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CUE-ELICITED NEURAL ACTIVITY AND FUNCTIONAL CONNECTIVITY AMONG SMOKERS ASSOCIATED WITH THE DECISION TO SMOKE

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ABSTRACT

Cue-reactivity, or the responses of drug users to drug cues, has been shown to be related to smoking behavior including relapse in smokers, but the mechanisms linking drug use to drug cues remain unclear. Dual systems approaches, which implicate the cognitive control system and the reward/affective system in contributing to addictive behavior, have been used in attempts to explain addictive behavior, and in particular may be used elucidate the relationship between drug cues and drug use. However, differing models have been proposed to explain the ways the dual systems may act or interact to contribute to drug use. The present study aimed to clarify this question by using uSEM on fMRI data to identify connectivity models in two groups of smokers as they were exposed to smoking (and neutral) cues and offered an opportunity to smoke, within 24 hours of initiating a quit attempt. The two groups modeled were: 1) the subjects who chose to smoke (n=19); 2) a matched sample of subjects who chose not to smoke (n=19). Results showed that smokers who were able to resist smoking displayed increased connectivity between networks, namely between the DLPFC and left anterior insula. This finding, along with past research, indicates that smokers who are able to remain abstinent may be engaging in top-down control of the feeling of smoking urge induced by smoking cues via representations of interoceptive smoking effects.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Introduction

As a leading cause of death and disease worldwide, cigarette smoking is a serious public health issue. Despite increased awareness over recent years of the negative health consequences of smoking, about one in five American adults (18%) are current smokers (CDC, 2014). Although the majority of current smokers (69%) report wanting to quit, and although quit attempts are common (43% attempted to quit in the last year) (US Dept. of Health and Human Services, 2014), achieving long-term smoking cessation is markedly difficult for many people; most quit attempts end in relapse (Hughes et al., 2004).

One of the main perspectives from which scientists have aimed to understand nicotine addiction and relapse is the cue-reactivity paradigm. Cue-reactivity, or the responses of drug users upon presentation of drug cues, has been extensively investigated within addiction research. The cue-reactivity paradigm has fundamentally been understood in terms of classical conditioning, wherein cue-reactivity is the response to cues that have previously been associated with drug effects (McDonough & Warren, 2001). Because reward-associated stimuli have been found to elicit reward-seeking behavior, cue reactivity is conceptualized as a central feature of drug use maintenance (Hogarth & Chase, 2011). Cue-reactivity research has demonstrated physiological, behavioral, and subjective responses to drug cues among drug users (Carter & Tiffany, 1999). It is presumed that these cue-elicited responses reflect the underlying motivational processes contributing to drug use maintenance and relapse. Indeed, cue-reactivity has been linked to self-reported drug craving (Carter & Tiffany, 1999) and relapse (Niaura, Rohsenow, Binkoff, Monti, Pedraza, & Abrams, 1988).

Among the many subtypes of cue-reactivity, recent research has focused in particular on neurobiological responses to drug cues. It is thought that, via activation of reward mechanisms in the brain, drug cues may elicit craving and thus lead to relapse (Weiss, F., 2005), although there is some debate surrounding craving as a construct as well as the way in which it relates to relapse (e.g. Perkins, 2009). Several recent meta-analyses have aimed to identify the neural correlates of cue-reactivity. Among these meta-analyses, the most commonly reported areas of cue-related activation are: the ventral striatum (Kuhn et al., 2011; Chase et al., 2011), left amygdala (Kuhn et al., 2011; Chase et al., 2011), extended visual system (Chase et al., 2011; Engelmann et al., 2012), posterior cingulate cortex (Chase et al., 2011; Engelmann et al., 2012), anterior cingulate cortex (Kuhn et al., 2011; Engelmann et al., 2012), and dorsal and medial prefrontal cortex (Chase et al., 2011; Engelmann et al., 2012), though many other areas of activation have also been reported.

Various findings indicate the clinical relevance of cue reactivity. Smokers attempting to quit cite smoking cues as a problem contributing to relapse (Shiffman et al., 1996). Research has substantiated and given insight into this phenomenon by demonstrating a strong relationship between cue-reactivity and lapse/relapse (e.g. Ferguson & Shiffman, 2009; Niaura et al., 1988). Ecological Momentary Assessment (EMA) data assessing real-time smoking behavior among quitting smokers indicate that smoking cues increase the risk of lapse (Shiffman et al., 1996). More recently, brain responses to smoking cues prior to a quit attempt have been found to predict relapse among quitting smokers (Janes et al., 2010).

Notwithstanding such findings, the clinical relevance of cue reactivity continues to be a matter of debate. Much of the criticism of the cue reactivity paradigm has been directed at the

field's use of self-reported craving as a measure of craving, as well as the fact that the construct of craving itself is poorly defined (Perkins, 2009). Much of the cue-reactivity research to this point has relied on self-reported craving as a dependent measure. As Perkins (2009) notes, the lack of research directly measuring cigarette use in relation to cue reactivity is a major weakness, leaving this field of research open to criticism that the presumed link between smoking cues and actual smoking use is a premature assumption. Given the theorized significance of smoking cues in driving smoking behavior, the lack of research in this area is surprising. Because of the paucity of research examining actual drug use behavior, many important questions remain about the mechanisms linking drug cues and drug use.

