Title

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Journal

Journal of Adolescent Health, 58(2)

ISSN

1054-139X

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Publication Date

2016-02-01

DOI

10.1016/j.jadohealth.2015.10.004

Peer reviewed

Journal of Adolescent Health 58 (2016) 186–194

JOURNAL OF ADOLESCENT HEALTH
www.jahonline.org

Original article

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

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Article history: Received May 4, 2015; Accepted October 8, 2015
Keywords: Adolescence; Brain development; Cigarette craving; fMRI; Smoking

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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1054-139X/
http://dx.doi.org/10.1016/j.jadohealth.2015.10.004

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.

Table 1
Characteristics of research participants

	Adolescent smokers (n = 19)	Adolescent nonsmokers (n = 20)	Adult smokers (n = 20)	Adult nonsmokers (n = 19)	*p* Stat
Sex (M/F)	15/4*, ‡	8/12‡	10/10	7/12*	*.04 ‡.07
Age	17.53 (.70)*, ‡, § (range: 13–18)	16.05 (1.28)*, ‖, # (range: 13–18)	27.05 (1.57)‡, # (range: 25–30)	27.63 (1.64)§, ‖ (range: 25–30)	*.01 ‡<.0001 §<.0001 ‖<.0001 #<.0001
Ethnicity					
Caucasian	5.26% (n = 1)*, ‡	25% (n = 5)‡	35% (n = 7)*	15.79% (n = 3)	*.04
African-American	15.79% (n = 3)*, ‡	0% (n = 0)‡	35% (n = 7)*	15.79% (n = 3)	‡.01
Hispanic/Latino	15.79% (n = 3)‡	50% (n = 10)‡	20% (n = 4)	21.05% (n = 4)	
Asian American	47.37% (n = 9)*, ‡	10% (n = 2)‡	0% (n = 0)*	10.53% (n = 2)	
Other/multiethnic	15.79% (n = 3)	15% (n = 3)	10% (n = 2)*	36.84% (n = 7)	
Intelligent Quotient	105.21 (11.46)‡	108 (13.45)§	105 (14.3)*	118.63 (14.2)*, ‡, §	*.01 ‡.02 §.07
Maternal Education					
Did not finish high school	5.26% (n = 1)	5% (n = 1)	5% (n = 1)	5.26% (n = 1)	
High school diploma	57.89% (n = 11)	20% (n = 4)	45% (n = 9)	26.32% (n = 5)	
GED	0% (n = 0)	10% (n = 2)	0% (n = 0)	0% (n = 0)	
AA Degree	21.05% (n = 4)	15% (n = 3)	15% (n = 3)	15.79% (n = 3)	
BA Degree	0% (n = 0)	15% (n = 3)	5% (n = 1)	15.79% (n = 3)	
Master's Degree	10.53% (n = 2)	20% (n = 4)	25% (n = 5)	21.05% (n = 4)	
Other	5.26% (n = 1)	15% (n = 3)	5% (n = 1)	15.79% (n = 3)	
Cigarettes/day	5.55 (4.63)*, ‡, §	0*	10.2 (5.59)‡, ‖	.05 (.23)§, ‖	*<.001 ‡<.0001 §<.001 ‖<.001
Fagerstrom Score	1.89 (1.76)*, §, ‖ (range: 0–8)	0*	3.2 (2.14)‡, § (range: 0–8)	0‡, ‖	*.004 ‡<.0001 §.04 ‖.005
Fagerstrom Score (revised scale)	1.21 (1.08)*, § (range: 0–6)	0*, ‖	1.52 (1.25)‡, ‖ (range: 0–6)	0‡, §	*<.0001 ‡<.0001 §<.0001 ‖<.0001
Smoking duration (months)	17.63 (14.82)* (range: 6 mo to 5 yr 4 mo)	N/A	70.85 (50.76)* (range: 1 yr to 15 yr)	N/A	*<.0001
Last smoked cigarette (in hours) before scan	26.93 (59.01)*	N/A	6.96 (1.93)*	N/A	*.02
Last reported alcohol consumption (in hours)	97.5 (82.25) (42.11% reported any use)	246 (317.41) (20% reported any use)	39.2 (21.98) (25% reported any use)	93 (80.31) (42.11% reported any use)	
Last reported marijuana consumption (in hours)	163.2 (212.23) (26.32% reported any use)	48 (33.94) (20% reported any use)	624 (868.82) (25% reported any use)	57 (18) (21.05% reported any use)	
Smokerlyzer breath CO level; intake session (range: 1–6)[a]	1.58 (.84)*, § 6–7 ppm	.94 (.24)*, ‖ 0–6 ppm	2.95 (1.23)‡, §, ‖ 10–11 ppm	1.06 (.24)‡ 0–6 ppm	*.07 ‡<.0001 §<.001 ‖<.001
Smokerlyzer breath CO level; scan session (range: 1–6)[a]	1.82 (1.07)*, § 6–7 ppm	1 (0)*, ‖, # 0–6 ppm	2.95 (1.19)‡, §, ‖, # 10–11 ppm	1.06 (.24)‡ 0–6 ppm	*.03 ‡<.0001 §<.001 ‖<.001 #.05
NicAlert urinary cotinine level; intake session (range: 0–6)[b]	2.75 (2.49)*, §, ‖ ~82–200 ng/mL	.71 (.77)*, # ~0–30 ng/mL	4.37 (1.64)‡, §, # ~500–1,000 ng/mL	.65 (.61)‡, ‖ ~0–30 ng/mL	*.01 ‡<.0001 §.03 ‖<.004 #<.0001
NicAlert urinary cotinine level; scan session (range: 0–6)[b]	3.67 (2.6)*, § ~300–500 ng/mL	.56 (.51)*, ‖ ~0–30 ng/mL	4.61 (1.65)‡, ‖ ~500–1,000 ng/mL	.63 (.62)‡, § ~0–30 ng/mL	*<.0001 ‡<.0001 §<.0001 ‖<.0001

