Article

Lower Ventral Striatal Activation During Reward Anticipation in Adolescent Smokers

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Objective: Adolescents are particularly vulnerable to addiction, and in the case of smoking, this often leads to long-lasting nicotine dependence. The authors investigated a possible neural mechanism underlying this vulnerability.

Method: Functional MRI was performed during reward anticipation in 43 adolescent smokers and 43 subjects matched on age, gender, and IQ. The authors also assessed group differences in novelty seeking, impulsivity, and reward delay discounting.

Results: In relation to the comparison subjects, the adolescent smokers showed greater reward delay discounting and higher scores for novelty seeking. Neural responses in the ventral striatum during reward anticipation were significantly lower in the smokers than in the comparison subjects, and in the smokers this response was correlated with smoking frequency. Notably, the lower response to reward anticipation in the ventral striatum was also observed in smokers (N=14) who had smoked on fewer than 10 occasions.

Conclusions: The present findings suggest that a lower response to reward anticipation in the ventral striatum may be a vulnerability factor for the development of early nicotine use.

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Adolescents are thought to be particularly vulnerable to addiction (1, 2), and the majority of adult dependent smokers started smoking during adolescence (3). Most functional neuroimaging studies of addiction have focused on cue reactivity, i.e., neural responses during processing of drug-related cues. In such studies, substance abuse is typically associated with an abnormally high response to drug-related cues in regions of the brain's reward circuit, including projection regions of the dopaminergic system, such as the ventral striatum as well as the orbitofrontal and ventromedial prefrontal cortex (4). These effects are also observed in adolescents with alcohol use disorder (5).

Studies examining the processing of nondrug rewards in addiction, on the other hand, have shown *lower* responses in these same regions, an effect that has been observed in smokers (6), alcoholics (7), pathological gamblers (8), and cocaine addicts (9). A low reward-related response in these regions may therefore constitute a risk factor for the development of addiction. Along similar lines, personality traits such as high novelty seeking and low harm avoidance predict early substance abuse (10, 11). In this study we addressed this issue in a large group of 14-year-old adolescent smokers (N=43) and matched comparison subjects (N=43) who were selected from the subject pool of the IMAGEN study, a European multicenter study of reinforcement behavior in adolescence (12). IMAGEN focuses on 14-year-old adolescents to investigate the neurobiological precursors of substance abuse and psychopathology. Specifically, we examined neural responses to reward anticipation, measured by using functional MRI (fMRI), in a modified monetary incentive delay task (13). In addition, we examined a range of behavioral measures of impulsivity.

Method

Characteristics of the Multisite Study

IMAGEN investigates reinforcement-related behavior and its neural and genetic basis in a large group (approximately 2,000) of 14-year-old adolescents. Adolescents were recruited through local public schools at eight sites across Europe (Dresden, Berlin, Mannheim, and Hamburg, Germany; London and Nottingham, U.K.; Dublin, Ireland; and Paris, France). The subjects completed extensive neuropsychological and psychiatric assessments as well as structural and functional neuroimaging at these sites. Additional personality questionnaires were administered for home assessment. Details of these procedures are provided elsewhere (12).

Participants

The adolescent smokers were matched on age, gender, and IQ with comparison subjects from the IMAGEN study group (12). The smokers had smoked at least one cigarette during the last 30 days, whereas the comparison subjects had never smoked a cigarette in their lives. Furthermore, given that the subjects completed extensive behavioral testing and structural neuroimaging under continuous supervision prior to completion of the monetary incentive delay task (as described in the following), the minimum length of abstinence from smoking was around 2 hours in all smokers. No volunteer was taking psychoactive medication.

Personality and Neuropsychological Measures

The subjects were screened for psychiatric disorders with the Development and Well-Being Assessment questionnaire (14). They also completed a range of questionnaires, reinforcement-related tasks, and structural and functional neuroimaging. The details of these procedures are summarized elsewhere (12). For the purpose of the present study, we focused on six measures. The Temperament and Character Inventory (15) and the Substance Use Risk Profile Scale (16) were used to assess novelty seeking and impulsivity. Alcohol use was assessed by using the Alcohol Use Disorders Identification Test (17), and nicotine and cannabis use were assessed with the European School Survey Project on Alcohol and Drugs questionnaires (18). For nicotine use, we also applied the Fagerström Test for Nicotine Dependence (19). An estimate of IQ was obtained for each participant by averaging the raw scores of four subtests (similarities, vocabulary, block design, and matrix reasoning) of the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) (20).