One major class of approach that may help shed light on this question is based on dual-systems models. Dual-systems models posit that decision-making is influenced by two distinct neural systems: 1) an emotional, impulsive, motivational system driven by immediate reward – sometimes called "hot" processing; and 2) a cognitive, reflective, regulatory system that is capable of higher order thinking and exerting inhibitory control – sometimes called "cool" processing (Metcalfe & Mischel, 1999; Strack & Deutsch, 2004). Such dual-systems models have been applied to explain addictive behavior (e.g. Bechara, 2005; McClure et al., 2004; Wiers et al., 2006; Hofmann et al., 2008), by proposing that such behavior is a result of some imbalance or dysfunction of these two systems. However, the exact nature of the imbalance remains unclear. For instance, addictive behavior could result primarily from hypersensitivity of the reward system (e.g., as suggested by Kalivas and Volkow, 2005) or from deficit of the control system (e.g., as suggested by Nestor et al., 2011). More focus has been placed recently on attempts to integrate the two systems and explore how they may interact within the context of

addiction (e.g. Gladwin et al., 2011; Pessoa, 2009). In this vein, addictive behavior could result from some abnormality or dysfunction in the integration between the two systems. Thus, taking a dual systems theory approach may elucidate the mechanisms underlying the apparent link between smoking cues and smoking behavior. Given the nature of this research question, connectivity analysis is an ideal method to explore these potential mechanisms.

Another important yet understudied point of clinical relevance within research on smoking relapse is how relapse relates to time elapsed since initiation of a quit attempt. Among self-quitting smokers, relapse is highest at the beginning of the quit attempt, especially during the first few days (Hughes, Keely, & Naud, 2004). In a study of smokers who attempted to self-quit, only 33% of them remained abstinent at 2 days (Hughes, Gulliver, Fenwick, Valliere, Cruser, Pepper, Shea, Solomon, & Flynn, 1992). In a study following female smokers as they made a quit attempt, half of those who eventually relapsed did so within the first 24 hours of initiating a quit attempt (Allen, Bade, Hatsukami, & Center, 2008). Despite this information, little research has focused on examining cue-reactivity and decision-making relating to smoking opportunity during this critical early period of time within a quit attempt.

Thus, there are three key knowledge gaps within the existing literature that the current study aims to address: 1) the paucity of research linking smoking cues to actual smoking behavior, with most past studies instead relying on self-reported craving; 2) the existence of differing potential models in explaining how the dual systems of reward and control may contribute to smoking behavior and relapse, specifically in the presence of smoking cues; 3) the lack of research examining smoking behavior and decision-making within the critical early timeframe of quit attempts, when risk of relapse is highest.

The current study aims to address the aforementioned knowledge gaps in the following ways: 1) By using actual smoking behavior (smoking choice) as the dependent measure of interest, rather than focusing on self-reported craving. It can be argued that, although a decrease in self-reported craving may be favorable, unless it translates to success in resisting smoking opportunities, it may not be as meaningful. Although some limitations certainly exist in this study design, using smoking outcome rather than self-reported craving is a novel method of analysis which avoids many of the pitfalls related to the use of self-reported craving. 2) By including for analysis brain regions heavily involved in the reward and cognitive control systems – with particular focus on the insula (as discussed further below) – and identifying connectivity models (based on smoking choice) amongst these regions. This type of analysis is ideal for the research question at hand in that it allows for a way to examine how the dual systems of control and reward relate to one another. Specifically, it allows for the comparison of the resulting connectivity models to various proposed explanations of the ways in which the dual systems act or interact to result in relapse and/or abstinence. 3) By using neuroimaging to examine the neural processes involved in cue-reactive decision-making related to smoking opportunity within the first 24 hours of initiation of a quit attempt.

The current study combines data from two prior studies (Wilson, Sayette, & Fiez, 2011; Wilson, Sayette, & Fiez, 2012) and compares fMRI data from two groups of participants (both of whom had initiated a quitting attempt): 1) Those who chose not to smoke when given an opportunity to do so; 2) A matched sample of participants who chose to smoke when given the opportunity. Identifying differences in brain activation and connectivity among these two groups

can assist in identifying why the participants who declined the smoking opportunity were able to do so.

Selection of regions of interest for the current study was challenging. Many brain regions have been shown to be linked in some way to the concepts of interest: the two broad systems of reward and cognitive control. However, consideration of the limitations of analytical computation and interpretation resulted in the decision to keep the number of ROIs relatively constrained. ROIs for the current study were empirically and conceptually derived. Conceptually, areas linked to reward/motivation and cognitive control/self-regulation, which are parts of the "hot" and "cool" systems and are thought to influence smoking behavior, were imperative to include. This is because, as detailed earlier, researchers have pointed to both hyperactivity of the reward system, as well as hypoactivity of the control system, as contributing to addictive behavior. Empirically, it was necessary to include areas that have been reliably linked to the domains of reward and control throughout past research.

Therefore, meta-analyses were used to select ROIs, satisfying both of these objectives. ROIs were based on coordinates reported in two meta-analyses reflecting the larger concepts of reward (Bartra et al., 2013) and control/executive function (Rottschy et al., 2012). The brain regions taken from Bartra et al. (2013) are reliable neural correlates of reward, in that more rewarding outcomes were associated with greater BOLD response in these areas. These ROIs are: the left ventral striatum, right ventral striatum, rostral anterior cingulate cortex, left anterior insula, and right anterior insula. The brain regions taken from Rottschy et al. (2012) are reliable neural correlates of cognitive control, in that they showed consistent activation during working memory tasks. These ROIs are: the left superior frontal gyrus, right superior frontal gyrus, left

dorsolateral prefrontal cortex, right dorsolateral prefrontal cortex, and dorsal anterior cingulate cortex. Thus a total of ten ROIs were selected: five associated with reward, and five associated with cognitive control. See Table 1 below for ROI coordinates and review.