F = female; M = male.
Superscripts *, ‡, §, ‖, and # indicate significant differences between groups, with statistics specified in the far-right column.
[a] The Smokerlyzer measures carbon monoxide in the breath as parts per million (ppm), with seven levels of reading that each represents a range of ppm (level 1 = 0–6 ppm [nonsmoker]; level 7 = >51 ppm [heavy smoker]).
[b] The NicAlert Test measures urinary cotinine concentration (in ng/mL), with seven levels of reading that each represents a range of ng/mL (level 0 = 0–10 ng/mL [nonsmoker]; level 6 = >1,000 ng/mL [heavy smoker]).

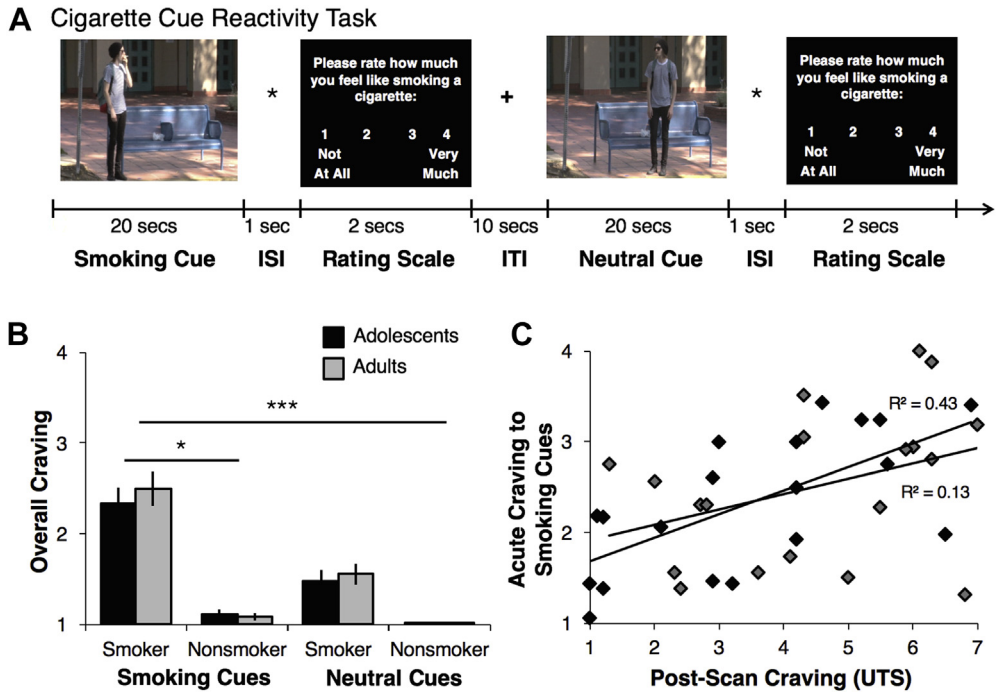

Figure 1. Cues eliciting craving in smokers. (A) Examples of a smoking cue trial and neutral cue trial. Participants viewed a 20-second video clip before reporting their acute craving on a Likert scale. [Note that the actual scale participants viewed during the scan contained the following: (1) It did not make me feel like smoking; (2) It kind of made me feel like smoking; (3) It really made me feel like smoking; (4) It really made me feel like smoking right now.] (B) Smokers reported greater craving to smoking versus neutral cues and nonsmokers reported no craving differences to either cue. (C) Cue-induced craving was significantly associated with urge to smoke following the scan in adolescent smokers. Error bars represent standard error. ISI = Interstimulus interval; ITI = Intertrial interval; UTS = Urge to Smoke. *p<.05; **p<.01; ***p<.001.

adolescents in naturalistic settings (e.g., waiting at a bus stop), whereas smoking cue videos matched neutral cue videos for setting but also included the same actors smoking a cigarette (e.g., waiting at a bus stop while smoking a cigarette). Both age groups viewed the same set of videos, which were presented randomly. Following presentation of each video cue, participants provided a rating of cigarette craving on a Likert scale of 1–4 (Figure 1A). Craving ratings were averaged by cue type for group comparisons. Response times of craving ratings to the cues were also recorded.

Behavioral data analysis

A series of repeated-measures analyses of variance (ANOVAs) with age group and smoking group as between-subject factors were conducted in IBM Statistical Package of the Social Science (IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, version 22.0., IBM Corp, Armonk, NY). Socioeconomic status (measured by maternal education), gender, hours since last cigarette, smoking duration, cigarettes per day, and revised Fagerstrom dependence scores were controlled in behavioral analyses. Outliers (beyond two SDs of the mean) were excluded from statistical analyses (n = 2).

