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The first day is always the hardest: Functional connectivity during cue exposure and the ability to resist smoking in the initial hours of a quit attempt

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ABSTRACT

Quitting smoking is the single best change in behavior that smokers can make to improve their health and extend their lives. Although most smokers express a strong desire to stop using cigarettes, the vast majority of quit attempts end in relapse. Relapse is particularly likely when smokers encounter cigarette cues. A striking number of relapses occur very quickly, with many occurring within as little as 24 h. Characterizing what distinguishes successful quit attempts from unsuccessful ones, particularly just after cessation is initiated, is a research priority. We addressed this significant issue by examining the association between functional connectivity during cigarette cue exposure and smoking behavior during the first 24 h of a quit attempt. Functional MRI was used to measure brain activity during cue exposure in nicotine-deprived daily smokers during the first day of a quit attempt. Participants were then given the opportunity to smoke. Using data collected in two parent studies, we identified a subset of participants who chose to smoke and a matched subset who declined ($n = 38$). Smokers who were able to resist smoking displayed significant functional connectivity between the left anterior insula and the dorsolateral prefrontal cortex, whereas there was no such connectivity for those who chose to smoke. Notably, there were no differences in mean levels of activation in brain regions of interest, underscoring the importance of assessing interregional connectivity when investigating the links between cue-related neural responses and overt behavior. To our knowledge, this is the first study to link patterns of functional connectivity and actual cigarette use during the pivotal first hours of attempt to change smoking behavior.

Introduction

Recent estimates indicate that nearly one billion men and women in the world smoke cigarettes on a daily basis (Ng et al., 2014). With respect to health-related behavior change, quitting smoking is the single best step that these individuals can take to reduce their risk for a host of negative outcomes, including premature death (USDHHS, 2014). Fortunately, most smokers express a strong desire to quit using cigarettes (CDC, 2011). Yet for many, translating the motivation to stop using cigarettes into sustained behavior change is a major barrier to smoking cessation. As many as 95–97% of untreated smokers relapse (return to regular smoking) within 6–12 months of initiating a quit attempt (Hughes et al., 2004). Even when receiving the best treatments currently available, roughly 70% of smokers relapse within 1 year (Piasecki, 2006). One of the most significant challenges currently facing tobacco researchers is fully characterizing what distinguishes successful quit attempts from unsuccessful ones, information that is crucial for devising ways to increase the likelihood of success for the large proportion of smokers who want to stop using cigarettes.

Relapse is particularly likely when smokers encounter cigarette-related stimuli (Ferguson and Shiffman, 2009). The use of functional brain imaging methods has become a particularly common approach to studying cigarette cue reactivity (Engelmann et al., 2012). This work has demonstrated that cigarette cue exposure is associated with widely distributed increases in brain activation, with the precise pattern varying as a function of several variables (Jasinska et al., 2014;

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Wilson and Sayette, 2015; Yalachkov et al., 2012).

Dual-systems models of brain functioning provide a useful framework for conceptualizing how such activation patterns may relate to smoking behavior. Broadly, dual-systems models posit that decision making is influenced by two distinct but interacting neural systems: an "automatic" system comprised of areas such as the ventral striatum that is driven by affective, reward-related, and visceral influences, and a "deliberative" system comprised of areas such as the dorsolateral prefrontal cortex (DLPFC) that supports working memory and other "cold" cognitive functions required for planning and inhibitory control (Bechara, 2005; Bickel et al., 2007; McClure and Bickel, 2014; Metcalfe and Mischel, 1999). From a dual-systems perspective, smoking cues may contribute to relapse because they evoke an imbalance between these brain systems, such that the automatic system exerts greater influence over behavior than the deliberative system (Heatherton and Wagner, 2011).

Emerging research indicates that the insula may play a particularly important role in altering the balance between the automatic and deliberative systems in a way that increases the likelihood of relapse (Addicott et al., 2015; Janes et al., 2010; Naqvi and Bechara, 2015; Naqvi et al., 2014; Noel et al., 2013a). Several lesion studies (Naqvi et al., 2007; Contreras, Ceric, & Torrealba, 2007; Gaznick et al., 2014; Suner-Soler et al., 2012) suggest that cigarette craving depends (at least partially) on the functional integrity of the insula. These studies are complemented by functional brain imaging research demonstrating that cigarette cues elicit increases in insular activation in smokers (Engelmann et al., 2012), which positively correlate with self-reported cigarette craving (Kuhn and Gallinat, 2011), and that greater functional connectivity between the insula and regions linked to executive (Janes et al., 2010) and motor (Addicott et al., 2015) control predicts improved smoking cessation outcomes.