Table 1. Regions of interest

Region	**MNI Coordinates**			**From:**
	x	**y**	**z**	
Left superior frontal gyrus	-28	0	56	Rottschy et al. (2012)
Right superior frontal gyrus	30	2	56	Rottschy et al. (2012)
Left dorsolateral prefrontal cortex	-46	26	24	Rottschy et al. (2012)
Right dorsolateral prefrontal cortex	44	34	32	Rottschy et al. (2012)
Dorsal anterior cingulate cortex	2	18	48	Rottschy et al. (2012)
Left anterior insula	-30	22	-6	Bartra et al. (2013)
Right anterior insula	32	20	-6	Bartra et al. (2013)
Left ventral striatum	-12	12	-6	Bartra et al. (2013)
Right ventral striatum	12	10	-6	Bartra et al. (2013)
Rostral anterior cingulate cortex	2	46	-8	Bartra et al. (2013)

It was hypothesized that connectivity among regions linked to cognitive control and those linked to reward/emotion would be related to differences in smoking choice. Regarding the latter regions, the insula was of particular interest. Although research is mixed on whether the insula is consistently activated in response to drug cues, (e.g. cue-reactivity meta-analyses by Chase et al. (2011) and Kuhn & Gallinat (2011) failed to find consistent insula activation, but a cue-reactivity meta-analysis by Engelmann et al. (2012) did report consistent insula activation), there is sufficient evidence to suggest that the insula plays an important role in addictive behaviors and related decision-making.

The insula has been shown to be related to a number of functions important in addiction, including emotional experience and awareness (Damasio, 2000; Craig, 2003), interoceptive

awareness – where interoception is defined as the sense of the physiological condition of the body (Craig, 2002), drug craving (Naqvi, 2007) and specifically cue-induced craving in smokers (Brody et al., 2002). In a landmark study (Naqvi, 2007), it was found that right or left insular damage in subjects who had suffered strokes was associated with disruption of smoking addiction, i.e. the ability to quit smoking easily and immediately without relapse or persistence of the urge to smoke. Although the study had some limitations, namely that it was retrospective in nature, it provided some of the first strong evidence that the insula plays an important role in addictive behavior, likely via modulating urge. These results were supported in a study on rats (Contreras et al. 2007), showing that deactivation of the insula via lidocaine injection reversed the rats' initial preference for an amphetamine-paired yet riskier environment; while the insula was deactivated, the rats instead opted for a safer, but not amphetamine-paired environment. As the lidocaine wore off and the insula returned to an active state, rats began to again prefer the amphetamine-paired environment.

In addition to studies involving insular deactivation, recent studies involving functional insular activation have provided additional insight into the role of the insula in addictive or risky behaviors. A review by Naqvi and Bechara (2008) indicated that many studies have shown a consistent link between insular activation and ratings of drug use urge. Relatedly, Xue et al. (2010) found that during a gambling task performed by healthy subjects, insular activity during decision making was predictive of risky decisions within and across subjects (i.e. stronger insular activation was shown on trials where subjects subsequently made a risky decision). The authors posited that insular activation is thus thought to signal the urge that influences the decision to take a risk. In a conceptually-related study, Addicott et al. (2012) compared neural activation of

smokers during the Wheel of Fortune decision-making task: once on a day when they were allowed to smoke freely, and once on a day when they were required to refrain from smoking. They found that insular activation was significantly higher on the day subjects were required to abstain, which they suggest could indicate higher emotive reward valuation, potentially related to representation of the interoceptive effects of drug use.

These studies as a whole indicate that the insula may contribute to addictive behaviors by translating interoceptive signals into what is experienced as a feeling of urge. It is still unclear, however, how this process may interact with the cognitive control system to affect smoking behavior. Although connectivity studies may help address this question, relatively few studies have examined insular connectivity within the context of addiction. One study by Janes et al. (2010) offers preliminary findings that could provide insight into how insular connectivity relates to addictive behavior. This study used fMRI to investigate neural activation and connectivity in smokers exposed to smoking cues, prior to initiating a quit attempt. Smokers who ended up relapsing demonstrated decreased functional connectivity between an ICA-identified insula-containing network (containing areas involved in emotion and interoceptive awareness) and cognitive control regions including the DLPFC and dACC. In addition, subjects who relapsed showed less connectivity between the overall network and the left insula. These results suggest decreased top-down regulation of emotion and thus higher drug cue-related interoceptive awareness amongst those who relapsed, as compared to those who were able to remain abstinent.

Despite convincing evidence for the important role of the insula in the maintenance of addictive behaviors (particularly in relation to the experience of craving), its exact role remains unclear. It is necessary to integrate knowledge of insular functions within addiction with

knowledge of fundamental processes within addiction (i.e. dual processes). As of yet, it remains unclear whether past research findings relating the insula to addictive behavior indicate a strengthening of processes that promote drug use (e.g. urges/reward), a weakening of processes that inhibit drug use (e.g. cognitive control) or both. Whereas Janes et al.'s (2010) research indicates some support for a weakening in top-down cognitive control of insular functions amongst smokers who relapse, some researchers such as Noel et al. (2013) and Naqvi & Bechara (2008) have suggested an alternate hypothesis: that the insula may "hijack" the cognitive resources needed for inhibitory control, in a way that subverts prefrontal cortex processes such as attention, planning, and decision-making towards the goal of drug use.

Bearing this in mind, the importance of going beyond the comparison of simple levels of insular activation in the current study is recognized; the proposed research aims to examine the role of the insula within the connectivity networks of two groups of smokers within the first 24 hours of a quit attempt: those who declined an opportunity to smoke after presentation of a smoking cue, and those who accepted an opportunity to smoke after presentation of a smoking cue. Because the existing literature regarding the insula indicates an important yet still unclear role in addictive behavior, a differential role of the insula among the two groups' connectivity networks is hypothesized, yet the exact nature of that difference is to be clarified through the analyses.