Delay Discounting

Delay discounting is the subjective (discounted) valuation of a future reward based on both its magnitude and its delay; the value typically declines in a hyperbolic manner over time. Delay discounting was assessed by using a previously published questionnaire (21) and consisted of 27 binary choices between a smaller, sooner and a larger, later hypothetical reward. We analyzed these data by applying the softmax choice rule (22),

$$P(o_i) = \frac{e^{(sv_{oi}/\beta)}}{e^{(sv_{o1}/\beta)} + e^{(sv_{o2}/\beta)}},$$

to estimate the probability of choosing the selected option (o_i) in a trial, given the values of the available options (sv_{o1} and sv_{o2}, corresponding to the smaller/sooner reward and the larger/later reward). The β parameter in this model describes the stochasticity in the subjects' choice behavior, corresponding to the steepness of the sigmoid function. The subjective value (SV) of each option was modeled by using the hyperbolic model of delay discounting (23):

$$SV = \frac{A}{(1 + kD)}.$$

In this model, A is the amount of the delayed reward, D is the delay in days, and k is a subject-specific discount rate. The best-fitting model parameters (k and β) were derived by maximum likelihood estimation (22) implemented by using MATLAB (MathWorks, Natick, Mass.) optimization functions. Discount rates were log transformed before the statistical analyses to account for their highly skewed distribution. High discount rates reflect steep discounting and impatient or impulsive choice behavior, whereas lower discount rates correspond to patient, more future-oriented preferences.

Modified Monetary Incentive Delay Task

The participants performed a modified version of a monetary incentive delay task (24). In short, each trial involved an anticipation phase, a response phase, a feedback phase, and a fixation period. During the anticipation phase, cues signaling the amount of reward that could be won in a given trial (large, small, or none) were shown for 4 seconds. The subject could win large or small numbers of points (10 or 2) by responding as quickly as possible to a response cue. The points were converted to food snacks (small chocolate candies) following testing (5 points per candy). The subject completed 22 trials per condition, yielding 66 trials in total. One cue (circle with two lines) signaled that a large reward could be won, another (circle with one line) signaled that a small reward could be won, and a third cue (triangle) signaled that no reward could be won in the respective trial. Following a random time interval, a response cue was displayed, and the subject was instructed to respond as quickly as possible to this cue by means of a button press. The time window in which responses were counted as "wins" was adjusted dynamically during the course of the experiment according to the subject's performance, such that on average the subject won in 66% of all trials. The response and feedback phases had a total duration of 2 seconds. Four seconds of intertrial fixation separated the trials.

Analysis of Behavioral Data

All group comparisons were conducted by using two-sample t tests with a two-tailed significance level of $p<0.05$. In the case of multiple subscales from the same test, correction for multiple comparisons was performed by using Bonferroni correction. Behavioral data from the monetary incentive delay task were analyzed by calculating the percentage of successful trials for each condition (large reward, small reward, and no reward). Reaction times were also analyzed for each condition separately. Because of technical problems, reaction times were unavailable for three comparison subjects and seven smokers.

For the correlation of reaction time with ventral striatal activation, we adopted a two-tailed significance level. The correlations of ventral striatal activation with smoking frequency and alcohol use were conducted by using a one-tailed significance level, because we tested the a priori hypothesis of a negative relationship between drug use and striatal activation, based on previous findings linking striatal hyporesponsivity to the severity of addiction (8).

fMRI Data Acquisition

Structural and functional MRI data were acquired by using 3-T MRI scanners from a range of manufacturers (Siemens, Philips, General Electric, Bruker), and the scanning variables were specifically chosen to be compatible with all scanners (12). For the present task, 300 volumes were acquired for each subject. Each volume consisted of 40 slices aligned to the line connecting the anterior-posterior commissure (2.4-mm thickness, 1-mm gap,

TR=2.20 seconds, TE=30 msec), and the total scanning time for the task was 11 minutes.

fMRI Preprocessing and Analysis

All preprocessing and analysis procedures were conducted by using SPM8 (Wellcome Trust Centre for Neuroimaging, London). In the first step, single-subject echo-planar images were coregistered with the T_1 structural image. Functional images were realigned and resliced to the first volume. A first-level model was constructed on the unsmoothed single-subject data by using the following regressors: 1) anticipation of large reward, 2) anticipation of small reward, 3) anticipation of no reward, 4) feedback indicating large reward, 5) feedback indicating small reward, 6) feedback indicating no reward. Each regressor was included twice, once for successful trials, i.e., hits, and once for unsuccessful trials, i.e., misses. Thus, there were a total of 12 regressors. Trials in which subjects failed to respond were modeled as separate error trials. Movement parameters from the realignment procedure were included as covariates in the first-level model for each subject. Next, contrast images of the parameter estimates were created for each subject. In the present investigation, we focused our analysis on the reward anticipation phase, i.e., greater neural responses during anticipation of rewards (pooled over large and small amounts) than during anticipation of no reward.