Magnetic resonance imaging data acquisition, processing, and analysis

Scanning was performed on a 3T Siemens Trio MRI scanner. Imaging data were preprocessed and analyzed using FMRIB Software Library (www.fmrib.ox.ac.uk/fsl). We analyzed our data to focus on the Blood Oxygenation Level Dependent (BOLD) signal, which primarily corresponds to the concentration of blood flow. The BOLD effect is based on the fact that when neuronal activity is increased in one brain region, there is also an increased amount of cerebral blood flow to that area. Specifically, fMRI analyses commonly focus on "contrasts" which refers to the contrast in BOLD signal in one condition versus BOLD signal in another condition (or a baseline condition). Four contrasts of interest were modeled: smoking > baseline, neutral > baseline, smoking > neutral, and neutral > smoking. In the present study, we focused on activation observed in the smoking > neutral contrast.

Our primary aim in this study was to examine the effects of smoking versus neutral cues on key nodes in the mesolimbic system in the adolescent brain. First, we performed a voxelwise analysis across all participants with the expectation that two a priori regions of interest (ROIs), the nucleus accumbens (NAcc) component of the VS and DLPFC, would show activation to the smoking > neutral contrast. Next, we extracted the peak signals from the VS and DLPFC for subsequent ROI analyses. See Appendix for details on MRI parameters, processing, and modeling.

Psychophysiological interaction analysis

A psychophysiological interaction (PPI) analysis [28] was conducted to determine whether craving during the fMRI task related to functional coupling (strong correlation of activation patterns between two regions) between regions involved in craving regulation and the VS. We defined the seed region, defined as the region

of most interest, for the PPI analysis as the bilateral NAcc (8, 12, −6; −8, 12, −6) using a 4-mm anatomical sphere from the Harvard–Oxford probabilistic atlas in FMRIB Software Library. See Appendix for additional details on PPI modeling.