If the "hijacking" theory proposed by some researchers (e.g. Noel et al., 2013; Naqvi & Bechara, 2008) is correct, greater connectivity between the insula-containing reward network and the cognitive control network would be expected amongst the group of participants who chose to smoke. If the "top down" theory referenced by Janes et al. (2010) is correct, greater

connectivity between the cognitive control network and the insula-containing reward network would be expected amongst the group of participants who were able to resist smoking.

Summary and Specific Aims of the Proposed Research

In summary, an extensive literature demonstrates increased activation in several brain areas among addicts when exposed to drug-related cues, and this activation is thought to be related to drug use behavior. Dual systems models are a major class of approach that has been used within addiction research to attempt to explain drug maintenance and relapse, particularly in the presence of drug cues. However, the exact way(s) in which various areas of the reward and control system may act or interact to influence smoking behavior remains unclear.

In particular, the insula has recently been implicated as a key area involved in addictive behavior, with research suggesting that it may be linked to the feeling of craving that arises from interoceptive states related to drug cues. Yet the exact function of the insula and its related neurocircuitry remains unclear. In addition, research has repeatedly shown that within the earliest stages of a quit attempt, relapse rates are highest. This critical early window of time within quit attempts has been severely understudied despite its importance. The proposed research aims to address these knowledge gaps by using fMRI to examine connectivity involving the insula in quitting smokers, within the first 24 hours of a quit attempt.

To our knowledge, this is also the first study to use smoking choice as a grouping variable for fMRI analysis. By comparing the ROI connectivity differences between these two groups, the current study aims to elucidate why some quitting smokers chose not to smoke – in

other words, what differentiates them from quitting smokers who chose to smoke? In particular, this study aims to clarify the involvement of the insula within the two groups of smokers. The information gleaned from this study can be used to help identify the neural mechanisms that can lead to maintenance of smoking behavior or, alternately, successful deterrence of smoking behavior. In turn, this information could be used to shape smoking treatment methods, particularly relevant to the beginning stage of a quit attempt.

Method

Participants

Participants were drawn from two previous studies (Wilson et al., 2011; Wilson et al., 2012). Study 1 investigated the impact of quitting motivation and smoking opportunity on brain activation related to smoking cue presentation. Study 2 aimed to examine neural correlates of self- versus other-oriented strategies to cope with craving induced by a smoking cue. In order to qualify for both initial studies, participants had to report smoking 15-40 cigarettes per day for the past year, be right-handed, be native English speakers, be between the ages of 18-45, and pass an MRI safety screening. The total number of participants was 100 for Study 1 and 60 for Study 2. Study 1 was composed of males and females, some of whom were motivated to quit smoking and some of whom were not, whereas Study 2 included only males who were motivated to quit smoking. Participants were recruited via media advertisements. Subjects were compensated $100 for their participation.

Participants across both studies who, after initiating a quit attempt, expected an immediate opportunity to smoke and chose not to do so when given the opportunity were included in the current study, along with a matched sample of participants who, after initiating a quit attempt, expected an immediate opportunity to smoke and chose to do so when given the opportunity. This results in a sample of 38 (19 in each group), since there were 19 participants total who chose not to smoke across both studies. 12 of these participants come from Study 1 and 26 come from Study 2. Participants were matched based on age, average number of cigarettes per day, number of years they have been smoking, sex, coping strategy (for Study 2 – i.e. self vs. other strategy, detailed below), and quitting motivation (motivated-to-quit vs. unmotivated-to-quit).

Procedure

Based on a telephone screening, eligible participants were scheduled for a baseline session in which they completed various questionnaires related to smoking habits (Shiffman, Paty, Kassel, Gnys, & Zettler-Segal, 1994), nicotine dependence (Fagerstrom Test for Nicotine Dependence; Heatherton, Kozlowski, Frecker, & Fagestrom, 1991), smoking abstinence self-efficacy (Relapse Situation Efficacy Questionnaire; Gwaltney et al., 2001), trait self-control (Self Control Scale; Tangney, Baumeister, & Boone, 2004), positive and negative affect (Positive and Negative Affect Schedule; Watson, Clark, & Tellegen, 1988), and tendency to behave in a socially desirable way (Balanced Inventory of Desirable Responding Version 6; Paulhus, 1991). They also performed a working memory assessment. These measures are not the focus of the current study and will not be further addressed in this paper.

Also at baseline, a carbon monoxide (CO) detection device was used to get a baseline reading of the amount of CO in participants' breath (this number increases with recent smoking). At this point, participants in Study 2 were trained to engage in either a self- or other-focused cognitive coping strategy (i.e. considering positive effects quitting would have on them personally as opposed to the positive effects it would have on a close other). Participants had been randomly assigned to either the self- or other-focused strategy, which would be employed at the following fMRI session. All participants across the two studies who were motivated to quit were referred for treatment and called a treatment program to enroll at the end of the baseline session, although no treatment was received during the duration of either study.

Within two weeks of the baseline session, participants were scheduled for an fMRI session. All participants were instructed to initiate an attempt to quit smoking 12 hours prior to their fMRI session, and were instructed not to smoke or use any tobacco-containing products for at least those 12 hours. CO was measured at the beginning of the session to ensure nonsmoking compliance – to continue with the session, CO had to be ≤50% of the initial CO reading from the baseline session. This cutoff was chosen after being used in similar prior research (Sayette, Loewenstein, Griffin, & Black, 2008). Next, participants completed a cue exposure task in the scanner, utilized in previous research (Wilson, Sayette, Delgado & Fiez, 2005). The cue exposure task began with a 48 second resting baseline in which participants were instructed to remain still and relaxed. Participants then had an object placed in their hand. The object was identified to subjects via intercom and instructions were given to hold and view the object (a live video feed projected on a screen allowed participants to view the object within the MRI machine). Participants held the object for a period of 74 seconds.

