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Neural Sensitivity to Smoking Stimuli Is Associated With Cigarette Craving in Adolescent Smokers

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A B S T R A C T

Purpose: Adolescents initiate cigarette smoking at disproportionately high rates, despite widespread knowledge of its health-compromising and long-term consequences. Psychosocial factors clearly play a role in adolescent smoking initiation, but the role of the developing adolescent brain in this behavior remains unclear. The goal of the present study was to determine whether greater neural sensitivity to smoking cues in adolescents compared to adults underlies increased proclivity toward smoking behavior and craving.

Methods: We addressed this question in a sample of adolescent (n = 39) and adult (n = 39) smokers and nonsmokers by assessing craving in response to smoking videos that featured late adolescents/young adults while participants underwent functional magnetic resonance imaging.

Results: Ventral striatal activation mediated the relationship between video-induced craving and subsequent desires to smoke following the scan in adolescent smokers only. We also found that functional coupling between striatal and cortical regions was associated with increased craving in adolescent smokers.

Conclusions: These novel results demonstrate that adolescent smokers may be more neurobiologically responsive to smoking stimuli than adults, perhaps because of ongoing ontogenetic changes in adolescents that normatively occur in frontostriatal circuitry.

IMPLICATIONS AND CONTRIBUTION

Neurobiological responses to cigarette cues underlie individual differences in subsequent smoking urges, with ventral striatal activity mediating the relationship between cue-induced and postscan craving in adolescent smokers only. Compared to adult smokers, adolescent smokers may be more sensitive to photographs or videos that depict cigarette smoking behavior due to ongoing ontogenetic changes in the brain.

The health-compromising risks of cigarette smoking are well known [1,2]. Although the number of new cigarette smokers in the United States declined in recent years, those who do start using are younger than in previous generations, and use of other tobacco products has increased [3,4]. Social influence clearly plays a role in this increase [5,6], but it alone does not explain high rates of initiation in adolescents. Evidence from rodent studies suggests that normative developmental changes that occur in the adolescent brain in regions associated with addiction (and which are homologous in humans) may also render it particularly susceptible to nicotine's addictive properties [7–9]. Whether this phenomenon applies to human adolescents has been surprisingly understudied. Evidence suggests that smoking cues elicit a desire to smoke in adolescents [10,11] and that this may be driven by increased activation in addiction-related regions to smoking cues [12]. Research examining neural responses to drug and alcohol cues have demonstrated similar findings [13,14]. However, no previous study has asked the developmental question: is the adolescent brain more responsive to smoking cues than adults? Relatedly, does cue-induced craving explain individual differences in the desire to smoke among adolescents? Addressing these questions may help elucidate why adolescents are at greater risk of smoking initiation than adults.

Conflicts of Interest: The authors declare no conflicts of interest.

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Adolescents undergo significant brain development in frontostriatal circuitry [15,16]. Regions in this circuitry, including the ventral striatum (VS) and dorsolateral prefrontal cortex (DLPFC), are particularly relevant to the current investigation as they are implicated in cigarette cue reactivity in adults [17–19]. During adolescence, the VS exhibits hypersensitivity to both the anticipation and receipt of rewards [20–22]. The DLPFC, implicated in cognitive regulation of cigarette craving [23], undergoes protracted development through adolescence [24]. This neurodevelopmental tempo may render adolescents especially susceptible to the allure of appetitive smoking cues via increased craving relative to adults. In this study, we used mediation analyses to test the hypothesis that greater neural responses to smoking videos in adolescent versus adult smokers would be predictive of greater craving in the adolescent smokers. In addition, because neural regions typically work in concert with other neural regions, we applied functional connectivity tools to test the hypothesis that the relationship between activation of regions that have previously been implicated in craving predicts greater craving in adolescents.

Methods

Participants

Using community and Internet advertising, 78 right-handed, English-speaking (n = 39 postpubertal adolescents, 13–18 years; n = 39 adults, 25–30 years) smokers and nonsmokers participated (Table 1; Appendix for demographic details). Participants aged ≥18 years provided written consent, whereas participants <18 years provided assent and parents provided written consent as approved by the University of California Los Angeles Institutional Review Board. All participants self-reported that they were free of developmental, neurologic, or psychiatric disorders.

