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Blunted Striatal Responses to Favorite Food Cues in Smokers*

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Abstract

Background—Although tobacco-smoking is associated with relatively leaner body mass and smoking cessation with weight gain, the brain mechanisms underlying these relationships are not well understood. Smokers compared to non-smokers have shown diminished neural responses to non-tobacco rewarding stimuli (e.g., monetary rewards), but brain responses to favorite-food cues have not been investigated relative to smoking status. We hypothesized that smokers would exhibit diminished neural responses compared to non-smokers in response to favorite-food cues in motivation-reward and emotion-regulating regions of the brain.

Methods—Twenty-three smokers and 23 non-smokers matched based on body mass index (BMI), age, and gender listened to personalized favorite-food-cue, stress, and neutral-relaxing audiotapes during fMRI.

Results—During favorite-food-cue exposure, smokers versus non-smokers exhibited diminished activations in the caudate, putamen, insula, and thalamus. Neural responses during stress and neutral-relaxing conditions were similar across groups. Subjective food-craving ratings were similar across groups.

Conclusions—The relatively diminished neural responses to favorite-food cues in smokers may contribute to lower BMI.

Keywords

smoking; BMI; fMRI; food cues

1. INTRODUCTION

A major barrier to quitting smoking (Chiolero et al., 2008) involves cessation-related weight gain (Filozof et al., 2004) and smoking-related leanness (Albanes et al., 1987, Chiolero et al., 2008). Concerns of weight gain may undermine smoking-cessation efforts and promote relapse (Meyers et al., 1997, Clark et al., 2004). Foods and drugs of abuse, including nicotine, activate brain circuits involved in motivation, learning, and behavioral reinforcement (Di Chiara, 2002, Volkow et al., 2008). Brain reward regions, such as the striatum, and increased dopaminergic transmission (Wang et al., 2001) therein are associated with exposure to palatable foods and food cues, with concomitant increases in food craving and eating motivations (Kelley et al., 2005, Small et al., 2001). Neural responses to food cues differ by body mass index (BMI; Martin et al., 2010, Stice et al., 2008, Stoeckel et al., 2008), with greater responsivity of brain-reward regions and subjective food craving associated with higher BMI (Pelchat et al., 2004, Simansky, 2005, Stice et al., 2008). Nicotine has been found to decrease appetite and neural differences between responses to food and control pictures in lean, never-smokers (Kroemer et al., 2013).

Given these data, we tested the hypothesis that smoking status would be associated with differences in neural responses in reward-motivation regions independent of BMI. We used an established fMRI task involving guided-imagery procedures employing individually generated personalized scripts. Using this procedure, we previously observed in obese and lean individuals differences in neural responses to favorite food-cues (Jastreboff et al., 2013). Here, we examined neural responses to favorite-food cues and stress in smokers and non-smokers of similar BMI. We hypothesized that smokers as compared to non-smokers would exhibit decreased neural response to favorite-food cues in corticostriatal-limbic regions.

2. METHODS AND MATERIALS

2.1 Subjects

Men and women, between ages 19–50 years, who were current daily smokers (10 cigarettes/day) and non-smokers (never smokers), but otherwise healthy, were recruited from the community via advertisement. Smoking status was assessed by number of cigarettes/day, age at onset of smoking, years of smoking, carbon monoxide (CO) level, and Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al., 1991). Exclusion criteria included chronic medical conditions, psychiatric disorders (DSM-IV criteria), neurological injuries or illnesses, chronic medication use for medical problems or psychiatric disorders, IQ<90, inability to read and write in English, pregnancy, and claustrophobia or metal in body incompatible with MRI. Mood ratings were assessed using the Center for Epidemiological Studies-Depression (CES-D) scale (Radloff, 1977). The study was approved by the Yale Human Investigation Committee. All subjects provided signed informed consent.

