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Brief report

Smoker–nonsmoker differences in neural response to smoking-related and affective cues: An fMRI investigation

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ABSTRACT

Smoking may sensitize brain systems to smoking cues while desensitizing systems to naturalistic rewards. This study examined smoker–nonsmoker differences in Functional magnetic resonance imaging (fMRI) blood oxygen level dependent (BOLD) response to smoking-related and emotional images. Smokers, relative to nonsmokers, exhibited greater reactivity to smoking and decreased reactivity to emotional cues in the left middle frontal gyrus.

1. Introduction

Evidence suggests that smoking-related and emotional cues enhance craving and often precipitate smoking relapse (Shiffman et al., 1996; Lochbuehler et al., 2009). Vulnerability to relapse has been attributed to increased incentive salience of drug cues and decreased salience of intrinsically pleasant stimuli (Koob and Le Moal, 2008; Robinson and Berridge, 2001). To quantify altered emotional processing in drug users, cue reactivity paradigms have been used to characterize neural response to drug-related and affective cues.

Functional magnetic resonance imaging (fMRI) studies of smokers have found increased blood oxygen level dependent (BOLD) response to smoking cues in brain regions associated with attention to salient and emotional stimuli, including the anterior cingulate cortex, amygdala, and prefrontal cortex (Engelmann et al., 2012; McClernon et al., 2005, 2009). These findings suggest that smokers' attention is sensitized to smoking-related cues. Decreased activation to natural rewards (e.g. erotic videos) is common in dependent drug users compared to controls (Garavan, 2000). However, few fMRI studies have reported smoker–nonsmoker differences in BOLD response to smoking-related and affective cues. Characterizing differential cue reactivity between smokers and nonsmokers could lead to a better understanding of altered reward processing networks associated with relapse in dependent drug users. The current study characterized smoker–nonsmoker differences in the fMRI BOLD response to smoking-related, positive, and negative images.

2. Methods

2.1. Participants

Nineteen male Caucasians (smokers=9; 20–35 years old) recruited from the community completed the study. Two additional individuals were excluded from analysis (one dropout and one due to scanner technical difficulties). Smokers smoked at least 7 cigarettes per day and had an expired breath CO concentration of $\geq$6 ppm. Nonsmokers were defined as having smoked $<$20 cigarettes in their lifetime, no cigarettes in the past year, and having a CO concentration of $<$4ppm. Smokers were instructed to smoke at least one cigarette on the day of the session. Exclusion criteria included significant health problems, reported use of psychoactive drugs or medications, current major psychiatric diagnosis, left-handedness, smokeless tobacco use, and current alcohol abuse. Participants completed a screening session, provided written informed consent approved by the Southern Illinois University Human Subjects Committee, and were compensated $50 for study completion.

2.2. Experimental setup and procedure

The experiment was programmed and run by E-prime (Psychology Software Tools, Pittsburgh, PA, USA). Stimuli were presented via an LCD screen (field of view=7.5°) that was mounted to the birdcage head coil. Stimuli included smoking-related and neutral pictures selected from the International Smoking Image Series (ISIS; Gilbert and Rabinovich, 1999) and affective stimuli (positive [erotic] and negative [mutilation]) selected from the International Affective Picture System (IAPS; Lang et al., 2008) and an in-house picture set. IAPS pictures

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included numbers 2095, 2550, 2703, 2900, 3030, 4670, 4694, 9421, and 9433. Copies of the other images used can be provided upon request from the corresponding author.

Image ratings were self-report measures on a 10-point Likert scale. Valence ratings for the smoking ($M=5.18$, S.D.$=1.1$), positive ($M=7.55$, S.D.$=1.1$) negative ($M=2.36$, S.D.$=1.2$), and neutral ($M=4.97$, S.D.$=1.0$) stimuli were obtained from a sample of male smokers ($N=80$) in the fourth author's laboratory. Craving levels induced by the smoking ($M=5.06$, S.D.$=2.2$), positive ($M=4.52$, S.D.$=2.7$) negative ($M=4.49$, S.D.$=2.8$), and neutral ($M=3.34$, S.D.$=2.2$) stimuli were obtained from the same sample.

Stimuli were presented in a blocked design, and each block consisted of 10.3 s stimuli of the same type. Stimuli within a block were presented without an interstimulus interval. Between block presentations, subjects completed a cued attention task (Posner and Cohen, 1984). There were a total of ten presentations of each block type.

2.3. Functional image acquisition and analysis

A 1.5 T Philips Intera 1 scanner was used to acquire 120 T2* - weighted scans with an EPI sequence using the following parameters: Repetition Time$=2500$ ms, Echo Time$=50$ ms, Flip Angle$=90^{\circ}$, Matrix Dimensions$=64\times64$, Field of View$=240\times240$ mm^2, Slices$=26$, Slice Thickness$=5.5$ mm, Gap$=3.75$ mm, In-plane Resolution$=3.75$ mm^2. Head movement was minimized by inserting a soft, foam padding between the subject's head and the head coil. Standard preprocessing procedures were conducted using statistical parametric mapping software (SPM8: Wellcome, London), including image realignment corrections for slice timing and head motion correction using rigid-body rotation and translation (Friston et al., 1994). The data was then normalized to standard $2\times2\times2$ mm^3 Montreal Neurological Institute space and spatially smoothed with a Gaussian full-width-at-half-maximum 8 mm filter.