We created a custom template from the T_1 images of 552 adolescents by using the DARTEL toolbox (25) as implemented in SPM8. Single-subject contrast images were normalized to Montreal Neurological Institute (MNI) space by means of this custom template on the basis of the individual subjects' DARTEL flow fields, and they were smoothed with a 6-mm Gaussian isotropic kernel. The normalized and smoothed single-subject contrast images were then taken to a second-level random effects analysis (two-sample t test of comparison subjects versus smokers). In this analysis, the IQ estimate, gender, total score on the Alcohol Use Disorders Identification Test, and scanning site were included as covariates of no interest. A separate covariate for each site was included, coded 1 for subjects scanned at that site and 0 otherwise. For the reported conjunction analysis, we used a conservative approach (26) that requires that a given voxel exceed the threshold in each of the examined contrasts separately.

We conducted two additional second-level models. First, gender effects and gender-by-group interactions were investigated by means of a full factorial model as implemented in SPM8. In keeping with the two-sample t test approach already described, site, alcohol use score, and IQ were also included as covariates of no interest in this model. Second, we examined whole-brain effects of smoking frequency in a multiple regression model with the covariates gender, IQ, alcohol use score, and smoking frequency.

For all analyses, the threshold was set to $p<0.05$, corrected for family-wise error, by using 12-mm spherical search volumes based on activation peaks reported in previous studies (i.e., independent data). Correction for the ventral striatum was based on a 12-mm sphere centered at x, y, z values of ±14, 8, –8 (27). Correction for the midbrain was based on a 12-mm sphere centered at coordinates ±9, –15, –15 (28). All images are displayed with a threshold of $p<0.001$, uncorrected, with at least 10 contiguous voxels for visualization purposes, and projected onto the mean structural scan of all 552 volunteers who were used for the construction of the DARTEL template.

Results

Personality and Demographic Characteristics

Smoking and neuropsychological characteristics of the participants are listed in Table 1 and Table 2, respectively. Notably, the scores for novelty seeking were significantly higher for the smokers than for the comparison subjects (Table 2 and Figure 1, top). The smokers also preferred smaller-and-sooner rewards over larger-and-later rewards significantly more than the comparison subjects, as reflected in significantly higher delay discount rates (Table 2 and Figure 1, bottom). The groups did not differ on IQ (see Method section for description of this measure) or gender distribution. Cannabis use, on the other hand, was more common in the smokers than in the comparison subjects (Table 1). Also, the smokers scored significantly higher on the Alcohol Use Disorders Identification Test, and the clinical ratings from the Development and Well-Being Assessment revealed a higher estimated probability of psychiatric disorders in the smokers (Table 2).

Behavioral Data

Behavioral data from the monetary incentive delay task are provided in Table 3. No differences in accuracy were observed between the smokers and comparison subjects, but the smokers had slower reactions, in particular for hits.

fMRI Data

No group differences were observed for the feedback period at $p<0.001$, uncorrected, and analysis of the fMRI data therefore focused on the reward anticipation phase. Specifically, we focused on contrasts showing greater responses to the anticipation of gains than to anticipation of no gain (see Method section). Note that we applied normalization to MNI space through a custom template created from a set of 552 T_1 images of 14-year-old adolescents by using DARTEL (25) to account for the fact that standard neuroanatomical templates may be inappropriate for adolescent neuroanatomy. We next analyzed group differences in a two-sample t test second-level model in SPM8; the model included gender, the IQ estimate, the total score on the Alcohol Use Disorders Identification Test, and the scanning site as covariates of no interest.