2.2 Imagery script development and fMRI

Prior to fMRI, guided-imagery scripts for favorite-food-cue, stress, and neutral-relaxing conditions were developed using previously established methods (Hommer et al., 2013, Jastreboff et al., 2013, Sinha, 2009). Participants presented for imaging during early afternoon, with instructions to have eaten approximately 2 hours prior to scanning to avoid being intensely hungry or full. Smokers were instructed to smoke approximately an hour before fMRI to avoid acute intoxication or withdrawal. We assessed subjective hunger ratings before and after scanning sessions; no between-group differences were observed ($t(38)=0.86, p=0.40$). In a counter-balanced order, subjects were exposed to personalized favorite-food-cue, stress, and neutral-relaxing imagery conditions. Six fMRI trials (two per condition) were acquired using a block design with each trial lasting 5.5 min. Each trial included a 1.5-min quiet baseline period followed by a 2.5 min imagery period (this included 2 minutes where they were to imagine their specific story as it was being played to them from a previously made audio-recording and 0.5 min of quiet imagery time during which they continued imagining the story while lying in silence) and a 1-min quiet-recovery period.

2.3 Task Validation

Subjective vividness ratings were obtained wherein subjects indicated how well they were able to visualize individual stories during fMRI. There was no between-group difference in imagery vividness ($t(44)=0.37$, $p=0.71$). Anxiety ratings were also obtained from subjects before and after each imagery script. As previously (Li et al., 2005, Sinha et al., 2004, 2005), subjects were asked how tense, anxious and/or jittery they felt using a Likert 10-point scale. There were no between-group differences in baseline anxiety ratings in smokers vs. non-smokers (Favorite-food-cue $p=0.89$, Stress $p=0.46$, Neutral-relaxing $p=0.87$). Anxiety ratings increased after stress-cue exposure in smokers ($p<0.0001$) and non-smokers ($p=0.03$) (Supplementary Table)¹, with greater changes in smokers versus non-smokers ($p=0.02$). There were no changes in anxiety ratings with favorite-food cue exposure (smokers: $p=0.40$; non-smokers: $p=0.80$) and no difference between smokers and non-smokers ($p=0.55$). Smokers reported significantly decreased anxiety from baseline after the neutral-relaxing condition ($p=0.02$), whereas non-smokers did not ($p=0.31$); there was no difference between smokers and non-smokers ($p=0.36$). Food-craving ratings were also obtained from subjects before and after each imagery script (see Results).

2.4 fMRI acquisition and statistical data analyses

Images were obtained in the Yale Magnetic Resonance Research Center (MRCC) using a 3-Tesla Siemens Trio MRI system (see Supplementary Material)². As in prior publications (Jastreboff et al., 2013, Hommer et al., 2013, Yip et al., in press), we contrasted (smokers and nonsmokers) regional whole-brain activation during each condition (favorite-food-cue, stress, and neutral-relaxing) using t-tests within BioImage Suite. The Bioimage Suite software employs a built-in nonlinear transformation from Montreal Neurological Institute (MNI) to Talairach coordinates (Lacadie et al., 2008). Data were corrected for multiple comparisons by the spatial extent of contiguous supra-thresholded individual voxels at $p<0.05$ for contrast brain maps (Cox, 1996). One obese smoker was excluded from the neuroimaging analysis as his neural activation deviated by more than 2 standard deviations (SDs), reflecting diminished activation. For descriptive statistics, between-group differences in subjective and clinical measures were tested using t-test, Fisher exact, and chi-square tests.

3. RESULTS

3.1 Group demographics and fasting metabolic parameters

Twenty-three otherwise healthy smokers and 23 non-smokers were matched on age (mean $\pm$ SD, smokers: 26.8 ± 7.2 years, non-smokers: 27.4 ± 7.0 years), gender (both groups 39% female), and BMI (smokers: 28.0 ± 4.7 kg/m², non-smokers: 26.9 ± 5.1 kg/m²) (Table 1). There were no between-group differences with regard to fasting insulin levels (mean $\pm$ SD, smokers: 14.1 ± 6.5 uU/mL; non-smokers: 13.9 ± 5.0 uU/mL, $t(42)=0.09$, $p=0.93$) or fasting plasma glucose levels (smokers: 93.3 ± 7.5 mg/dL, non-smokers: 93.5 ± 8.5 mg/dL; $t(42)=0$, $p=1.0$). Both groups were somewhat insulin resistant as assessed by HOMA-IR

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(Homeostatic Model Assessment of Insulin Resistance) (smokers: 3.3 ± 1.5 , non-smokers: 3.2 ± 1.3 ; $t(42)=0.03$, $p=0.97$).