Three runs of the task were completed, in which the objects were: a notepad (control), a roll of electrical tape (neutral), and a cigarette of the participant's brand of choice (smoking cue). Order of cue presentation was kept constant in the sequence listed, due to evidence that once smoking cues are presented, neural activity may continue to be affected for subsequent items (Sayette, Griffin, & Sayers, 2010). Upon presentation of the cigarette, participants were instructed via intercom that they would be taken out of the scanner shortly and would then be given an opportunity to smoke the cigarette immediately. While all participants in Study 2 were told they would be given an opportunity to smoke immediately, participants in Study 1 were assigned randomly to an expect-yes or expect-no condition – i.e. they were either told they would be able to smoke immediately upon impending removal from the scanner, or they were told they would get an equivalent break but would not be permitted to smoke throughout the remainder of the study. For the purposes of the current study, only participants in the expect-yes condition are included. Participants in Study 2 were instructed upon presentation of the cigarette to engage in either a self- or other-oriented coping strategy, whereas participants in Study 1 received no such instructions.

Participants were scanned using a 3-Tesla head-only Siemens Allegra magnet (Siemens Corporation, New York, NY) with a standard transmit/receive head coil. Using a standard T2-weighted pulse sequence, a 40 slice oblique-axial anatomical series was obtained (3.125 x 3.125 x 3.0mm). Using a magnetization-prepared rapid gradient-echo sequence, a 1 x 1 x 1mm 3D structural volume was also obtained. Then, functional images were obtained using a one-shot echo-planar imagine pulse sequence [TR = 2000 ms, TE = 25ms, FOV = 20cm, flip angle = 79°].

For the functional images, coverage included 38 center slices from the same plane as the 40 anatomical slices.

Analysis

The following software programs were used to preprocess the fMRI data: Analysis of Functional NeuroImages (AFNI, Version 2.6; Cox, 1996), Automated Image Registration (AIR, Version 3.08; Woods, Cherry, & Mazziotta, 1992), FMRIB's Software Library (FSL, Release 4.1; Smith et al., 2004), and the NeuroImaging Software Package (NIS 3.5; Laboratory for Clinical Cognitive Neuroscience, University of Pittsburgh, and the Neuroscience of Cognitive Control Laboratory, Princeton University). The Functional Imaging Software Widgets graphical computing environment (Fissell et al., 2003) was used for software integration and conversion of image format.

Several preprocessing steps were conducted with the fMRI data with the aim of correcting for any individual anatomical differences as well as possible artifact. These steps corrected for head movement and adjusted for drift. In addition, each participant's anatomical images were co-registered with a reference anatomy. This step used a six-parameter rigid-body automated registration algorithm and produced a transformation matrix which was then employed on participants' functional images. These images were then mean-normalized and smoothed by means of a 3D Gaussian filter with an FWHM of 4mm.

Primary analyses were conducted using unified structural equation modeling (developed by Kim, Zhu, Chang, Benthler, & Ernst, 2007), incorporating a recently developed automatic optimal model search technique (Gates, Molenaar, Hillary, Ram & Rovine, 2010) to estimate

pathways between ROIs. Research has shown many benefits of using uSEM in block design fMRI experiment analysis (Gates et al., 2010). Incorporation of the automatic optimal model search is also appropriate for the current study due to the competing outcomes/ connectivity models that may be predicted from theory. It is also beneficial because it takes into account both contemporaneous and lagged effects.

As noted previously, the ROIs involved in the connectivity analysis included the following: the left ventral striatum, right ventral striatum, rostral anterior cingulate cortex, left anterior insula, right anterior insula, left superior frontal gyrus, right superior frontal gyrus, left dorsolateral prefrontal cortex, right dorsolateral prefrontal cortex, and dorsal anterior cingulate cortex. Each ROI was 8mm in diameter. Time series were extracted from Studies 1 and 2 corresponding to when participants held the neutral object (tape) and the smoking cue object (cigarette) – although the entire signal related to these events was used for uSEM analysis, signal corresponding to the initial 26 seconds of cue exposure was not included in ROI activation analysis, on the basis of allowing time for stabilization after responses occur that were related to hearing instructions, etc. USEM was assessed using the Group Iterative Multiple Model Estimation (GIMME) program (Gates & Molenaar, 2012) for both groups: participants who chose not to smoke when given the opportunity to do so and participants who chose to smoke when given the opportunity to do so. This resulted in connectivity networks for each group of smokers, which were examined for differences. As noted above, it was predicted that smoking choice would be associated with differences in interaction among regions linked to cognitive control/regulation and those linked to affect/motivation, particularly considering the insula and its connections.

Although the primary goal was to characterize outcome-related differences in effective connectivity, analyses to determine whether the groups exhibited differences in mean activation within individual ROIs were also conducted. Toward this end, a series of ANOVAs were run in SPSS using the extracted ROI activation levels (averaged across the time-points of the cue exposure period and the voxels comprising the ROI). Among all participants, in accordance with past cue-reactivity findings, it was predicted that mean activation corresponding to presentation of the smoking cue would be greater for all ROIs than mean activation corresponding to presentation of the neutral cue. It was also predicted that the difference between activation corresponding to presentation of the smoking and neutral cues would be greater for the group who chose to smoke than the group who chose not to smoke.