In this model, we first examined reward anticipation in the smokers and comparison subjects separately. This revealed significant activation in the ventral striatum in both groups. For the comparison subjects (Figure 2A) the peak x, y, and z coordinates (in millimeters) were –9, 5, 1 ($t=10.64$, $df=41$, $p<0.001$, corrected for whole-brain volume), and for the smokers (Figure 2B) the coordinates were –8, 6, 0 ($t=4.02$, $df=41$, $p_{SVC}=0.04$, corrected for small volume; see Method section); for complete fMRI results see Supplementary Tables 1 and 2 in the data supplement accompanying the online version of this article. Next we identified regions of the reward circuit (ventral striatum and midbrain) showing smaller responses to reward anticipation in the smokers than in the comparison subjects (Figure 2C). Smokers showed lower responses to reward anticipation in the left ventral striatum (–9, 3, 1 [$t=4.73$, $df=74$, $p_{SVC}=0.002$]) and a more lateral region of the left putamen (–21, 11, –3 [$t=4.35$, $df=74$, $p_{SVC}=0.006$]). Similar results were observed in

TABLE 1. Cigarette and Cannabis Use by Adolescent Smokers and Matched Comparison Subjects

Characteristic	Comparison Group (N=43)		Smokers (N=43)	
	N		N	
Sex				
Male	24		24	
Female	19		19	
European School Survey Project on Alcohol and Drugs (18)				
Number of lifetime occasions of smoking				
None (score=0)	43		0	
1 or 2 (score=1)	0		2	
3–5 (score=2)	0		5	
6–9 (score=3)	0		7	
10–19 (score=4)	0		4	
20–39 (score=5)	0		4	
40 or more (score=6)	0		21	
Smoking frequency in preceding 30 days				
None (score=0)	43		0	
Less than 1 cigarette per week (score=1)	0		17	
Less than 1 cigarette per day (score=2)	0		10	
1–5 cigarettes per day (score=3)	0		9	
6–10 cigarettes per day (score=4)	0		4	
11–20 cigarettes per day (score=5)	0		2	
More than 20 cigarettes per day (score=6)	0		1	
Number of lifetime occasions of cannabis use				
Never (score=0)	42		29	
1–2 (score=1)	1		4	
3–5 (score=2)	0		4	
6–9 (score=3)	0		2	
10–19 (score=4)	0		1	
20–39 (score=5)	0		1	
40 or more (score=6)	0		2	
Cannabis use frequency in preceding 30 days				
None (score=0)	42		30	
1 or 2 (score=1)	1		6	
3–5 (score=2)	0		2	
6–9 (score=3)	0		3	
10–19 (score=4)	0		0	
20–39 (score=5)	0		1	
40 or more (score=6)	0		1	
	Mean	SD	Mean	SD
Score for lifetime smoking	—		4.53	1.70
Score for smoking in preceding 30 days	—		2.23	1.32
Age at first cigarette (years)			12.67	0.99
Age at beginning of daily smoking (years)			13.35	0.74
Age at first cannabis use (years)	15[a]		13.43	0.94
Score on Fagerström Test for Nicotine Dependence			2.12[b]	—

[a] Only one subject reported any cannabis use.
[b] Range, 0–6.

two locations in the right ventral striatum (8, 17, –3 [t=3.91, df=74, p_{SVC}=0.03] and 8, 9, 0 [t=3.71, df=74, p_{SVC}=0.04]) and one location in the more lateral right putamen (18, 11, 3 [t=3.70, df=74, p_{SVC}=0.04]). A region in the right midbrain showed a similar pattern but did not survive small-volume correction (–10, –15, –15 [t=3.34, df=74, p_{SVC}=0.74]).

For completeness, we also performed an exploratory test for gender-by-group interactions, using an additional 2×2 full factorial second-level model, with gender (male or female) and group (smoker or comparison) (see Method section). Although the lower ventral striatal responses in the smokers appeared to be somewhat more pronounced in boys than girls, this interaction effect did not survive correction for multiple comparisons across the ventral striatum region of interest (p=0.08).