3.2 Between-Group and Between-Condition Neural Contrasts

Smokers relative to non-smokers demonstrated diminished neural activation during exposure to favorite-food cues in the caudate, putamen, insula, thalamus, brainstem, and cerebellum (Supplementary Table 2,³). In between-group contrasts, smokers and non-smokers showed no differences in the stress or neutral-relaxing conditions. Neural responses to each condition (favorite-food-cue, stress, and neutral-relaxing) for each group (smokers and non-smokers) are shown (Supplementary Figure 1)⁴.

3.3 Food craving following favorite-food and stress cues

Smokers and non-smokers did not differ in baseline food-craving prior to each imagery trial ($t(39)=0.55$, $p=0.59$). Across groups, there was a significant effect of imagery condition on food craving ($F(2,117)=5.38$, $p=0.006$), with increased levels following favorite-food-cue but not stress or neutral-relaxing conditions. Smokers and non-smokers did not differ in favorite-food-cue-induced craving ratings ($p=0.69$). There was no increase in food craving following stress cues (smokers $p=0.56$; non-smokers $p=0.63$) or neutral-relaxing cues (smokers $p=0.51$; non-smokers $p=0.98$) in either group. There were no group ($F(1,117)=0.46$, $p=0.50$) or group-by-condition ($F(2,117)=0.06$, $p=0.94$) effect.

4. DISCUSSION

In this study, we examined neural responses to favorite-food cues and stress in smokers and non-smokers. Smokers, versus non-smokers, exhibited relatively blunted corticostriatal- limbic activations to favorite-food cues. Consistent with findings in lean adolescents showing that light smokers relative to non-smokers exhibited diminished activation in the insula, putamen, inferior frontal cortex, and rolandic operculum in response to pictures of desirable foods (Rubinstein et al., 2011), we found that during exposure to favorite-food cues, smokers, relative to BMI-matched non-smokers, demonstrated diminished activation in the striatum and thalamus, regions involved in motivation-reward and the relay of peripheral sensory information to the cortex (Sherman, 2007). Our results raise the possibility that smokers, irrespective of body weight, may be desensitized to “natural” food-related rewards in motivation-reward regions of the brain (Volkow et al., 2004). These findings may partially explain why smoking status is associated with lower body weight (Albanes et al., 1987, Chiolero et al., 2008) and smoking cessation with weight gain (Filozof et al., 2004). As smokers abstain from nicotine, they may consume food to substitute for reward-pathway stimulation they would have received from using tobacco (Epstein and LeDdy, 2006). Conversely, as prior-smokers lose weight, and thus forego the “substitute” substance (i.e., palatable foods), they may relapse to smoking. Consistent with this notion, 100% of obese smokers who had recently quit smoking and then undergone bariatric surgery relapsed to smoking following surgery (Adams et al., 2012). Although it is tempting to

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hypothesize that alterations in the function of cortical and striatal regions may underlie these clinical observations, this possibility warrants direct examination, as does the possible role for dopamine and other neurotransmitter systems in these processes.

