Brief Report

Adolescent Smokers Show Decreased Brain Responses to Pleasurable Food Images Compared With Nonsmokers

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Received January 26, 2011; accepted February 22, 2011

Abstract

Introduction: Nicotine acts on the mesocorticolimbic circuits of the brain leading to the release of dopamine. Repeated elevations of dopamine in the brain may cause smokers to become less sensitive to “natural reinforcers.” To test the theory that adolescents with low nicotine exposure may already have decreased activation when exposed to a natural reinforcer, we looked at the effect of visual cues representing “pleasurable” food on light adolescent smokers compared with nonsmokers.

Methods: Twelve adolescent light smokers (aged 13–17 years, smoked 1–5 cigarettes/day) and 12 nonsmokers (aged 13–17 years, never smoked a cigarette) from the San Francisco Bay Area underwent functional magnetic resonance imaging scanning. During scanning, they viewed blocks of photographic images representing pleasurable foods (sweet, high fat, and salty foods) and control cues.

Results: Smokers reported smoking a mean of 3.6 cigarettes/day. There was no difference in body mass index between groups (24.1 vs. 24.0, respectively, $p = .99$). Food images elicited greater activations in nonsmokers in multiple areas including the insula ($T = 4.38$, $p < .001$), inferior frontal region ($T = 5.12$, $p < .001$), and rolandic operculum ($T = 6.18$, $p < .001$). There were no regions where smokers demonstrated greater blood oxygenation level–dependent activations compared with nonsmokers when viewing food versus neutral images.

Conclusions: The finding of decreased activation to pleasurable food among adolescent light smokers supports the theory that these adolescents are displaying decreased sensitivity to at least one natural reinforcer. This also supports the theory that nicotine may affect the brain early in the trajectory of smoking, thus underscoring the need for early intervention among adolescent smokers.

Introduction

As with other drugs of abuse, nicotine acts on the mesocorticolimbic circuits of the brain, leading to the release of supraphysiologic levels of dopamine (Di Chiara, 2002; Koob & Bloom, 1988). Repeated elevations of dopamine in these areas of the brain have a number of effects. First, dopamine appears to facilitate conditioned learning through the development of increased salience of drug-related stimuli (e.g., cue reactivity; Schultz, Tremblay, & Hollerman, 2000; Wise, 2002). Over time, exposure to previously neutral visual stimuli such as a cigarette lighter or an ashtray will produce increases in dopamine in the absence of nicotine itself (Ito, Dalley, Howes, Robbins, & Everitt, 2000; Volkow, Fowler, Wang, & Swanson, 2004). Second, after repeated exposure to supraphysiologic elevations of dopamine brought about through drugs of abuse, such as nicotine, the addicted individual becomes less sensitive to physiologic-level increases in dopamine associated with “natural reinforcers” such as pleasurable food and sex (Barr, Fiorino, & Phillips, 1999; Barr & Phillips, 1999; Cassens, Actor, Kling, & Schildkraut, 1981; Volkow & Li, 2004; Volkow et al., 2004). As a result of their relative dopamine deficient state, addicts begin to preferentially crave these supraphysiologic reinforcers over natural reinforcers (Garavan et al., 2000; Martin-Soelch et al., 2001; Volkow, Fowler, Wang, Swanson, & Telang, 2007; Volkow et al., 2004).

Using behavioral measures, some argue that the brains of adolescents are hypersensitive to these effects, displaying behaviors consistent with these brain alterations after much lower exposure to nicotine compared with adults (Kandel & Chen, 2000). Recently, as part of a study to document the effects of nicotine on the brains of early adolescent smokers using functional magnetic resonance imaging (fMRI), we reported that early adolescent light smokers already display patterns of cue reactivity in the mesolimbic addiction centers which correspond to those of addicted adult smokers (Rubinstein et al., 2011). Specifically, we found that visual cues associated with smoking resulted in greater activation than neutral stimuli as

doi: 10.1093/ntr/ntr046

Advance Access published on March 31, 2011

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measured by relative increases in blood oxygenation level-dependent (BOLD) activation in the mesolimbic dopamine centers of the brain.

To test the theory that adolescent smokers, even at an early stage, will have decreased brain activation when exposed to a natural reinforcer compared with nonsmokers, we used fMRI to measure brain responses to visual cues representing “pleasurable” food in adolescent light smokers compared with nonsmokers.

Methods

Twelve adolescent light smokers (1–5 cigarettes/day) and 12 adolescent nonsmokers (never smoked even a puff) aged 13–17 years ($M = 16.0$, $SD = 1.4$) were recruited as part of a study on smoking cue responses. In brief, participants were screened to exclude those who were currently or previously reported using nicotine replacement, Zyban (bupropion HCL), or psychiatric medication (e.g., dopamine antagonists) in the prior month. The research design and procedures were reviewed and approved by the University of California San Francisco Institutional Review Board. Informed written assent from the adolescent subject and consent from one parent were obtained for each subject before data collection.