These findings raise the obvious question of whether lower striatal responses are the consequence or cause of smoking. We therefore next examined a subset of smokers with extremely mild smoking habits, i.e., fewer than 10 total lifetime occasions of smoking. Even in these very mild

TABLE 2. Neuropsychological Characteristics of Adolescent Smokers and Matched Comparison Subjects

Characteristic	Comparison Subjects (N=43)		Smokers (N=43)		Difference Between Groups
	Mean	SD	Mean	SD	p[a]
Temperament and Character Inventory (15) scores					
Novelty seeking (total)	108.6	12.04	121.98	10.16	<0.000001[b]
Subscales					
Exploratory excitability	33.20	4.02	34.28	4.06	0.22
Impulsivity	26.09	4.23	30.00	4.10	<0.00001[b]
Extravagance	27.34	5.47	33.02	4.67	<0.00001[b]
Disorderliness	21.98	4.26	24.67	3.20	0.002[b]
Substance Use Risk Profile Scale (16) scores					
Anxiety sensitivity	11.28	2.32	11.02	1.90	0.58
Negative thinking	13.42	2.50	14.56	2.63	0.05
Impulsivity	11.68	2.46	13.10	1.80	0.004[b]
Sensation seeking	13.58	3.00	13.72	2.75	0.82
Alcohol Use Disorders Identification Test (17) total score	1.34	2.34	6.00	3.98	<0.00001[b]
Delay discount rate (21) (log transformed)	–2.07	0.69	–1.74	0.44	0.02[b]
Wechsler Intelligence Scale for Children (WISC-IV) (20)					
IQ estimate (average of subscale scores)	40.01	7.97	37.88	7.78	0.42
Subscale scores					
Similarities	31.05	7.15	29.19	7.18	0.23
Vocabulary	51.28	11.25	49.37	10.96	0.43
Block design	50.47	13.28	57.37	12.01	0.26
Matrix reasoning	27.26	5.48	25.60	5.48	0.17
	N		N		
Development and Well-Being Assessment (14) estimated probability of any psychiatric disorder					
None	6		10		
~0.2%	35		21		
~2%	0		4		
~20%	2		8		
~75%	0		0		

[a] Two-sample t test, two-tailed.
[b] Significant group difference after Bonferroni correction for multiple comparisons (for multiple subscales from the same test).

smokers, in whom an alteration of reward processing due to chronic nicotine use is extremely unlikely, the left striatal reward anticipation response was still significantly attenuated (two-sample t test at the peak voxel in the left ventral striatum: p=0.02, Figure 2D). The same was true for the non-cannabis-using subgroup of the smokers (p=0.003, Figure 2D). We also examined responses in this region in a subset of smokers matched to the comparison subjects on scores on the Alcohol Use Disorders Identification Test (mean total score=2.42, SD=1.46; paired t test of difference between groups: p>0.07). The smokers matched for alcohol use also showed significantly less ventral striatal activation than the comparison subjects (p<0.001, Figure 2D).

In the next step, we examined the relationship between smoking frequency and reward-anticipation responses in these regions in the smoker group. Smoking frequency scores were calculated by averaging the scores from the European School Survey Project on Alcohol and Drugs questionnaires (18) for recent smoking frequency (over the last 30 days) and lifetime smoking frequency, two measures that were highly correlated in our group of 43 smokers (r=0.55, p=0.0001). fMRI activity in all left striatal regions showed negative correlations with smoking frequency (left ventral striatum: r=–0.23, p=0.054; left putamen: r=–0.41, p=0.004; Figure 2C). These correlations were still significant when subjects with a history of cannabis use (N=14) were excluded from the smokers group (left ventral striatum: r=–0.32, p=0.05; left putamen: r=–0.43, p=0.01). Similar correlations with smoking frequency were observed in the right striatum (right ventral striatum, two clusters: r=–0.20, p=0.10; r=–0.25, p=0.06; right putamen: r=–0.23, p=0.07), linking hypoactivation of these regions to the frequency of nicotine use. For completeness, we report results from a whole-brain analysis (see Method section) of the correlation with smoking frequency in the smokers group in the online Supplementary Table 3.

Finally, we formally tested for a present but low reward anticipation signal in the smokers, performing a triple conjunction analysis testing for regions exhibiting main effects of reward anticipation in each group separately but also showing a significant attenuation in the smokers (p<0.001, uncorrected for each contrast). Only the left ventral striatum showed this pattern (coordinates –8, 5, 1; t=3.71, df=74, p_{SCV}=0.04; Figure 3A). Furthermore, this

TABLE 3. Performance on a Monetary Incentive Delay Task[a] by Adolescent Smokers and Matched Comparison Subjects