Results

Behavioral results

There was a significant main effect of cue type [$F(1, 29) = 4.21$, $p = .05$] and a significant cue type × smoking group interaction on craving [$F(1, 29) = 50.19$, $p < .0001$]. Participants reported more craving during smoking ($M = 1.75$, SD = .88) versus neutral cues ($M = 1.26$, SD = .44), with higher craving reports by smokers ($M = 2.42$, SD = .80) compared to nonsmokers ($M = 1.10$, SD = .21) during smoking cues compared to neutral cues (Figure 1B). There were no main effects of age group or significant interactions with age group.

There was a significant main effect of smoking group on baseline craving, where smokers ($M = 4.13$, SD = 1.53) versus nonsmokers ($M = 1.08$, SD = .28) reported higher baseline craving [$F(1, 30) = 15.57$, $p < .0001$]. Post hoc tests showed no significant differences in prescan craving between adolescent ($M = 3.80$, SD = 1.52) and adult ($M = 4.44$, SD = 1.52) smokers. There was also a significant main effect of smoking group on postscan craving, such that smokers ($M = 4.05$, SD = 1.94) reported significantly higher craving ratings relative to nonsmokers ($M = 1.02$, SD = .06) [$F(1, 30) = 27.00$, $p < .0001$]. Craving ratings to smoking cues were correlated with postscan ratings for smokers ($r = .52$, $p = .001$), an effect driven by the adolescent smokers ($r = .66$, $p = .002$; adult smokers, $r = .36$, $p = .13$; Figure 1C). Ratings to neutral cues were correlated with postscan ratings for adolescent smokers only ($r = .56$, $p = .01$). Change in craving rating was a difference score calculated by subtracting the mean average of prescan craving from the mean average craving following the fMRI task. There were no significant differences between adolescent ($M = .07$, SD = 1.64) and adult ($M = .41$, SD = 1.31) smokers in overall change in craving levels.

Functional magnetic resonance imaging results

Our first analysis examined the main effects of smoking and neutral videos. Whole-brain analyses show that both smoking and neutral videos activated several frontolimbic regions (Supplementary Table 2 lists significant regions). Because the present study focused on the effects of smoking cues on regions that are implicated in craving and which undergo the most adolescent neurodevelopment, the remaining analyses were conducted within a priori ROIs.

Based on the whole-brain analyses for the smoking > neutral contrast, we used an ROI approach to extract the parameter estimates with the highest *z*-statistic from two a priori regions: the NAcc (−10, 20, −4; $z = 2.89$) and DLPFC (30, 46, 32; $z = 3.75$). There was a significant main effect of smoking group on NAcc activation, with less NAcc activation exhibited by smokers ($M = -.003$, SD = .03) compared to nonsmokers ($M = .01$, SD = .02) to the smoking versus neutral cues contrast [$F(1, 30) = 7.29$, $p = .01$]. There was no significant main effect of age group. An age group × smoking group interaction revealed greater NAcc activation in adolescent smokers ($M = .007$, SD = .04) relative to adult smokers ($M = -.01$, SD = .02) [$F(1, 37) = 3.84$, $p = .05$; Figure 2A].

