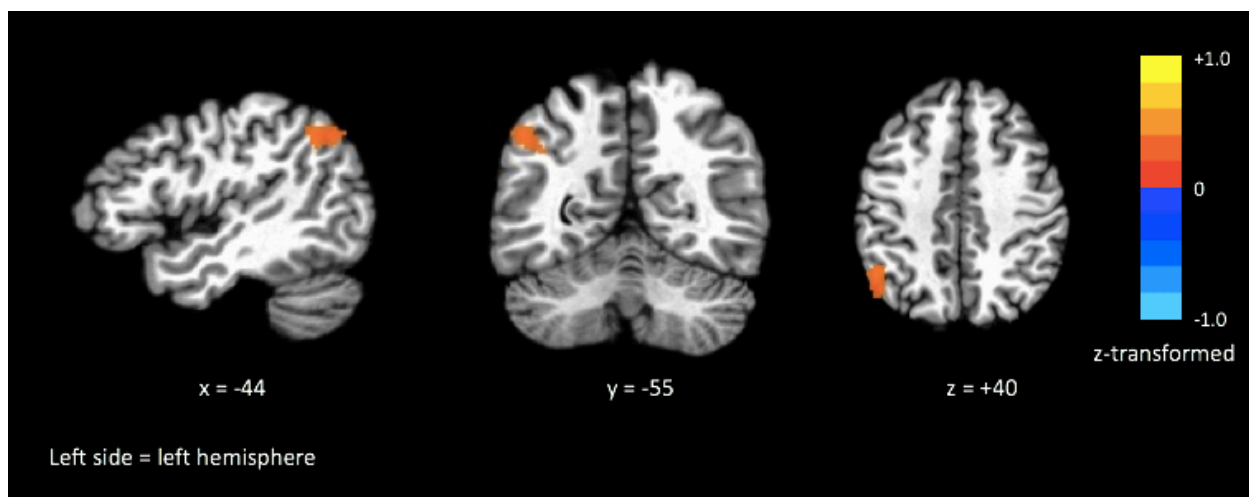
Note. NAcc = nucleus accumbens; Warm color indicates that that the rsFC strength is stronger for tobacco users compared to non-tobacco users; voxel level threshold $p < .005$; cluster level threshold $\alpha = .06$.

Figure C8. Scatter plot: Right NAcc – Left Precuneus



Note. NAcc = Nucleus accumbens

Figure C9. Significant correlation between negative urgency and rsFC strength: Right Temporal Pole – Left Supramarginal Gyrus



Note. Warm color indicates that a positive correlation between negative urgency and the rsFC strength; voxel level threshold $p < .005$; cluster level threshold $\alpha < .05$.