Participants completed confidential questionnaires that assessed their smoking behavior and other behavioral and demographic indices. In addition, as part of a magnetic resonance imaging (MRI) safety questionnaire, participants’ heights and weight were collected. All participants received a monetary payment of \$100 for their participation.

Cue Reactivity Paradigm

Cues consisted of photographs of pleasurable foods and neutral images. The food images were collected from various Web sites and comprised pictures of sweet (ice cream), high fat (cheeseburgers), and salty foods (chips). Neutral cues consisted of everyday objects (such as staplers and lamps) and were obtained from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2008). During fMRI scanning, all visual stimuli were presented onto an LCD screen behind the participant’s head, which the participant viewed through a mirror mounted on the head coil. Each fMRI acquisition began with the presentation of a fixation cross for 18 s. Stimuli were presented in blocks lasting 18 s. Each block consisted of three images from the same condition (food or neutral), for a duration of 6 s per image. Between each block, the fixation cross was presented again for 18 s. The fMRI acquisition run consisted of three blocks of each of the two conditions (food and neutral). The order in which blocks were presented as well as the order in which individual images appeared were randomized for each participant. Stimuli were presented using E-prime 2.0 (Psychology Software Tools, Inc.).

Imaging Parameters

A Siemens 3 Tesla MAGNETOM Trio Tim scanner was used for fast echo-planar imaging. Following a localizer series, high-resolution T1-weighted structural images were obtained (TR/TE/TI = 10/4/300 ms, 15° flip angle, 1.0×1.0 mm² in plane resolution and 1-mm slab thickness). Next, functional images were

acquired using an echo-planar pulse sequence with T2-weighted images sensitive to BOLD contrast (TR = 2 s; TE = 40 ms; flip angle = 90, matrix = 64×64 , FOV = 40×40 cm, 33 slices, 3 mm thickness).

fMRI Data Analysis

Statistical analysis of fMRI data was performed using MATLAB (Mathworks Inc.) and SPM5 software (www.fil.ion.ucl.ac.uk/spm). Prior to analysis, the functional images were converted to 3D Analyze format volumes. Images were corrected for motion artifacts using a 6-parameter rigid body affine transformation and corrected for differences in slice acquisition timing. The resulting images were normalized to a standard stereotaxic space (Montreal Neurological Institute Template) using a 12-parameter affine/nonlinear transformation and then spatially smoothed with a 8-mm full-width half-maximum isotropic Gaussian kernel.

For each subject, the fMRI data were analyzed using a general linear model in which blocks of each condition (food and neutral) were modeled by a separate regressor, consisting of the block onset and duration convolved with SPM’s canonical hemodynamic response function. Additional regressors were included to model motion correction parameters as covariates. Contrasts of interest were performed to compare food and neutral cue conditions. Second-level random effects analyses were performed to examine this contrast between the two groups. Each of these analyses was performed on the data from the whole brain. Activations were considered significant at $p < .001$, with a minimum cluster size of 20 voxels.

Results

As previously reported in Rubinstein et al. (2011), participants had a mean age of 16 years ($SD = 1.4$), were racially diverse (62% White, 17% Hispanic), and 42% female. Smokers reported smoking a mean of 3.6 cigarettes/day ($SD = 1.3$) with a mean duration of daily smoking of 1.9 years ($SD = 1.1$). The median time smokers reported smoking their last cigarette was 1.9 hr prior to the scan ($SD = 7.9$ hr, range 1–24.5 hr). There was no significant difference in body mass index (BMI) between the smokers and nonsmokers (24.1 vs. 24.0, respectively, $p = .99$). Nearly all smokers and a third of nonsmokers reported using alcohol and marijuana.

Food images elicited greater activations in nonsmokers as compared with adolescent smokers in multiple areas including the insula ($T = 4.38$, $p < .001$), putamen ($T = 4.24$, $p < .001$), inferior frontal cortex ($T = 5.12$, $p < .001$), and rolandic operculum ($T = 6.18$, $p < .001$; see Table 1 and Figure 1). There were no regions where smokers demonstrated greater BOLD activations compared with nonsmokers when viewing food versus neutral images.

Discussion

We found that, even at low levels of nicotine exposure, brain regions linked to reward have decreased responses to pleasurable food images compared with nonsmokers. This suggests that these early adolescent light smokers are already demonstrating

Table 1. Brain Areas in Which the Blood Oxygenation Level–Dependent Response to Food Cues Was Greater in Nonsmokers Compared With Smokers

Hemisphere	Brain region	No. of voxels	MNI coordinates; x, y, z	T value
R	Rolandic operculum/insula	54	44, –8, 16	6.18
R	Inferior frontal	58	44, 32, 2	5.12
R	Insula	36	40, 14, 8	4.38
R	Mid occipital	21	46, –82, 10	4.33
R	Calcarine	20	22, –66, 10	4.32
R	Putamen	21	26, –2, 12	4.24

Note. MNI = Montreal Neurological Institute. Minimum cluster size ≥ 20 voxels.