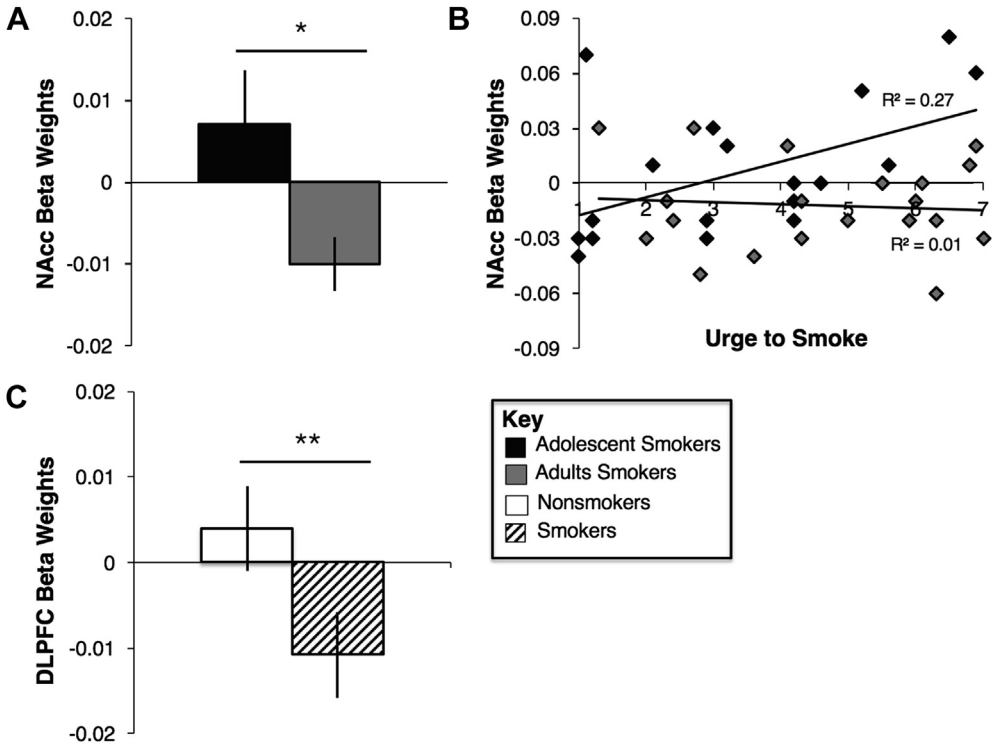

Figure 2. Neural activation in response to smoking versus neutral cues. (A) Adolescent smokers exhibited significantly greater nucleus accumbens (NAcc) activation than adult smokers (−10, 20, −4; $z = 3.89$). (B) Greater NAcc activation was associated with subsequent urges to smoke. (C) Nonsmokers exhibited significantly greater activation than smokers in dorsolateral prefrontal cortex (DLPFC; 30, 46, 32; $z = 3.57$). Error bars represent standard error.
*p<.05; **p<.01.

NAcc activation was not correlated with hours since last cigarette or prescan craving.

A significant main effect of smoking group on activation in the DLPFC revealed that smokers ($M = -.015$, SD = .04) showed less DLPFC activation than nonsmokers ($M = .0098$, SD = .03) to smoking versus neutral cues [$F(1, 30) = 8.88$, $p = .004$; Figure 2C]. There was no main effect of age group or interactions on DLPFC activation. Greater DLPFC activation was correlated with lower baseline craving and lower craving to the smoking cues and were driven by the nonsmokers (baseline craving: $r = -.38$, $p < .001$; craving to smoking cues: $r = -.44$, $p = .01$), which means nonsmokers showed a stronger correlation between DLPFC and craving than smokers. In smokers, greater DLPFC activation was also significantly correlated with higher changes in craving scores ($r = .36$, $p = .02$), an effect driven by the adolescent smokers (adolescent smokers: $r = .24$, $p = .04$; adult smokers: $r = .19$, $p = .42$). DLPFC activation was not related to prescan or postscan craving, daily cigarette use, hours since last cigarette, or Fagerstrom scores.

To further investigate whether greater cue sensitivity in adolescent smokers was also predictive of cue-related and postscan craving, NAcc activation was regressed onto cue-induced craving and postscan ratings. For adolescent smokers only, greater NAcc activation significantly correlated with higher postscan ratings following the scan ($r = .53$, $p = .02$) (Figure 2B) and a trend toward greater acute craving to smoking cues ($r = .44$, $p = .06$).

We next conducted mediation analyses using a series of regressions to determine whether NAcc activation mediated the relationship between self-rated craving to the smoking videos and greater change in craving scores (from prescan to postscan). For adolescent smokers, the relationship between smoking cue-induced craving reports and change in craving scores was mediated by NAcc activation (Figure 3A). NAcc activation showed significant relationships with both cue-induced craving ($\beta = .71$, $p = .001$) and change in craving scores ($\beta = .57$, $p = .05$). The standardized β coefficient between acute craving to the smoking cues and change in craving scores ($\beta = .36$, $p = .01$) significantly decreased when controlling for NAcc activation in adolescent smokers ($\beta = .20$, $p = .46$). A Sobel test [29] confirmed that NAcc activation mediated the relationship between reported craving during the scan to smoking cues and changes in pre-to-post urges to smoke among adolescent smokers ($Z = 1.85$, $p = .05$). These mediation effects were not observed among adult smokers (Figure 3B), nor were they significant for neutral cues in either group.