Performance Variable	Comparison Subjects (N=43)[b]		Smokers (N=43)[b]		Two-Sample t Test, Two-Tailed (p)
	Mean	SD	Mean	SD	
Percentage of hits					
Large reward	70.09	9.04	67.86	7.84	0.10
Small reward	69.56	9.01	68.39	9.56	0.57
No reward	52.22	13.32	50.95	16.04	0.70
Reaction time (msec)					
Hits					
Large reward	226.3	25.0	241.1	24.7	0.02
Small reward	228.8	25.9	243.4	24.1	0.01
No reward	234.7	29.5	247.7	24.0	0.04
Misses					
Large reward	283.0	69.1	318.1	71.8	0.04
Small reward	296.9	74.0	319.6	65.1	0.17
No reward	327.6	78.3	350.3	54.0	0.16

[a] Modified version of a task described by Knutson et al. (24).
[b] Reaction times were unavailable for three comparison subjects and seven smokers.

region showed the same pattern as the ventral striatal peak in the group comparison discussed earlier, i.e., lower responses in the smokers were also observed when cannabis users were excluded (p=0.04), when subjects were matched for alcohol use (p=0.003), and when only mild smokers were included (p=0.06).

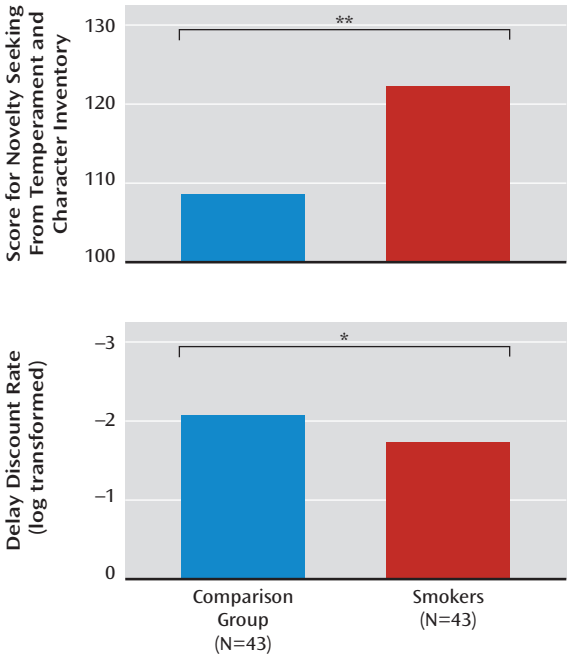
Brain-Behavior Correlations

In light of the observed differences in reaction times between groups, we correlated individual responses to reward anticipation in the ventral striatum (at the peak of the triple conjunction) with individual differences in reaction times. There was a negative correlation of ventral striatal activation with reaction time, such that faster-responding subjects showed greater ventral striatal activation. The correlations were similar in the two groups, and the relationships between activation and reaction times for hits are shown in Figure 3B; the correlation fell short of significance in the comparison subjects. Similar correlations were observed in analyses using mean reaction times for misses and for overall reaction times (data not shown).

Discussion

We examined impulsivity and neural responses to reward anticipation in a large group of 14-year-old smokers and strictly matched comparison subjects to examine neurocognitive correlates of early substance abuse. Previous studies have shown low neural responses during the processing of nondrug rewards in addiction in adult subjects (6–9), and we have now replicated this finding in a large group of adolescent smokers. The smokers showed markedly smaller neural responses during reward anticipation in the ventral striatum and midbrain. Furthermore, in all of these regions the response was significantly correlated with the frequency of nicotine use, such that frequent smokers showed a greater response reduction than mild