* $p < .001$.

reduced sensitivity to a natural reinforcer compared with their nonsmoking counterparts. Specifically, nonsmokers show greater activation in the insula and rolandic operculum both of which are part of the somatosensory cortex and have been shown to play a role in anticipatory food reward and craving as well as drug craving (Pelchat, Johnson, Chan, Valdez, & Ragland, 2004; Small, Gerber, Mak, & Hummel, 2005; Wang et al., 2004; Yamamoto, 2006). The putamen, which resides in the striatum and is a key part of the mesolimbic dopamine center of the brain, was also preferentially activated in nonsmokers. Finally, the right inferior frontal area, which is part of the orbital frontal complex (OFC), showed increased activation in nonsmokers. The OFC is a critical part of the brain's dopaminergic reward system and is involved with the attribution of motivational value to rewards including pleasurable foods and drugs (Volkow & Fowler, 2000; Wang et al., 1999, 2004).

The fact that these regions of reduced BOLD activity reside in dopamine responsive centers of the brain is suggestive of decreased dopaminergic activity within these regions in adolescent light smokers. However, BOLD response is a measure of oxygenated to deoxygenated hemoglobin, not actual dopamine release, and thus, differences in dopamine activity can only be inferred.

Figure 1. SPM image showing the areas with greater blood oxygenation level–dependent activation in nonsmokers versus smokers. RO = rolandic operculum; In = insula; OFC = orbital frontal complex/ventrolateral prefrontal cortex.

In our prior report (Rubinstein et al., 2011), we demonstrated that adolescent smokers display increased sensitivity to smoking-related cues even at relatively low levels of nicotine exposure. These new findings suggest that these same adolescent smokers also display decreased sensitivity to a naturally reinforcing cue (e.g., pleasurable food). While these preliminary findings support evidence from pre-clinical research, showing that adolescents appear to be more susceptible to the effects of nicotine on the brain, these results need to be reproduced using other natural reinforcers such as sexually arousing images. Furthermore, the causal direction of this effect needs to be established through future research. For example, we know that these light smokers are less responsive to at least one natural reinforcer (e.g., pleasurable food), but we do not know whether nicotine exposure caused this change or whether a relative inability to achieve pleasure at baseline lead to the pursuit of nicotine to augment a relative dopamine deficiency. Future research will need to study early experimenting adolescents who later take up regular smoking and prior smokers who have quit smoking to determine where these activation patterns occur in the smoking trajectory and when, if at all they return to normal following cessation.

Limitations

While self-report is not an ideal way to collect data on weight, subjects were informed that the MRI scanner power settings are calibrated from their weights. There was no difference in calculated BMI between groups, and we have no reason to assume that one group would be less accurate in their reporting than the other. We did not collect data on time of last meal. However, all participants had to abstain from eating both during the hour prior to scanning while they completed the surveys and the hour of scanning, resulting in a fasting time of at least 2 hr. There is also a possibility that nicotine itself may have acutely influenced participant's hunger, which may have in turn affected their responsiveness to food images. Unfortunately, we did not collect data on self-perceived hunger. However, nicotine has a relatively short half-life of 2 hr (Benowitz, Jacob, Jones, & Rosenberg, 1982), meaning that the effect of any nicotine in these light smoking participants was greatly reduced, given the median time since last cigarette was roughly 2 hr and ranged to greater than 24 hr. Finally, more smokers used alcohol and marijuana than nonsmokers, which may have contributed to some of the difference in brain activation patterns between groups. While addressing this issue is beyond the scope of this pilot study, it

would be ideal to perform another larger study with participants who only smoke cigarettes and do not drink alcohol to tease out any possible contribution from other substance use.

Conclusions

The finding of decreased activation to pleasurable food among adolescent light smokers supports the theory that these adolescents are displaying decreased sensitivity to at least one natural reinforcer. This also supports the theory that nicotine affects the brain early in the trajectory of smoking. As such, adolescents may be particularly vulnerable, experiencing alterations in brain function with very little nicotine exposure. Clearly, further research is necessary to clarify the causality of these results, but these results add to the growing literature supporting early intervention among adolescent smokers.

Funding

Funding for this study was provided by National Cancer Institute (NCI) grant R01 CA140216. NCI had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.

Declaration of Interest

None declared.

Acknowledgments

The authors would like to thank Paul Keselman for technical support, data processing, problem solving, and general assistance on this project. The authors would also like to acknowledge the time and effort of all the participants.

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