Smoking behavior

Participants completed two visits. At the intake session, participants provided self-reports on cigarettes smoked per day, smoking duration, and nicotine dependence via the Fagerstrom Test for Nicotine Dependence (FTND) [25]. A revised FTND score excluding statements less applicable to adolescents[1] was calculated to control for smoking experience across age categories. There were no significant differences in nicotine dependence scores between the revised FTND and original measure for adolescents and adults; therefore, the revised FTND scores were used in analyses. Demographic and smoking variables that differed between groups (Table 1) were controlled in analyses, and implications for these significant differences are provided in the Discussion.

Smoking status was measured by daily cigarette consumption and verified by exhaled carbon monoxide (CO) levels (Smokerlyzer; Bedfront Scientific, Kent, UK) and urinary cotinine (NicAlert test strips; Nymox Pharmaceutical Corp., Hasbrouck Heights, NJ) at both sessions (Table 1). Nonsmokers reported less than five cigarettes in their lifetime and tested negative on tests. Smokers reported five or more cigarettes daily for ≥6 months and met qualification thresholds for exhaled CO (≥6 ppm) and urinary cotinine (≥200 ng/mL) measurements. To capture naturalistic smoking habits, smokers were not instructed to abstain before the visit; self-reported time since last cigarette was controlled in analyses. Participants with other tobacco use (e.g., e-cigarettes) and comorbid substance use (except marijuana) were excluded during telephone screening. Participants who reported regular marijuana use were instructed to abstain for a minimum of ≥24 hours before test days; visits were rescheduled if the urine drug screen tested positive for marijuana use (Instant-View Multi-Panel 12-Test Drug Screen; ALFA Scientific Designs Inc., Poway, CA).

Functional magnetic resonance imaging procedure

The functional magnetic resonance imaging (fMRI) occurred ~1 week after the intake visit. Before the scan, participants reported hours since last cigarette, alcohol, and marijuana consumption (Table 1). To assess baseline craving before the scan, participants completed the Shiffman–Jarvik Withdrawal (SJ) Scale, which asked about desire to smoke if freely permitted, extent of missing a cigarette, the current urge to smoke, and likability of smoking (1–7: 1 = definitely not, 7 = definitely) [26]. To assess post-task craving, participants rated the same items on the Urge To Smoke (UTS) Scale (1–7: 1 = definitely not; 7 = definitely) following the scan [27]. Because cigarette craving was assessed using two different measures, we focused on the four items that were the same on the SJ and UTS scales; for each measure of cigarette craving, the items were averaged, and the composite was used for all analyses. The internal consistency of these four items was high ($\alpha_{baseline}$ = .93 and $\alpha_{post\text{-}task}$ = .96). Although adolescent and adult smokers differed in number of hours since last cigarette ($M_{adolescents}$ = 26.93, standard deviation [SD] = 59.01; M_{adults} = 6.96, SD = 1.93; Table 1), there were no differences in nicotine withdrawal levels (as measured by the SJ Scale; $M_{adolescents}$ = 3.01, SD = .74; M_{adults} = 3.29, SD = .58). However, there was a significant difference in CO level between adolescent and adult smokers (Table 1), which may be attributed to age differences in hours since last cigarette.

Following the scan, participants listed the top five cues that elicited the greatest craving and attributed a primary reason for why that specific cue made them feel like smoking (Supplementary Table 1). The same set of smoking cues featuring late adolescents/young adults elicited similar craving ratings and reasons for craving from both adolescent and adult smokers (Appendix; Supplementary Table 1).

Cigarette cue reactivity functional magnetic resonance imaging task

During the scan, participants completed a cigarette cue reactivity task. So as not to rely on static smoking cues (e.g., photographs), this task consisted of sixteen 20-second videos created by a local filmmaker that were developmentally appropriate, meaning that all the actors were young adults/late adolescents; this is a novel contribution to this area of research. Ecologic validity is difficult to approximate in a scanner, and dynamic videos of real people smoking in realistic situations presumably elicit a more salient response. Furthermore, youth are more likely to attend to videos that feature individuals in the same age group. The videos were classified as either neutral or smoking cues (Figure 1A). Neutral cue videos depicted late

[1] For example, "How soon after you wake up do you smoke your first cigarette?" may not be indicative of adolescent dependence because parental presence may preclude smoking first thing in the morning.