Figure C10. Scatter plot: Right Temporal Pole – Left Supramarginal Gyrus

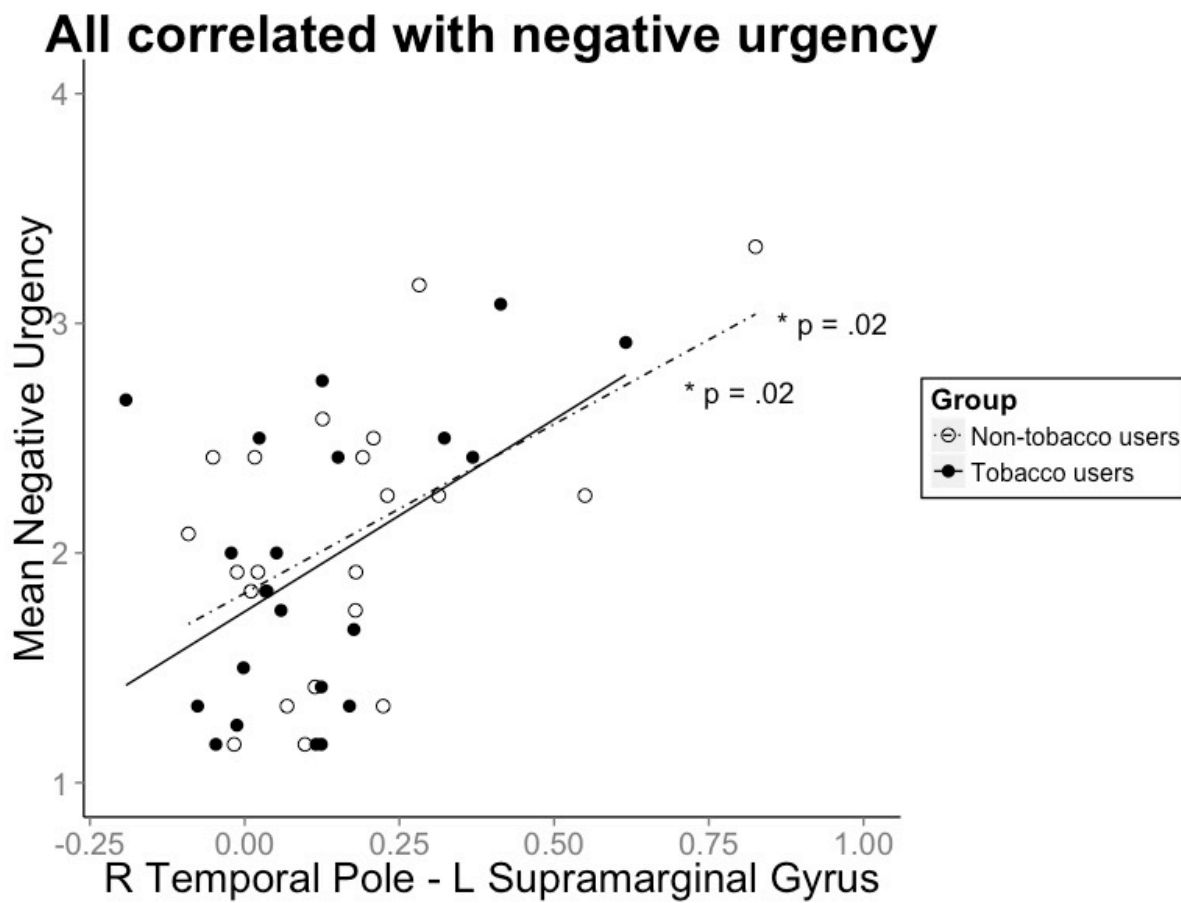
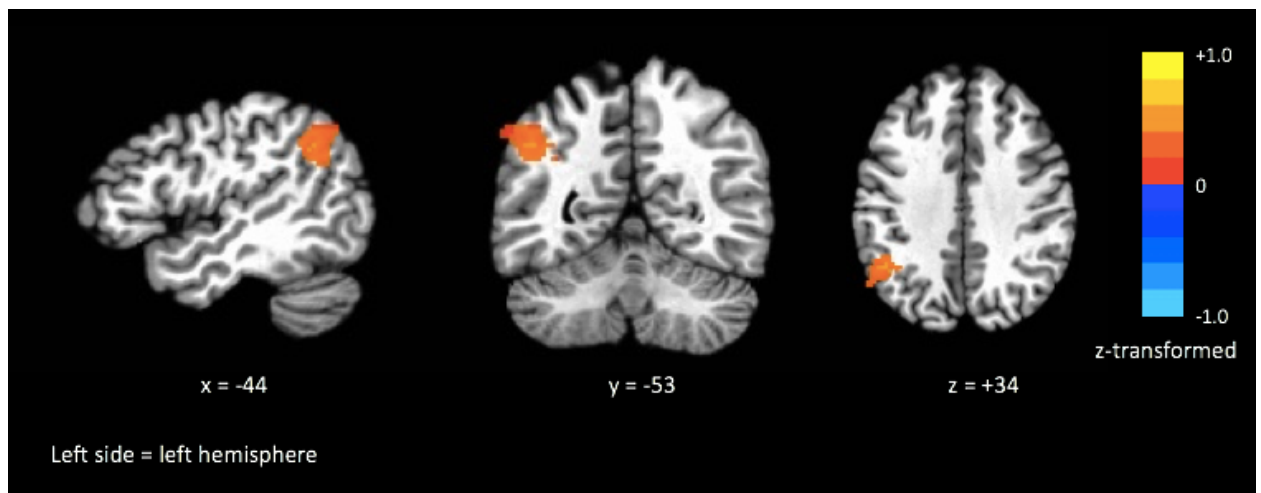


