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Clarifying the neural basis for incentive salience of tobacco cues in smokers

Joshua C. Gray [a], Michael T. Amlung [b], John Acker [a], Lawrence H. Sweet [a,d], Courtney L. Brown [c], James MacKillop [a,e,*]

[a] Department of Psychology, University of Georgia, Athens, GA 30602, USA
[b] Department of Psychological Sciences, University of Missouri, Columbia, MO 65211, USA
[c] Department of Health Psychology, University of Missouri, Columbia, MO 65211, USA
[d] Department of Psychiatry and Human Behavior, Brown University, Providence, RI 02912, USA
[e] Department of Behavioral and Social Sciences, Brown University, Providence, RI 02912, USA

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ABSTRACT

In functional magnetic resonance imaging (fMRI) studies, smoking cues have been found to elicit increases in brain activity in regions associated with processing rewarding and emotional stimuli. However, most smoking cue studies to date have reported effects relative to neutral control stimuli with no incentive properties, making it unclear whether the observed activation pertains to value in general or the value of cigarettes in particular. The current fMRI study sought to clarify the neural activity reflecting tobacco-specific incentive value versus domain-general incentive value by examining smoking cues, neutral cues, and a third set of cues, monetary cues, which served as an active control condition. Participants were 42 male daily smokers. Compared to neutral cues, significantly greater activation was found in the left ventral striatum in response to tobacco and money cues. Monetary cues also elicited significantly increased activation in the right inferior frontal gyrus and cuneus compared to the other two cue types. Overall, the results suggest that the salience of monetary cues was the highest and, as a result, might have reduced the incentive salience of tobacco cues.

1. Introduction

Cigarette smoking is responsible for the death of approximately 440,000 U.S. citizens each year and 6,000,000 deaths worldwide (National Institute on Drug Abuse, 2009; World Health Organization, 2011). In addition to its impact on health, tobacco use is responsible for hundreds of billions of dollars of economic burden worldwide every year (World Health Organization, 2011). Among current U.S. adult smokers, approximately two-thirds report that they want to quit smoking, although the majority are unsuccessful (American Society of Addiction Medicine, 2010; Centers for Disease Control and Prevention, 2011).

One of the major theories of nicotine dependence is that it is a disorder of learning and memory (Franklin et al., 2007; Olausson et al., 2003). From this perspective, environmental cues play an important role and partially elicit substance use behavior through associative (classical) conditioning. Specifically, neutral environmental stimuli (e.g. people, places, things) that precede drug use become associated with the actual drug use and acquire motivational properties. In the context of smokers, drug-related cues (e.g. a cigarette, another smoker, a cup of coffee) become associated with the act of smoking and, over time, the smoking related cues begin to trigger conditioned responses, including subjective craving and psychophysiological arousal (Conklin et al., 2010, 2013; Thewissen et al., 2007). Furthermore, these associated cues putatively become highly salient over time, triggering compulsive drug seeking and taking even if the expectation of pleasure is diminished (Berridge et al., 2009; Robinson and Berridge, 1993).

Considerable empirical research supports this perspective. Animal and human research has shown that these previously neutral stimuli elicit a number of conditioned drug responses, including physiological indices (Winkler et al., 2011), attentional indices (Robinson and Berridge, 1993), and actual drug seeking and taking behavior (Le Foll and Goldberg, 2006). Following extinction of nicotine-seeking behavior, rats have been shown to reinstate their nicotine-seeking behavior upon presentation of the conditioned stimulus (LeSage et al., 2004). In human cue reactivity studies, nicotine dependent individuals exhibit increases in affect, heart rate, skin conductivity, and subjective craving following the presentation of smoking-related stimuli (e.g. images of cigarettes) (Carter and Tiffany, 1999; Payne et al., 2007; Tiffany et al., 2000;

* Corresponding author at: Department of Psychology, University of Georgia, Athens, GA 30602, USA. Tel.: +1 706 542 3033; fax: +1 706 542 327.
E-mail address: jmackill@uga.edu (J. MacKillop).