Results

Participant Characteristics and Urge Ratings

Participant characteristics are shown in Table 2. Smoking choice groups did not significantly differ in age, cigarettes per day, number of years smoking, nicotine dependence as measured by FNTD, baseline CO, or experiment CO (p values > .05). However, they did differ across all three self-reported ratings of urge, given on a 0-100 scale prior to the scan and after the second and third runs of the cue exposure task, respectively. A repeated measures ANOVA with a Greenhouse-Geisser correction for sphericity determined that urge differed significantly between time points across all participants (F (1.17, 42.19) = 6.043, p < .05. Post hoc tests using the Bonferroni correction showed that reported urge increased over time: Although the

incremental increases in urge from Time 1 to Time 2 ($p = .08$) and from Time 2 to Time 3 ($p = .42$) did not reach statistical significance, the increase in urge from Time 1 to Time 3 was significant ($p < .05$). The ANOVA also showed a significant difference in reported urge between the two smoking choice groups, such that the group that chose to smoke rated their urge to smoke as consistently higher (F (1,36) = 27.618, $p < .0001$). The interaction between time and group was not significant ($p > .05$).

Table 2. Participant Characteristics and Urge Ratings

	Choice-Yes (n = 19)	Choice-No (n = 19)
Mean Age (SD)	33.89 (7.40)	32.95 (7.34)
Mean Cigarettes per day (SD)	18.53 (2.86)	18.11 (2.47)
Mean Number of years smoking (SD)	16.68 (6.86)	14.63 (8.13)
Mean FTND (SD)	5.11 (1.24)	4.47 (1.54)
Mean Baseline CO (SD)	33.53 (16.46)	30.63 (10.13)
Mean Experiment CO (SD)	13.47 (6.35)	11.50 (4.82)
Mean Urge 1 (SD)	**61.42 (24.74)**	**33.63 (24.86)**
Mean Urge 2 (SD)	**77.47 (19.01)**	**38.37 (29.24)**
Mean Urge 3 (SD)	**82.11 (17.01)**	**40.26 (31.95)**

Note: FTND = Fagerstrom Test for Nicotine Dependence

Individual Activation

A two-way mixed ANOVA showed a significant main effect of cue, such that activation was significantly higher in the cigarette as opposed to tape condition for the majority of ROIs (LSFG, RSFG, LDLPFC, RDLPFC, dACC, L Insula), as predicted (see Table 3). The remaining ROIs (R Insula, L VS, R VS, rACC) also showed more activation in the cigarette condition as opposed to the tape condition; however these differences did not reach statistical significance.

The ANOVA results failed to show a main effect of group: there were no significant differences when comparing independent ROI activation between participants who chose to smoke and participants who declined smoking ($p > .05$ for each ROI).

The analysis failed to show any interaction between cue and group across all ROIs ($p > .05$ for each ROI).

Table 3. ANOVA results showing Cigarette > Tape activation

ROI	**Mean Difference in Activation (Cig – Tape)**	***F*** **(*df* = 1,36)**	***p***
L SFG**	.059	8.30	.007
R SFG*	.056	6.95	.012
L DLPFC**	.065	8.97	.005
R DLPFC**	.063	8.36	.006
dACC*	.063	5.92	.020
L Insula*	.058	6.51	.015
R Insula	.032	2.00	.166
L VS	.044	2.91	.096
R VS	.020	0.58	.450
rACC	.026	0.33	.569

* = p < .05, ** = p < .01

Effective Connectivity

The euSEM analyses revealed a common model for participants who chose to smoke, as well as a common model for participants who declined the opportunity to smoke (see Figure 1). Final connectivity models had excellent fit to the individual-level data, as assessed by CFI, NNFI, SRMR, and RMSEA criteria (see Table 4).

Both models are shown in Figure 1, where each arrow represents a connection present in the group model and thus fit for all participants within that group. Solid arrows represent

contemporaneous relations while dashed arrows represent lagged relations. Arrow directionality is based on BOLD activity in one ROI predicting BOLD activity in another ROI (or in the same ROI at a later time point).

Choice-Yes group

Figure 1 (model A) shows the group model for participants who chose to smoke when given the opportunity. This model shows connectivity between several regions associated with cognitive control (L DLPFC, L SFG, R SFG, dACC), as well as connectivity between several regions associated with reward and emotional processing (L VS and R VS, L Insula and R Insula). Absent was any connectivity between these two networks.

Choice-No group

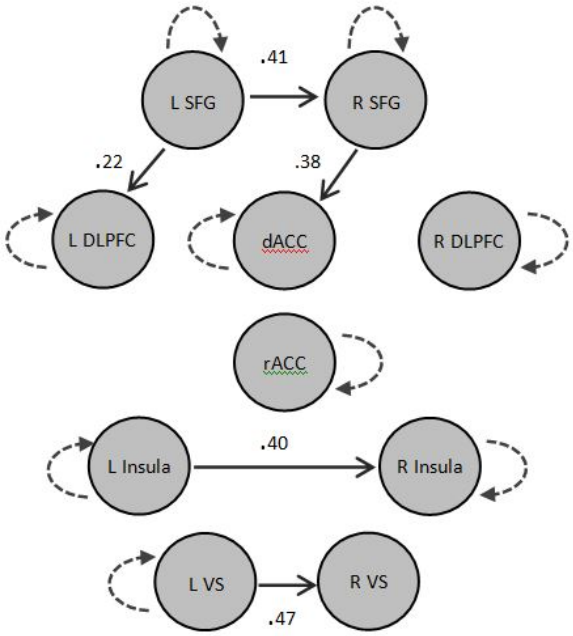
As depicted in Figure 1 (model B), participants who chose not to smoke demonstrated many of the same connectivity patterns as those who chose to smoke, but there were significant differences. Namely, the insula appears to play a more important role in the Choice-No model, showing increased connectivity with other areas. Of high importance is the connection between the left DLPFC (an area associated with cognitive control) and the left insula. In addition, this model shows connectivity between the right insula and the left ventral striatum, which was not seen in the Choice-Yes model.

Tests for correlation showed that strength of connection (as measured by pathway beta weights) for both models was not related to urge or nicotine dependence measures.