Figure C11. Significant correlation between negative urgency and rsFC strength: Left Temporal Pole – Left Supramarginal Gyrus



Note. Warm color indicates that a positive correlation between negative urgency and the rsFC strength; voxel level threshold $p < .005$; cluster level threshold $\alpha < .05$.

Figure C12. Scatter plot: Left Temporal Pole – Left Supramarginal Gyrus

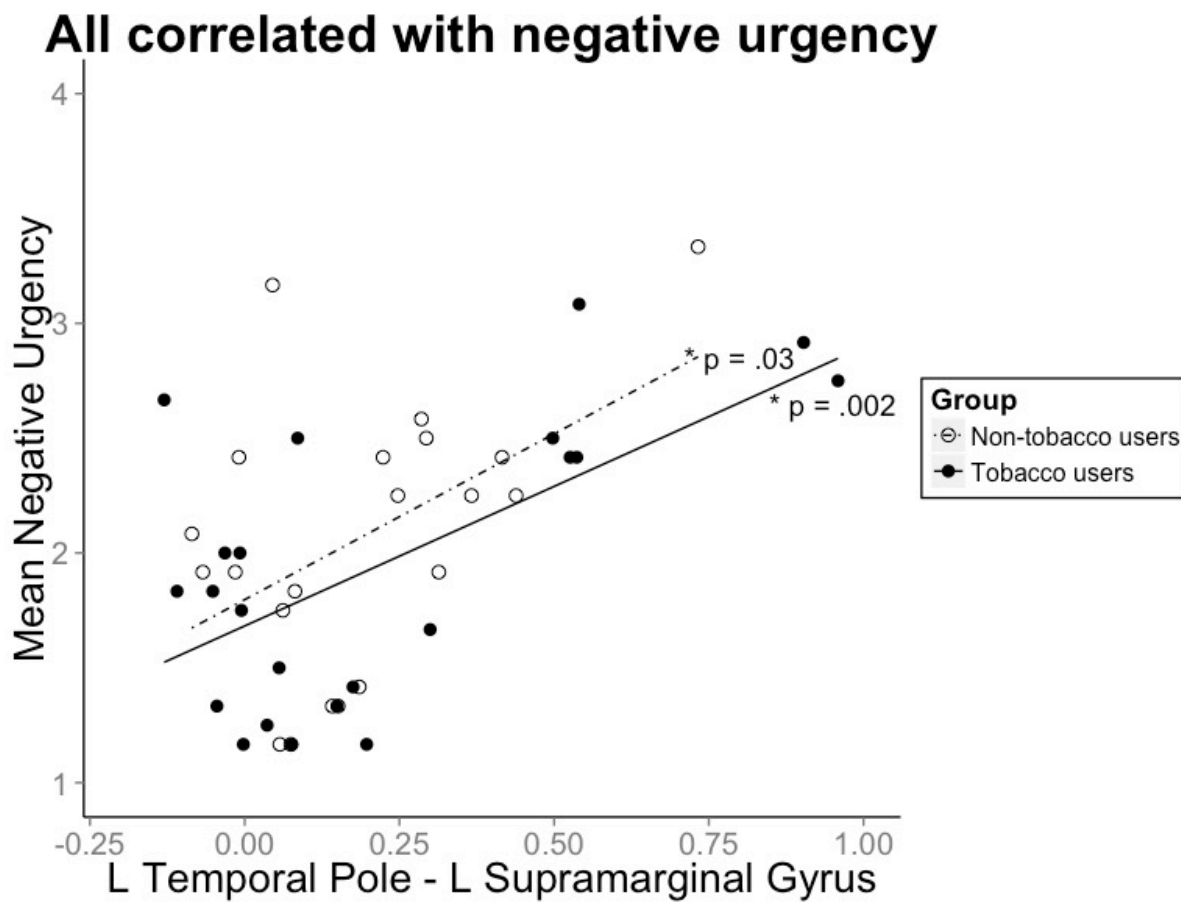
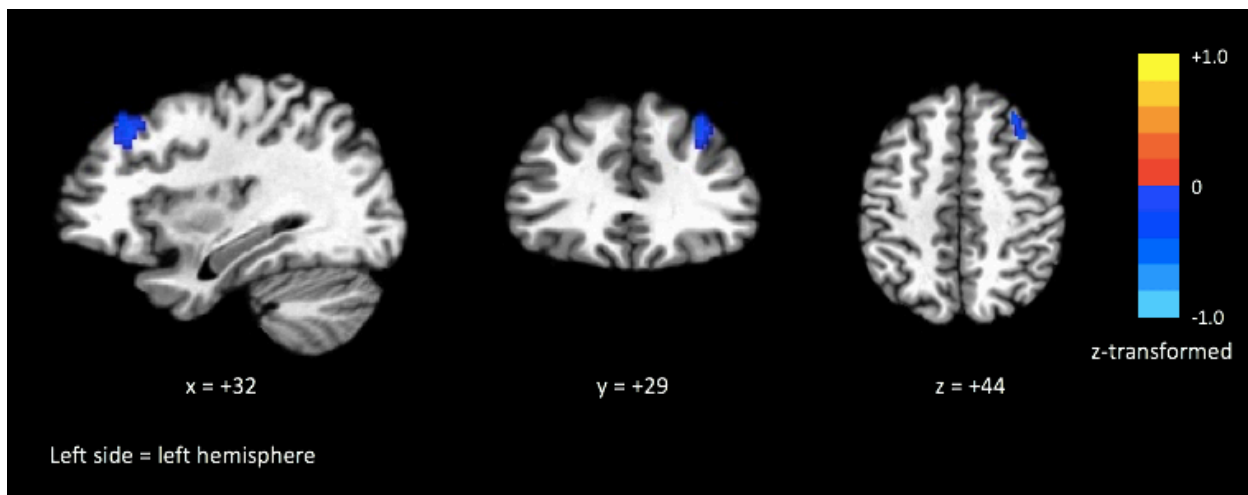