Despite convincing evidence that the insula plays an important role in cue-elicited craving and relapse, there are important questions about the nature of the interactions between the insula and other areas in the context of smoking behavior. Whereas prior research provides some support for the idea that poorer smoking cessation outcomes are associated with weaker cognitive control over insular functions (Janes et al., 2010), it has also been proposed that the insula may drive drug use by simultaneously increasing craving and redirecting attention towards the goal of drug taking (i.e., "hijacking" deliberative functioning) (e.g., Naqvi and Bechara, 2009; Noel et al., 2013b). Currently, it remains unclear whether the link between insula connectivity and smoking relapse reflects a weakening or redirection of processes that inhibit drug use, a strengthening of processes that promote drug use, or some alternative to these possibilities (e.g., lack of information flow or network coordination; Bressler and Tognoli, 2006).

A second critical gap in the literature concerns the time frame over which connectivity between the insula and other brain regions predicts clinically meaningful behavior in quitting smokers. Although two recent studies have demonstrated smoking cessation outcomes are predicted by insula connectivity over a period of weeks (Addicott et al., 2015; Janes et al., 2010), it is not known whether insula connectivity also predicts more immediate relapse outcomes. This is an important question, as research has repeatedly shown that relapse rates are highest during the earliest phases of a quit attempt. Data indicate that 50–75% of untreated smokers relapse within one week (Hughes et al., 2004). A sizeable proportion are unable to maintain a quit attempt for as little as 24 h (Allen et al., 2008; Carpenter and Hughes, 2005), a time during which abstinence has been found to improve the likelihood of later success (Westman et al., 1997). It is crucial, conceptually and clinically, to distinguish processes involved in cigarette abstinence or relapse to smoking during the critical early moments of a quit attempt when behavior change often falls apart.

The goal of the current study was to address these issues by examining the association between functional connectivity during cigarette cue exposure and smoking behavior during the first 24 h of a quit attempt. Using dual systems theory as a guiding framework, we focused on connectivity among areas of the brain thought to be key constituents of the systems supporting automatic and deliberative processing. Importantly, our prior work has highlighted activation in and connectivity among these regions as significant in relation to cue reactivity and craving (Wilson et al., 2004, 2012, 2013a, 2013b). We were particularly interested in functional connectivity of the insula. Based on prior research (Addicott et al., 2015), we hypothesized that smokers who declined an opportunity to smoke immediately following cigarette cue exposure would exhibit stronger connectivity between the insula and other brain regions (particularly areas implicated in deliberative processing, such as the DLPFC) compared to those who chose to smoke.

Methods

Participants

Participants were drawn from two previous studies. Study 1 investigated the impact of quitting motivation and smoking opportunity on activation during smoking cue presentation (Wilson et al., 2012). Study 2 examined neural correlates of self- versus other-oriented strategies to cope with cue-elicited craving (Wilson et al., 2013b). For each, participants were required to be right-handed native English speakers between ages 18–45, report smoking 15–40 cigarettes/day for the past year, and pass an MRI safety screening. Study 1 was composed of males and females, some of whom were motivated to quit smoking and some of whom were not; Study 2 included only males who were motivated to quit smoking. Participants from both studies who reported that they were motivated to quit smoking, who initiated a quit attempt 12-h before participating in an fMRI-based cigarette cue exposure protocol (described below), and who were given the opportunity to smoke immediately following cue exposure were considered for inclusion in the current study. We selected two subgroups from the pool of participants meeting these criteria: (1) those who declined the opportunity to smoke (Chose-No; $n = 19$) and (2) a matched subset who chose to smoke when given the opportunity (Chose-Yes; $n = 19$).[1]

Cue exposure task

Participants completed a cue exposure procedure adapted from prior research (Wilson et al., 2005). Each run began with a 48-s period during which participants were instructed to remain still and relaxed. Participants then had an object placed in their left hand. The object was identified 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 in real-time). Participants held the object for a period of 74 s. 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). Upon presentation of the cigarette, a prerecorded message was delivered informing participants that they would be removed from the scanner in 40 s and would be able to smoke immediately if they chose to do so. Participants verbally rated their smoking urge on a 0–100 scale prior to placement in the scanner (urge-baseline), after the conclusion of the neutral cue run (urge-neutral cue), and after the conclusion of the smoking cue run (urge-smoking cue). The first run served as a practice run and was

[1] Subgroups were matched according to age, ethnicity, smoking rate, years smoking, sex, coping strategy (for Study 2 – i.e. self vs. other strategy), and quitting motivation (motivated to quit vs. unmotivated to quit). Each subgroup included 17 males and 2 females. Twelve participants (6 Abstainers and 6 Lapsers) were selected from Study 1 and 26 participants (13 Abstainers and 13 Lapsers) were selected from Study 2.