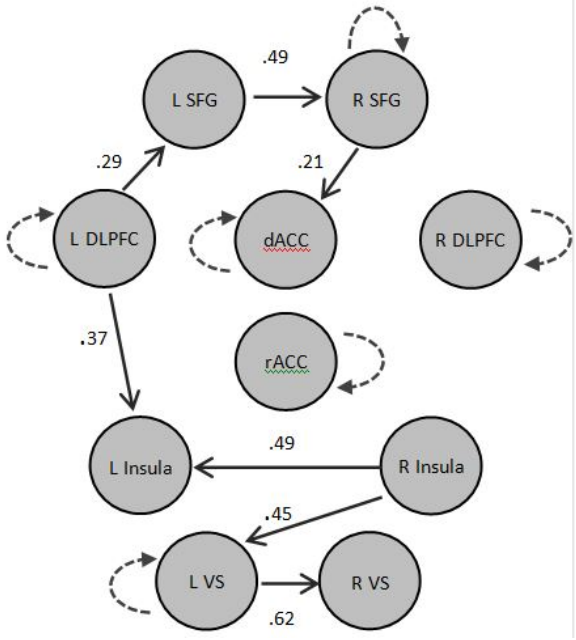
Figure 1.

Effective connectivity maps for smoking choice groups

A. Choice-Yes Group



B. Choice-No Group



Note:
Solid lines represent contemporaneous relations, dashed lines represent lagged relations
Numbers by each arrow represent connection beta weights

Table 4. Mean fit indices for effective connectivity maps

Smoking Choice	CFI	NNFI	SRMR	RMSEA
No	1	0.84	0.95	1
Yes	1	0.79	1	1

Note. CFI: confirmatory fit index; NNFI: non-normed fit index; SRMR: standardized root mean square residual (SRMR); RMSEA: root mean square error of approximation.

Discussion

As predicted, connectivity differences between the two smoking choice groups were observed, particularly differences involving the interaction of the reward and cognitive control systems. Participants who were able to abstain from smoking showed greater connectivity between areas involved in reward and cognitive control. In particular, a connection between the left DLPFC and left insula was present for this group that was absent for the group of participants who chose to smoke.

Consistent with prior research (Janes et al., 2010), the presence of this type of connectivity in the abstaining group's model suggests the exertion of top-down control over insular functions, i.e. feeling states driven by interoceptive responses to smoking cues, leading to decreased awareness of these feeling states and thereby lowering sense of urge to smoke. In turn, the absence of equivalent connectivity pathway within the model of the group who chose to smoke could indicate attenuated top-down control over emotional regulation, leading to increased focus on cue-induced interoceptive feeling states, and thus contributing to higher experienced urge to smoke (as reported by participants within this group; see Table 2). These findings extend Janes et al.'s (2010) research, since whereas their results were found prior to a quit attempt, the current study confirms that similar connectivity patterns are related to smoking behavior in the actual moments when a choice to smoke or not is made.

A number of additional studies have found that attenuated connectivity between the DLPFC and insula is associated with risky behavior, including drug use. Cox et al. (2010) found that, among a healthy sample, those with weakened resting state connectivity between the

DLPFC and insula demonstrated higher risk-taking. A recent study (Lerman et al., 2014) examined resting state connectivity in healthy smokers at two time points: once when the subjects were allowed to smoke as usual prior to the scan, and once when they were not allowed to smoke for 24 hours prior to the scan. Results from the scans conducted during smoking abstinence showed weakened interconnectivity between the default mode network, the executive control network, and the salience network (of which the insula is an integral part). The authors suggest that this weakened connectivity reflects less ability in abstinent smokers to shift from a focus on their own inner state and associated feelings to focusing on outward goals and planning. These results highlight the importance of the control network in enabling top-down control over salient feelings and interoceptive signals, which facilitates continued smoking abstinence. Research also points towards the significance of structural connectivity involving the insula and DLPFC. A study utilizing fractional anisotropy (Lane, 2010) showed that cocaine users had less connectivity within the corona radiata, a white matter tract that connects the DLPFC, insula, and ACC. This attenuated connectivity also corresponded with riskier decision-making as measured by the Iowa Gambling Task.

The anterior insula – particularly the left anterior insula – has also been implicated as a junction between the executive and interoceptive networks (Seeley et al., 2007; Menon and Uddin, 2010). While some researchers have suggested that addictive behavior may result from a "hijacking" of the cognitive control system by the insula (Naqvi and Bechara, 2010), the current study suggests that addictive behavior may instead result from a deficit in connectivity between the two, i.e. the anterior insula may not be functioning as a junction between systems as it normally would.

In relation to individual activations, as hypothesized, activation within all ROIs was higher in the cigarette cue condition as opposed to the neutral cue condition, regardless of smoking choice. However, analyses failed to show any interaction between difference in activation (cigarette - tape) and group membership (smoking choice group). These results were unexpected, yet important in showing that connectivity differences alone may be associated with differential drug use behavior, individual activations notwithstanding. Even though both groups of participants showed similar levels of insula and DLPFC activation, for example, the group that was able to remain abstinent was likely able to do so because of the connectivity they displayed between the two regions, indicating top-down control exerted over the feeling of urge stimulated by the insula. These results highlight the fact that simple activation analyses do not give a complete picture of neural processes, and that we can glean crucial information from also considering connectivity within the brain.