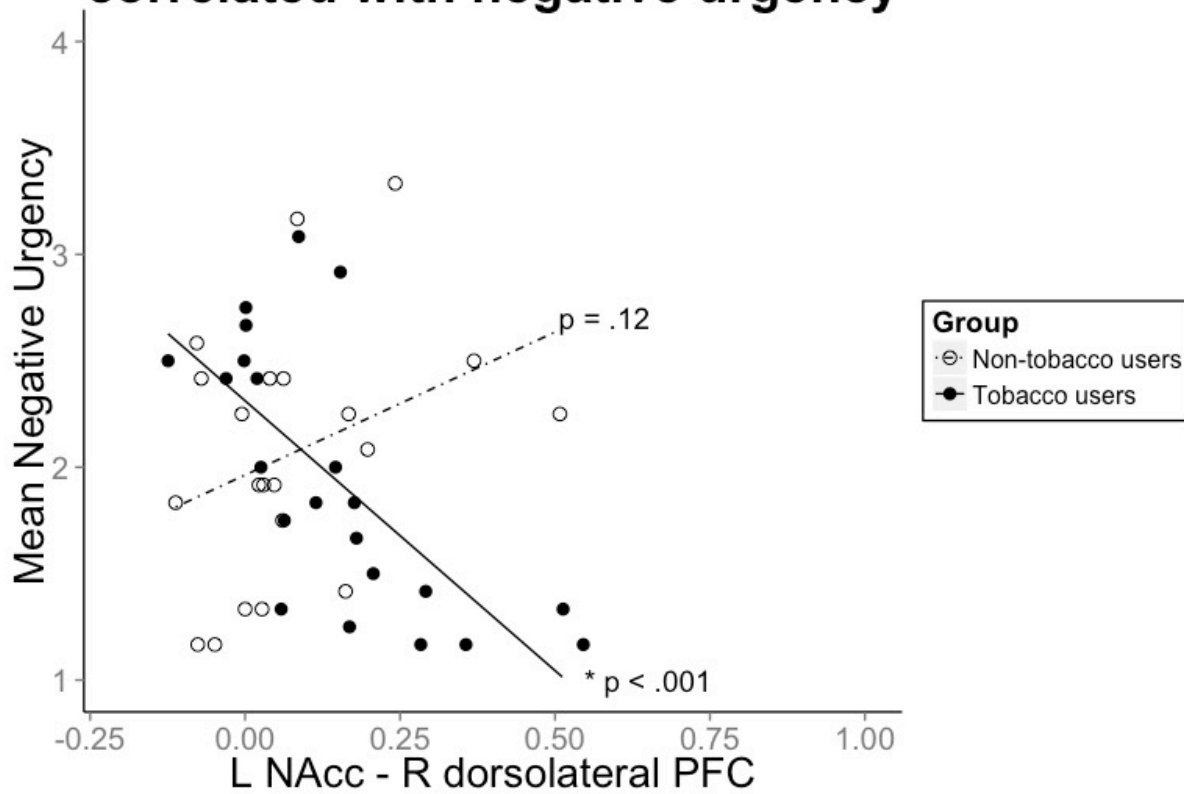
Figure C13. Trend in differing relationships between rsFC strengths and negative urgency across groups: Left NAcc – Right DLPFC