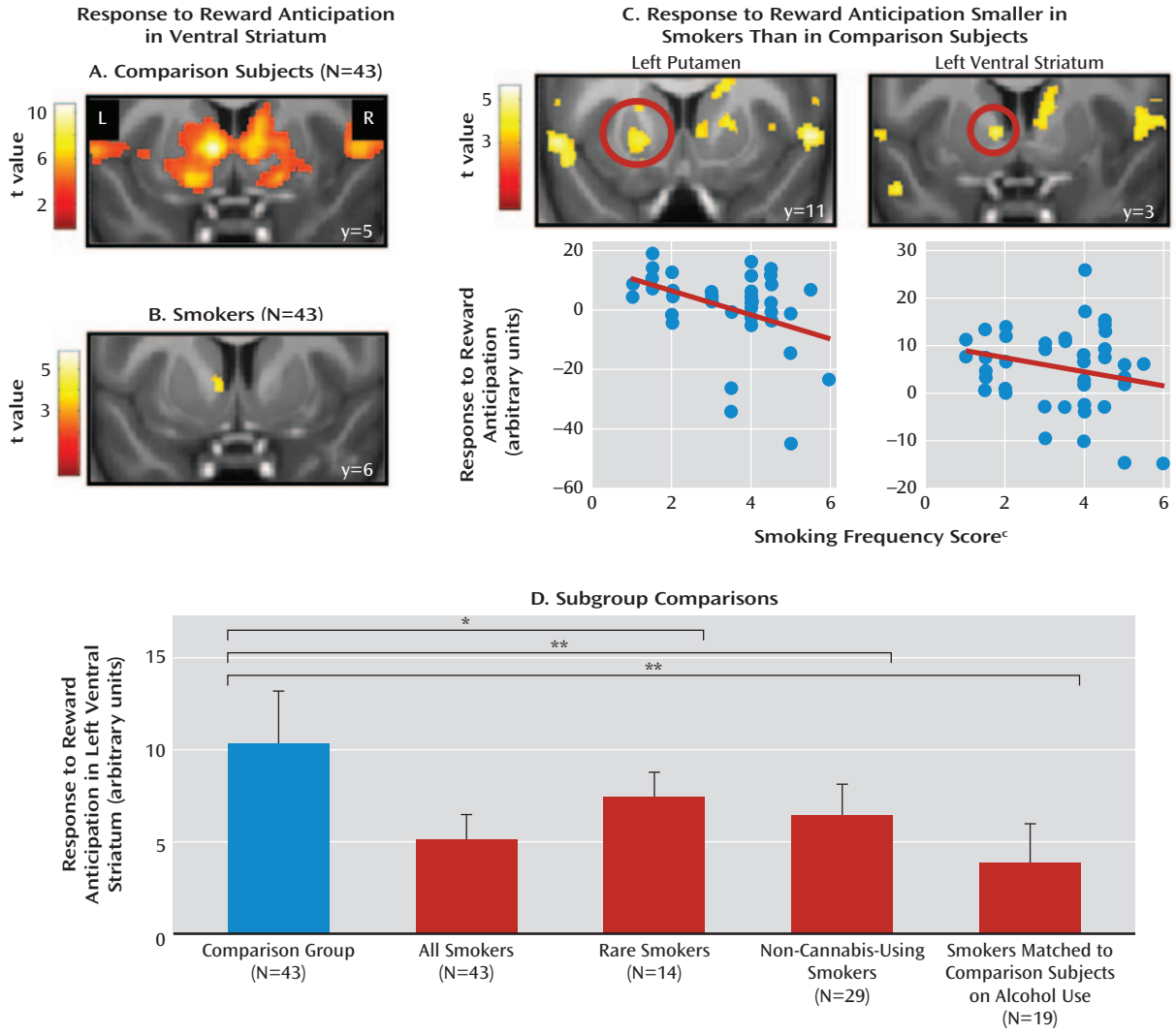
FIGURE 1. Scores for Novelty Seeking and Discounting of Delayed Rewards[a] in Adolescent Smokers and Matched Comparison Subjects[b]



[a] Discount rates were log transformed to account for their skewed distribution.
[b] Differences between groups were analyzed with two-sample t tests, two-tailed.
* p=0.02. **p<0.001.

smokers. Regarding the personality profile of adolescent smokers, we replicated two major findings. First, relative to comparison subjects, smokers in the present study showed significantly more novelty seeking (15), a measure that has previously been shown to predict the degree of substance use in adolescence (11). We also found that adolescent smokers, like adult smokers, discount delayed rewards more steeply than do comparison subjects (29, 30).

FIGURE 2. Response to Reward Anticipation[a] in the Striatum of Adolescent Smokers and Matched Comparison Subjects[b]



[a] fMRI activation that was greater in response to anticipation of a reward than in response to anticipation of no reward. The display threshold was set to p<0.001, uncorrected, with at least 10 contiguous voxels.

[b] Both the comparison subjects (A) and smokers (B) showed reward-anticipation-related activation in the ventral striatum. Relative to the comparison subjects, the smokers showed less reward-related activity in the striatum (C), including the left putamen and left ventral striatum. In the smokers, reward-related activity was negatively correlated with smoking frequency in the left putamen (r=–0.41, p=0.004), and the correlation for the left ventral striatum was nearly significant (r=–0.23, p=0.07); see text for further results. At the striatal peak voxel in the group comparisons (D), responses were also significantly attenuated in the individuals who smoked only rarely, smokers who did not use cannabis, and a subgroup of smokers who were matched to comparison subjects on alcohol use (analyses conducted with two-group t tests, two-tailed).