Although the connectivity difference between smoking choice groups involving the DLPFC and insula was of primary interest as it represents important differences in the ways in which the control and reward systems interact, an additional connectivity difference was found related to the insula and ventral striatum: The connectivity model of the group that was able to resist smoking included a connection between the right insula and the left ventral striatum, whereas the model of the group that chose to smoke lacked this connection. Although interpretation of this finding is less clear, this could indicate the downstream effects of the DLPFC in firstly engaging in top-down control of urge based on interoceptive signals (represented within the insula), and then, as the feeling of urge is reduced, the corresponding reward processing within the ventral striatum is also impacted accordingly. In effect, the lower

the sense of urge to smoke is, the less rewarding smoking may be considered. Further research would be needed to confirm this idea, although past research has revealed cortical projections from the insula to the striatum, and in particular, has shown that insular projections to the ventral striatum in primates have been found to be associated with integrating feeding behavior with reward and memory (Chikama et al., 1997). Due to the similar nature of food and drugs in terms of their relation to interoceptive awareness, this study may provide additional support for the abovementioned interpretation. This interpretation also highlights the role of the insula as an inter-network hub (Menon and Uddin, 2010; Seeley et al., 2007). A conceptually related study revealed that resting state connectivity between an insula-ACC network and an insula-striatal network is reduced amongst cocaine dependent subjects in comparison to healthy controls, and that this decreased connectivity is associated with greater impulsivity (Wisner, Patzelt, Lim, & MacDonald, 2013).

The results of the current study offer compelling clinical implications. The connectivity findings suggest different potential points of intervention; working towards increasing top-down cognitive control, decreasing the feeling of urge related to interoceptive drug effects, or facilitating connectivity between the networks may all help promote smoking abstinence.

In terms of cognitive control, a promising avenue for future investigation is the development of treatments that facilitate cognitive control, particularly within the DLPFC, in the presence of smoking cues. Research has already shown that repeated transcranial magnetic stimulation of the DLPFC reduces nicotine cue craving (Li et al., 2013). Neurofeedback could also be utilized to increase DLPFC activity while exposed to smoking cues. In addition,

therapies such as cognitive behavioral therapy or motivational interviewing could help enhance cognitive control.

Intervening at the insular level is also a crucial area for future development. Given that the group who lapsed appeared to have difficulty in engaging in top-down control of the insula, it is possible that intervening at this level may be more effective for them. In addition to modulation of insular cue reactivity via pharmacologic methods as mentioned by Janes et al. (2010), modulation of the insula could also be attempted using rTMS or deep brain stimulation. However, a more feasible and accessible treatment for most smokers would focus directly on the interoceptive effects that are thought to lead to the feeling of urge within the insula. To this end, smokers could be encouraged to decrease the interoceptive effects paired with smoking cigarettes (e.g. by using nicotine patches or gum), or to attempt to replace them (e.g. denicotinized cigarettes; as well as what has been attempted with e-cigarettes, although more research on their safety and effectiveness is needed). Indeed, some researchers have already shown that replacing certain interoceptive effects of smoking (e.g. with denicotinized cigarettes) appears to be effective in promoting abstinence (Buchhalter et al., 2005; Rezaishiraz et al., 2007). In addition, future research may examine potential positive interoceptive effects of not smoking, and explore whether, in the face of smoking cues, having quitting smokers focus on these alternate interoceptive effects may assist in resisting the opportunity to smoke.

In addition to targeting these regions/networks independently, the connectivity findings of the current study suggest that perhaps the optimal approach for clinical intervention would be to address both the control and reward/affective elements complementarily. Advances in neurofeedback techniques could allow for the modulation of relative activation of the DLPFC

and insula, for example, and perhaps in the near future, could allow for feedback relating to the modulation of connectivity between the regions. In addition, research may benefit from focusing on the development and implementation of training geared explicitly at the interaction between cognitive control and affect/reward (as opposed to a simple cognitive control training, e.g. a working memory training).

Limitations

Although this study offers a novel methodology, meaningful findings, and promising directions for future research, there were several notable limitations that should be considered.

Firstly, the sample size was relatively small. In terms of sample size, this study was limited by the small proportion of participants who were able to resist smoking. A larger sample would allow for increased power and robustness of results.

In addition, the number of regions of interest included for analysis was kept relatively constrained, for analytical and interpretive purposes. Although ROIs were carefully selected on conceptual and empirical bases, this study did not explore whether other areas contribute to these models.

Another potential limitation relates to the protocol discrepancies between Study 1 and 2. In particular, Study 2 participants were instructed to use a self- or other-focused cognitive coping strategy (i.e. considering positive effects quitting would have on them personally as opposed to the positive effects it would have on a close other), whereas Study 1 participants received no such instructions. Whether and how participants engage in strategies to resist smoking could

certainly impact their brain activation and connectivity. However, participants were matched based on which study they came from, as well as which coping strategy they used if from Study 2, alleviating some of the concern related to these study differences. Nevertheless, instructing subjects to resist smoking via a particular strategy could limit the variability of results; it is possible that some subjects would otherwise utilize different strategies to attempt to resist smoking. This issue could affect the generalizability of the study results.

There is also the possibility that some differences between groups may be related to quit motivation. Although participants were matched based on quit motivation (motivated to quit vs. unmotivated to quit), this binary measure may not capture important differences in quitting motivation, and it could be the case that the Choice-No group may have been taking the quit attempt more seriously and trying harder to quit, thus reflecting motivational differences as opposed to true differences in cognitive control capabilities or actual connectivity deficit.

Conclusions

Consistent with prior findings (Janes et al., 2010), it was found that smokers who were able to remain abstinent in the presence of smoking cues soon after initiation of a quit attempt displayed increased connectivity between areas related to the cognitive control network and the reward/affect network, namely the DLPFC and left anterior insula. This increased connectivity is thought to reflect these smokers' engagement of top-down control over the feeling of urge induced by smoking cues via representations of interoceptive smoking effects, and provides compelling groundwork for future research and clinical implications. With regard to individual

ROI activations, a main effect of cue was found (smoking > neutral), but not a main effect of smoking choice group nor an interaction between cue and group; these findings further highlight the importance of connectivity differences in shaping smoking behavior.

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