Note. NAcc = nucleus accumbens; DLPFC = dorsolateral prefrontal cortex; Cold color indicates that the stronger negative relationship between negative urgency and the rsFC strength in tobacco users than non-tobacco users; voxel level threshold $p < .005$; cluster level threshold $\alpha < .05$.

Figure C14. Scatter plot: Left NAcc – Right DLFPC

Tobacco users vs. Non-tobacco users correlated with negative urgency



Note. NAcc = nucleus accumbens; DLFPC = dorsolateral prefrontal cortex

Table C15. Relationships between rsFC strengths and tobacco-related variables in tobacco users

| Connectivity | Age at first tobacco use | | FTND | | Length of tobacco use | | Past 6-month frequency of tobacco use | |
|--|--------------------------|----------|----------|----------|-----------------------|----------|---------------------------------------|----------|
| | <i>r</i> | <i>p</i> | <i>r</i> | <i>p</i> | <i>r</i> | <i>p</i> | <i>r</i> | <i>p</i> |
| <i>Group differences between tobacco users and non-tobacco users</i> | | | | | | | | |
| R Amygdala – L mOFC/vmPFC | .02 | .93 | -.18 | .43 | -.14 | .57 | -.43 | .07 |
| R NAcc – R TPJ | .03 | .91 | -.42 | .06 | -.11 | .65 | -.12 | .64 |
| R NAcc – L Precuneus | .13 | .59 | -.25 | .28 | -.18 | .45 | -.15 | .53 |
| <i>Correlation between negative urgency and rsFC strength in overall groups</i> | | | | | | | | |
| R Temporal pole – L SMG | .17 | .49 | -.48 | .03* | -.05 | .84 | -.30 | .21 |
| L Temporal pole – L SMG | .02 | .93 | -.24 | .30 | .25 | .29 | -.19 | .43 |
| <i>Differences in correlations between negative urgency and rsFC strength between groups</i> | | | | | | | | |
| L NAcc – R DLPFC | .09 | .71 | -.16 | .49 | -.30 | .20 | -.15 | .55 |

Note. L = left; R = right, mOFC/vmPFC = medial orbitofrontal cortex/ventromedial prefrontal cortex, NAcc = nucleus accumbens; TPJ = temporoparietal junction; SMG = supramarginal gyrus; DLPFC = dorsolateral prefrontal cortex