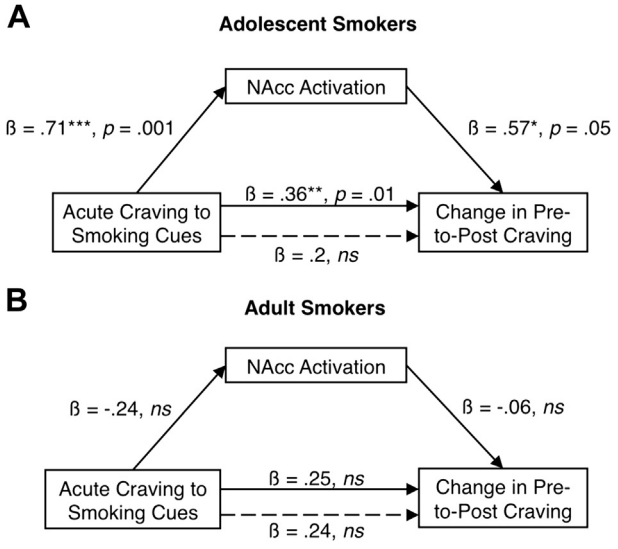

Figure 3. (A) Nucleus accumbens (NAcc) activation mediated the relationship between acute craving to smoking cues and pre-to-post scan craving levels in adolescent smokers. (B) This association was not observed in adult smokers. *$p<.05$; **$p<.01$; ***$p<.001$.

To further probe a possible mechanism for the relationship between NAcc activation and postscan craving, we conducted a post hoc PPI analysis using the NAcc as a seed region (Figure 4A). Because NAcc activation only mediated the relationship between acute craving to smoking cues and change in pre-to-post craving for adolescent smokers, we restricted the analyses to this group. Craving ratings to the smoking > neutral cues was associated with increased functional coupling between the NAcc and multiple cortical regions (Figure 4B; see Appendix for a complete list of regions), which included the superior parietal lobule (24, −52, 48, $z = 3.90$) and paracingulate cortex (2, −12, 38, $z = 2.95$). Next, we investigated how functional coupling between the NAcc and these cortical regions related to craving ratings from adolescent smokers but only observed the following effects: increased functional coupling between the NAcc and superior parietal lobule was marginally associated with cue-induced craving to smoking cues ($r = .40$, $p = .09$; Figure 4C) and increased functional coupling between the NAcc and paracingulate cortex was related to slower reaction times in response to smoking ($r = -.51$, $p = .03$) and neutral cues ($r = -.43$, $p = .07$).

Discussion

The goal of this study was to characterize neural correlates of cigarette craving in adolescent smokers and to determine if the adolescent brain is more responsive to cigarette cues than adults. The findings reveal four novel advancements to this understudied question: (1) adolescent smokers report the same level of craving in response to cigarette cues as adult smokers, despite having a significantly shorter history of smoking; (2) exposure to smoking cues predicts changes in subsequent smoking urges in adolescents; (3) VS activation mediates the relationship between acute craving during the cues and change in craving levels from pre-to-post cue exposure in adolescent smokers only; and (4) functional coupling between striatal and cortical regions is associated with increased craving in adolescent smokers.

In the present study, smoking cue-induced craving was paralleled with greater activation of the VS in adolescent versus adult smokers and reduced activation of the DLPFC in smokers versus nonsmokers. The data also highlight individual differences in smoking behaviors that may arise from an imbalance between reward-related and cognitive control systems in adolescence, such that adolescent smokers' VS activation mediates the relationship between acute craving to smoking cues and the change in subsequent urges to smoke and was predictive of increased functional coupling between the VS and frontal regions. Thus, the developing brain may render adolescents, relative to adults, especially responsive to smoking stimuli.