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MacKillop et al., 2012). Parallel findings have been found for alcohol and other psychoactive drugs (MacKillop and Lisman, 2005; MacKillop et al., 2010; Robbins et al., 1999).

Functional magnetic resonance imaging (fMRI) studies have extended smoking cue reactivity research to understand neural responses, finding that smoking-related cues elicit greater blood-oxygenation-level-dependent (BOLD) activation in regions associated with the processing of reward and emotional stimuli (Due et al., 2002; David et al., 2005; McClernon et al., 2005; Franklin et al., 2007, Versace et al., 2011). These studies typically employ a passive-viewing task, in which participants are instructed to observe photographs or videos of smoking cues and neutral cues. In addition, some of the studies incorporate holding a cigarette and holding a neutral object.

A number of neural profiles have been found to be consistently associated with the presentation of tobacco cues in smokers and hold potential to provide further insight into reward processing and contributors to relapse. Kühn and Gallinat (2011) reviewed 13 studies of daily smokers exposed to smoking-related versus control cues, and found that the ventral striatum, amygdala, anterior cingulate cortex (ACC), and the temporo-parietal junction are consistently activated more by smoking cues versus control cues. Although it was not demonstrated to be consistently active in this meta-analysis, the anterior insula is also thought be important in the experience of appetitive craving and has been associated with the maintenance of tobacco use through cue reactivity and the experience of craving (Engelmann et al., 2012; Versace et al., 2011, Naqvi et al., 2007).

The ventral striatum, amygdala, and ACC all potentially play a unique role in the reactivity of drug addicted individuals to associated substance cues. The ventral striatum is associated with motivational behavior including reward reactivity (Parkinson et al., 1999; Chase et al., 2011). The amygdala is associated with emotional and reward processing (Phillips et al., 2003), and greater activation in this region has been associated with intensity of tobacco cue-induced craving (Smolka et al., 2006). Activity in the ACC is also associated with increases in craving (Goldstein and Volkow, 2002; Jentsch and Taylor, 1999), and it is thought to play a role in the exertion of inhibitory control over behavior and in conflict processing and monitoring (Lubman et al., 2004). Brain imaging studies have demonstrated that both nicotine abstinence and the expectations that smoking will take place can modulate the response of the ACC to smoking cues (McBride et al., 2006; McClernon et al., 2005; Wilson et al., 2005). Furthermore, recent research has found the BOLD response to smoking cues in the ACC and amygdala to predict smoking lapse in nicotine dependent individuals seeking to quit smoking (Janes et al., 2010).

Importantly, most cue reactivity fMRI studies to date have used neutral visual control conditions (e.g. office supplies, non-smoking faces), but have not used an active incentive value control. An exception to this is a study by Versace et al. (2011), who examined neural activity elicited by smoking-related cues, pleasant (e.g. erotic and romantic), unpleasant (e.g. mutilation and sad), and neutral cues. They found only the insula to have a greater BOLD response to cigarette cues relative to all other categories, while in all other clusters, erotic stimuli elicited greater magnitude of BOLD responses. Nonetheless, this is the only study to date that has sought to contextualize tobacco-related neural activity within the larger category of reinforcers and punishments.

The goal of the current study was to extend research on tobacco-specific reactivity by examining it in relation to both conventional control cues and also with a novel set of monetary cues. Money is a powerful nonspecific reinforcer and, as such, can serve as excellent control for brain activity associated with incentive value in general. In addition, as sex differences are present for erotic pictures (Lang et al., 1998; Hamann et al., 2004; Sabatinelli et al., 2004), money is considered advantageous because of no known gender differences. Given the motivational significance of cigarette and money cues, we hypothesized that both would elicit greater BOLD activation than neutral cues in the ventral striatum, amygdala, and ACC. In addition, we hypothesized that smoking cues would elicit significantly greater activation than money cues in the ACC and amygdala, based on the known associations of these regions with craving, inhibitory control, and emotional processing. Finally, given the novelty of this cue reactivity paradigm, exploratory analyses were utilized to examine additional activation differences between the cigarette cues, monetary cues, and neutral cues.