4.1 Smokers exhibit relatively diminished neural responses in corticostriatal-limbic regions

Within-group contrasts indicated that non-smokers, but not smokers, showed increased activation in corticostriatal-limbic regions in response to favorite-food-cue exposure. The rewarding effects of both nicotine (Corrigall et al., 1992, Di Chiara, 2002) and food (Volkow et al., 2008) are in part mediated through mesolimbic, dopaminergic pathways involved in motivation, learning, and behavior reinforcement. A central component of reward-motivation neurocircuitry involves the striatum, a structure implicated in reward processing, reward-based learning, valuation, and anticipation of rewards (Volkow et al., 2008). Food administration is associated with activation in the nucleus accumbens (Small et al., 2001), a region of the ventral striatum implicated in the pleasure or reward obtained from drugs. Nicotine also acts on the striatum, in particular in the core of the accumbens, increasing extracellular dopamine (Di Chiara, 2002). Repeated exposure to increased (superphysiologic) dopamine levels may lead to decreased sensitivity to non-drug-related “natural reinforcers” such as food (Volkow et al., 2004), thus perhaps explaining the diminished BOLD signal response observed in smokers in the striatum. Additionally, other drugs besides tobacco have been associated with hyperphagia and weight gain during withdrawal or with cessation of use (Edge and Gold, 2011); for example, a preference for sweets has been observed during recovery from opioid dependence (Gold, 2011). Alternate explanations (e.g., relating to pre-existing differences in smokers and non-smokers) also warrant consideration. Future studies (directly investigating dopamine systems over time) would help to better understand the factors leading smokers to exhibit relatively diminished activation to food cues.

Although smokers and non-smokers differed with respect to patterns of neural activation in response to favorite-food cues, they reported similar subjective responses to the cues. The findings of comparable subjective responses and different neural responses suggest that the between-group differences underlying responses to favorite food cues may be occurring subconsciously.

4.2 Limitations

As this was a cross-sectional study involving smokers who were not interested in smoking cessation, we could not explore how smoking cessation (and changes in BMI) may impact neural responses; future studies should investigate these processes. The sample included individuals with a range of BMI values; future studies should investigate lean smokers and obese smokers to explore possible differences in craving and neural responses between these groups. Although participants were asked to eat two hours prior to the scanning session in order to avoid being intensely hungry or full, we cannot verify the extent to which they followed these directions when they were outside of the research facility. Finally, smokers had relatively low FTND scores and late onsets of smoking; but irrespective of their low

nicotine dependence, we observed blunted neural responses, suggesting that these changes are associated with smoking even in “light” smokers.

4.3. Conclusions

In summary, we found that independent of BMI, smokers relative to non-smokers demonstrated diminished neural responses to favorite-food cues, suggesting smokers may be desensitized in reward-motivation neurocircuitry to natural food-related rewards. The identified differences in neural responses to favorite-food cues in smokers may contribute to their relatively lower BMIs. It is intriguing to speculate that in the absence of the rewarding drug, weight gain seen with attempts to quit smoking may be related to an increase in consumption of foods that elicit reward responses, which may have otherwise been elicited from smoking cigarettes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

Relatively diminished activation of the striatum, insula and thalamus was observed in smokers versus non-smokers during exposure to favorite-food cues

The findings suggest a biological mechanism for diminished body mass indices associated with active tobacco smoking.

Figure 1. Between-group contrast maps

Group comparison during favorite-food-cue condition: smokers vs. non-smokers. Smokers demonstrate relatively diminished activation in striatal-limbic regions during exposure to favorite-food cues.

Table 1

Demographic data and metabolic parameters for smokers and non-smokers. CO, carbon monoxide; FTND, Fagerstrom Test for Nicotine Dependence; CES-D, Center for Epidemiological Studies-Depression.

	Smokers (N=23)	Non-smokers (N=23)	
	Mean± SD	Mean± SD	<i>p</i>
Demographics			
Age (years)	26.7 ± 7.1	27.4 ± 7.3	NS
Gender (Female)	43 %	39 %	NS
IQ	112.1 ± 8.6	112.6 ± 9.6	NS
BMI (kg/m ²)	28.0 ± 4.6	26.8 ± 5.1	NS
Metabolic Measures			
Glucose _{fasting} (mg/dL)	95.3 ± 11.5	93.5 ± 8.5	NS
Insulin _{fasting} (uU/mL)	16.2 ± 11.9	13.9 ± 5.0	NS
HOMA-IR	4.0 ± 4.0	3.2 ± 1.3	NS
Smoking Measures			
Cigarettes per day	9.4 ± 7.1	0	-
FTND score	2.5 ± 2.0	0	0.001
CO levels	12.5 ± 9.3	2.4 ± 1.0	<0.0001
Years smoked	7.5 ± 9.0	0	-
Age at onset of smoking	18.2 ± 2.5	0	-
Mood Measure			
CES-D	11.48 ± 7.8	10.52 ± 8.5	NS