Compared to nonsmokers, adolescent and adult smokers reported greater craving in response to smoking cues. The similarity in smoking cue-induced craving supports a recent finding which found little discrimination between occasional and daily adolescent smokers in cue-induced craving [11], suggesting that adolescent and adult smokers may endorse similar craving

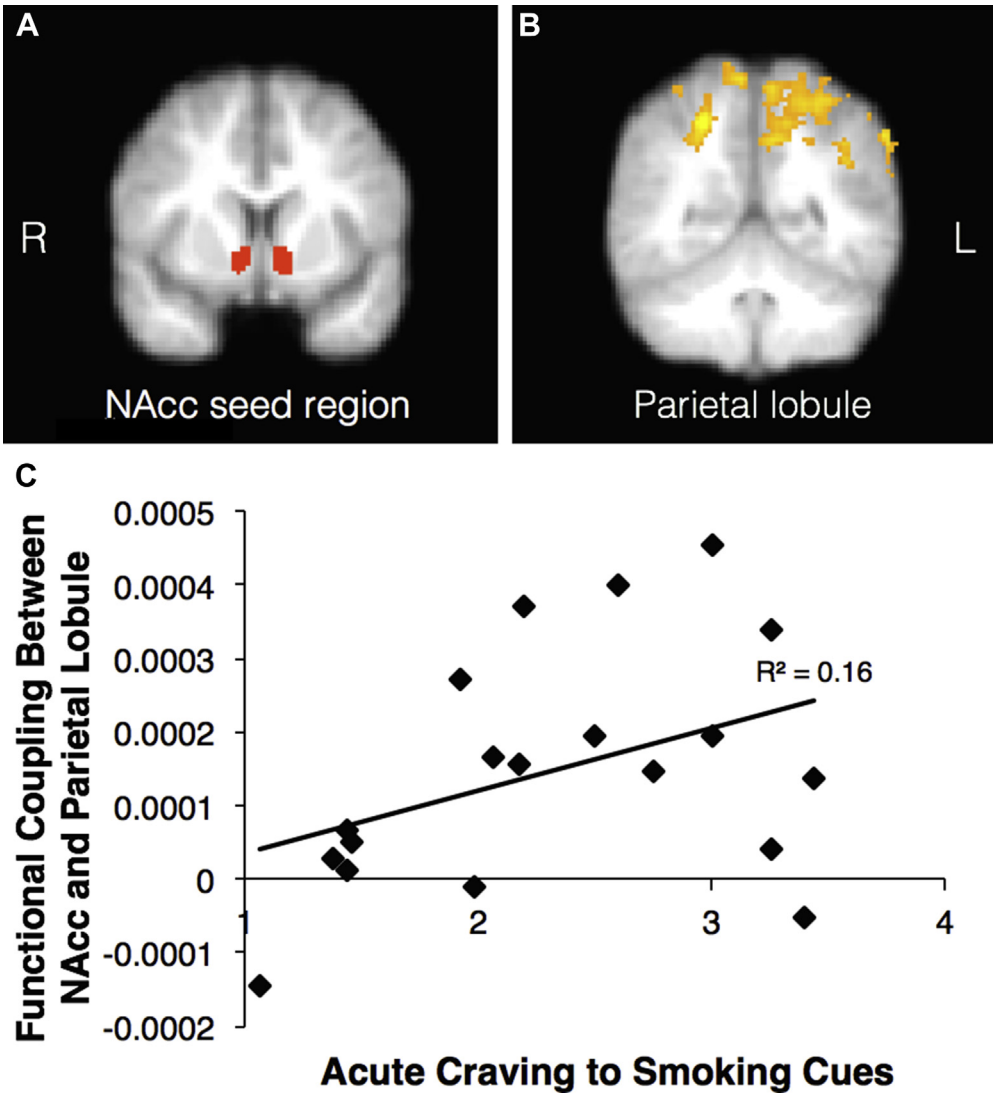

Figure 4. Parietal–striatal functional connectivity to cues is associated with craving in adolescent smokers. (A) The seed region was defined as a 4-mm sphere centered in the nucleus accumbens (NAcc) based on an anatomical sphere from the Harvard–Oxford probabilistic atlas in FMRIB Software Library. (B) Psychophysiological interaction analyses reveal increased functional coupling between the NAcc and multiple cortical regions, including the parietal lobule shown here, for adolescent smokers following smoking vs. neutral cues. (C) Increased coupling between the NAcc and parietal lobe was positively correlated with greater acute craving to smoking cues in adolescent smokers. Note: Right = left.

patterns regardless of nicotine dependence severity. Understanding this relationship is important as increased craving levels in response to smoking cues can lead to difficulty with cessation attempts and relapse in smokers [30,31]. Thus, these findings highlight adolescence as a critical period to target cessation efforts.