2. Method

2.1. Participants

Daily smokers were recruited via flyers, print, and internet advertising. Inclusion criteria for participation in the study were as follows: 1) male; 2) right handed; 3) 18–55 years old; 4) self-reported smoking of >5 cigarettes a day; 5) baseline expired carbon monoxide (CO) >5 parts per million (ppm); 6) at least a 10th grade education; and 7) computer use >4 days a week to ensure adequate familiarity with computerized assessments. Females were not included because gender differences in cue reactivity have been reported in prior research (Field and Duka, 2004; McClernon et al., 2008; Niaura et al., 1998) and the study was not powered to systematically examine sex differences. Exclusionary criteria were as follows: 1) any head injury more severe than a mild traumatic brain injury (TBI) or >2 mild TBIs; 2) MRI contraindications (e.g. metal implant, claustrophobia); 3) received mental health services within the last six months or prescribed psychotropic medications; 4) actively seeking treatment to reduce tobacco use or having undergone treatment for nicotine dependence in the past 90-days; 5) weekly illicit drug use, other than marijuana; and 6) living with someone who has participated in the study. Forty-four participants were enrolled, with two participants excluded for invalid data (i.e. noncompliant smoking during the session; non-responding during in-scanner assessments, suggesting sleeping). No participants were excluded for excessive in-scanner movement (>3.5 mm) along the *x*-, *y*-, or *z*-axes, leaving a final sample of 42 (76.2% white, 21.4% African American, 2.4% Asian; median income $=<\$30{,}000$, IQR $=<\$15{,}000$–$\$44{,}999$; age $M=26.6$, S.D.$=7.1$; cigarettes per day $M=15.9$ S.D.$=7.5$; Fagerström Test for Nicotine Dependence [FTND] $M=3.1$, S.D.$=1.9$; fMRI session expired CO $M=18.9$, S.D.$=11.3$; past three months marijuana use, median = monthly or less).

2.2. Measures

Subjective motivation for cigarettes and money was assessed immediately before and after the cue reactivity paradigm by asking participants how much they desired each commodity (i.e. money and cigarettes) via a 9-point Likert scale. Level of nicotine dependence was assessed using the FTND (Heatherton et al., 1991). Expired CO was assessed during the screening session and at the start of fMRI session, using a PiCO+ Smokerlyzer (Bedfont Scientific Ltd., Rochester, UK). Demographic information was also collected (e.g. ethnicity, income, and age).

2.3. fMRI protocol

Imaging data were collected at the University of Georgia Bio-Imaging Research Center with a General Electric 16-channel fixed-site Signa HDx 3.0 Tesla MRI scanner. Structural imaging used a high-resolution T1 scan (voxel size 1 mm^3, field of view $=25.6^2$ mm, matrix $=256^2$, slice thickness $=1$ mm). Functional imaging used echo planar imaging (EPI) of T2* scans using a single-shot gradient echo pulse sequence (TR $=2000$ ms, TE $=25$ ms, field of view $=22.5^2$ cm, matrix $=64^2$, voxel size $=3.52\times3.52\times3.5$ mm^3, with 40 contiguous 3.5 mm slices collected axially). Three dummy TRs preceded the functional scans to permit the scanner to reach steady-state equilibrium.

2.4. fMRI stimuli

High-resolution image stimuli sets were developed in three categories: tobacco-related (i.e. images of cigarettes), money-related (i.e. images of US dollar bills), and neutral (i.e. images of visually-matched office supplies). Sample stimuli and a schematic of the paradigm are shown in Fig. 1. The individual pictures were identified via Internet searches and were selected in matched triplets (one tobacco image, one money image, one neutral image) to have analogous layout and complexity, to minimize difference in shapes perceived, in an extra effort to isolate differences in incentive value. There were 32 images of each category chosen and no images were shown twice. Stimuli were programmed using E-Prime 2.0 software (Psychology Software Tools, Sharpsburg, PA, USA) and presented via MR-compatible stimulus-presentation goggles (Resonance