First-level single subject SPMs were created for conditions (smoking, negative, positive, neutral) by modeling each as a boxcar canonically convolved hemodynamic response function (duration$=30$ s). Contrast images for smoking > neutral, negative > neutral and positive > neutral were created and input into a random effects analysis. Contrast images were then entered into a 2 (Smoker Status: Smoker, Nonsmoker) $\times$ 3 (Valence: Smoking, Negative, Positive) repeated measures ANOVA. Statistical images were thresholded with an inclusive automated anatomical labeling mask (Tzourio-Mazoyer et al., 2002) containing regions of interest associated with emotional reactivity and attention. These included bilateral posterior, dorsal and paracingulate cortices, inferior, middle and superior frontal gyri, inferior parietal lobule, insula and amygdala. Resulting activations were considered significant if they passed a statistical threshold of $p<0.005$, uncorrected, and were part of a 1536-μL cluster of contiguous significant voxels, resulting in a cluster-corrected $p<0.05$. Significant cluster size for the comparisons was determined through Monte Carlo simulations (Ward, 2000).

3. Results

The smoker status x valence ANOVA revealed a significant interaction in the left middle frontal gyrus (MFG) ($x=-30$, $y=12$, $z=46$), (Zmax$=3.72$; μL$=1656$). As displayed in Fig. 1, smokers exhibited greater activation to smoking stimuli and decreased activation to positive and negative stimuli, whereas nonsmoker controls exhibited the opposite pattern.

4. Discussion

The finding that BOLD response to smoking and emotional stimuli was moderated by cigarette smoking status is consistent with the incentive sensitization model of drug dependence (Robinson and Berridge, 2001). Studies of dependent drug users have previously identified the left MFG as a region associated with cue-induced craving, and activity in this area may be a reliable measure of attention (Garavan et al., 2000; Yamasaki et al., 2002). A recent fMRI study also found increased BOLD response to smoking cues in the MFG of smokers (Versace et al., 2011a). Although the MFG is not typically associated with drug-related reward networks, the MFG is believed to subserve attentional control and provides feedback to ventral-affective neural networks (e.g. amygdala and striatum). Thus, the pattern of results found in the current study replicates previous studies that have found sensitization and increased attentional allocation to smoking-related stimuli in smokers relative to nonsmokers. However, the current results also provide evidence for a desensitization to affective stimuli in smokers. Although fMRI studies have found decreased BOLD activation to natural rewards in dependent cocaine users compared to controls (Asensio et al., 2010), previous studies have not identified a blunted response to emotionally positive or negative stimuli in smokers. To our knowledge, this is the first study to find smoker–nonsmoker differences in BOLD response to naturally rewarding and negative images in the middle frontal gyrus.

Prior fMRI research with smokers suggests that BOLD response to emotional stimuli is modulated by an interaction between smoking state and affective states and traits (Froeliger et al., 2011a, b). The differential activations observed in the current study occurred despite a state of minimal smoking deprivation, providing evidence for a sustained attentional bias in smokers. However, limitations include a small sample size, light smokers, and lack of standardized state and trait measures of nicotine dependence and craving. Cue-induced craving and emotional reactivity are controlled by a complex interplay of situational (e.g. cue valence, participant mood, experimental setting) and trait factors (e.g. degree of nicotine dependence, genotype, personality variables Gilbert, 1997). For example, Versace et al.

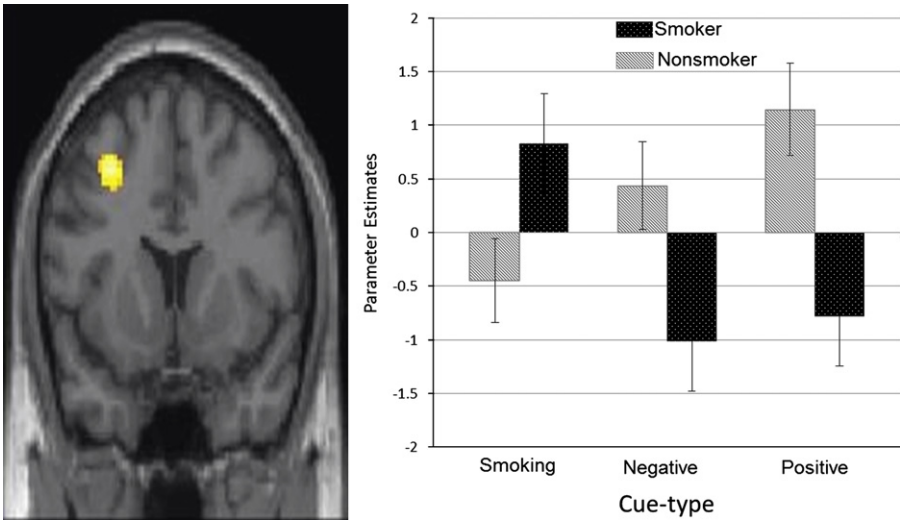

Fig. 1. A smoker status x cue-valence interaction was observed in the left mfg.

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(2011b) found that smokers with blunted cue reactivity to positive images were at higher risk for relapse than smokers with higher reactivity to positive stimuli. Future research should continue to identify individual factors that influence smoking-related behavioral outcomes. Better characterization of the individual personality measures associated with cue reactivity and relapse could lead to more efficacious forms of treatment for substance dependence.

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