Cue exposure has consistently been associated with increases in craving and VS activity [12,32,33]. Our findings further suggest that the relationship between acute craving to smoking cues and subsequent changes in craving levels is mediated by activation of the VS in response to smoking cues in adolescent smokers only; these effects may not be observed in adult smokers because the smoking cues (featuring young smokers) were not as engaging for them. This relationship highlights how impactful exposure to smoking stimuli can be on eliciting neural activity during adolescence relative to adulthood, which may increase reward sensitivity and influence youth toward initiating tobacco use.

In response to smoking versus neutral cues, smokers exhibited diminished DLPFC activation compared to nonsmokers; this neural activation was positively correlated with higher changes in pre-to-post craving scores, an effect driven by adolescent smokers. These findings are intriguing in light of two previous findings. First, a previous study reported that the DLPFC helped cigarette smokers regulate their self-reported cigarette craving, which was based on the observation that those who exhibited decreased VS activation and increased DLPFC activation evinced greater decreases in craving [23]. Other studies have also found that the prefrontal–striatal pathway is involved in the control of craving and habitual use of drugs [17,34]. Second, the DLPFC shows a protracted neurodevelopmental trajectory that persists through adolescence and into early adulthood [35], a

phenomenon that renders adolescents less adept than adults at regulating limbic-based urges [36]. These two findings suggest that the region individuals need most for successful inhibition of craving (the DLPFC) is not yet fully engaged during adolescence, which may preclude effective craving regulation in adolescent smokers. Indeed, our findings underscore the meaningful relationship between frontostriatal circuitry and craving that together predict subsequent smoking urges.

Acute craving to smoking cues was also associated with increased functional coupling between the VS and cortical circuitry (i.e., strong correlation between activation in the VS and activation in the cortex), which included the DLPFC, superior parietal lobule, and motor cortices. Previous research delineating this frontoparietal network reveals that the automaticity of smoking behaviors is attributed to subconscious imitation triggered by smoking stimuli [37]. Wagner et al. found greater cue-related activity in frontal regions implicated in planning manual actions. Similarly, increased functional coupling between the VS and superior parietal lobe predicted greater craving following smoking cues in the present study [38], suggesting that action representation acquired while viewing others' smoking inspired later feelings of "wanting a cigarette."

A major strength of this study is its examination of individual differences in cigarette craving and neural sensitivity to smoking cues and ontogenetic differences between adolescent and adult smokers. However, a few limitations are noted. One limitation is that participants were not instructed to refrain from smoking beforehand, which may lead to variability in the last cigarette smoked and initial craving levels. However, both time since last cigarette and prescan craving were not related to neural activity to the cues for adolescent or adult smokers. In addition, there were ethnic and sex differences in our sample; yet, these were consonant with the demographic makeup of our target recruitment sites (i.e., greater Los Angeles). Because it is challenging to recruit a large sample of smokers for an fMRI study who do not present with comorbid substance use, we did not have exclusion criteria for ethnicity or sex. However, these group differences are consistent with the literature, such that higher smoking prevalence is typically found in males [4,39] and ethnic minority groups [40], with greater daily cigarette consumption and smoking dependence found in adult smokers [39]. Additionally, the statistically significant differences in craving between neutral and smoking cues were admittedly modest so the clinical application warrants a replication study and further investigation. Finally, one alternative explanation of the results is that they reflect neural desensitization in adults (as long-time and heavier users) rather than hypersensitivity in youth.

In conclusion, our data offer further evidence that neurobiological responses to cigarette cues underlie individual and developmental differences in subsequent smoking urges between adolescent and adult smokers. The finding that VS activity mediated the effect of smoking cue-induced craving and changes in pre-to-post craving was restricted to adolescent smokers, which underlines the importance of targeting efforts toward reducing smoking initiation during this highly sensitive developmental window.

Acknowledgments

The authors thank the participants and helpful comments from members of the Galván Lab.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jadohealth.2015.10.004.

Funding Sources

This work was supported by a grant from the California Tobacco-Related Disease Research Program (#19KT-0026) to AG.

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