[c] Average of scores on the European School Survey Project on Alcohol and Drugs questionnaires (18) for recent smoking (in past 30 days) and lifetime smoking.

*p<0.05. **p<0.005.

Our results are striking, as most of the smokers showed relatively mild smoking habits and did not meet the formal criteria for nicotine dependence. For example, only eight subjects had scores above 0 on the Fagerström Test for Nicotine Dependence (19), and the maximum score that was observed was 6 (out of a possible 10). This appears to contrast with previous findings, which suggested that adolescents may exhibit a particular vulnerability to addiction (1, 2). However, the mean age at the first cigarette use was 12.67 years (range=11–14). Therefore, given that all subjects were 14 years old, one possibility is that more time may be required for addiction to develop sufficiently to be reflected in higher Fagerström scores. More important, the aim of the present study was to assess the neurobiological precursors of early substance abuse, rather than addiction per se.

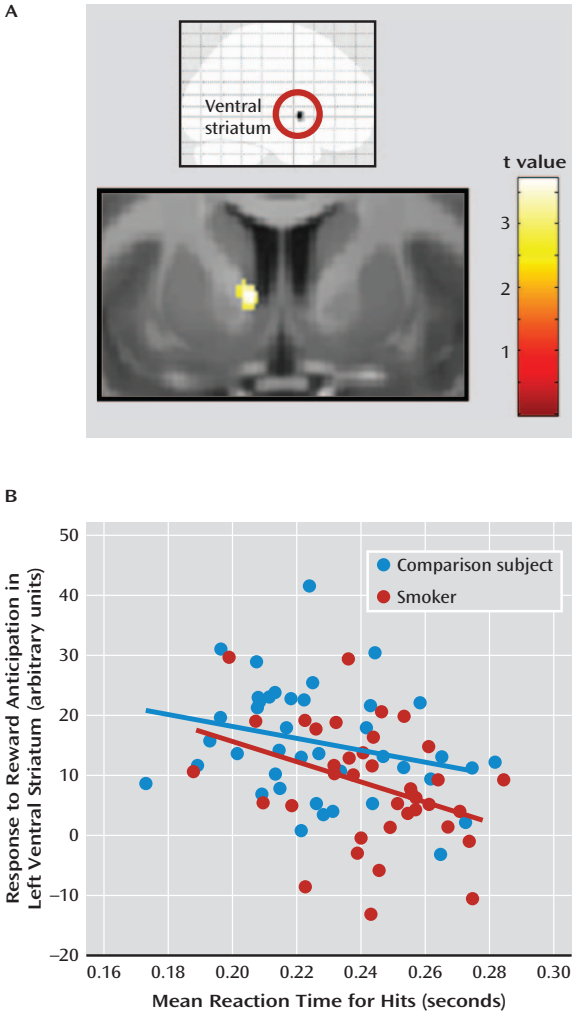
Nonetheless, even when we restricted the analysis of the neuroimaging data to extremely mild smokers (with fewer than 10 lifetime occasions of smoking), the ventral striatal hypoactivation during reward anticipation was

still significant. This suggests that adolescent smokers may exhibit low neural responses to reward anticipation, beyond a possible reduction associated with long-term effects of nicotine exposure. Our data therefore suggest that hyporesponsivity of the reward system may increase the likelihood of early nicotine use. The observation that smoking frequency significantly correlates with hypoactivation in the ventral striatum and midbrain additionally suggests either that more frequent smoking further attenuates reward-related activations in these regions or that subjects with a particularly hyporesponsive reward system are more likely to increase their nicotine use. We hope to disentangle these two possibilities in future studies.

Differences in striatal responses between the smokers and comparison subjects were observed during reward anticipation, but no differences emerged during outcome processing (i.e., feedback). In line with this finding are the results of a previous study, in which comparable neural responses occurred in the ventral striatum in smokers and comparison subjects during outcome processing in a sequential investment task (31). In that study, adult smokers showed fictive prediction error responses in the ventral striatum during outcome processing, but in contrast to the comparison subjects, the smokers did not show an effect of these signals on behavior. Normal outcome processing can therefore be observed in smokers in the presence of marked behavioral abnormalities. Furthermore, previous studies of genotype effects on neural reward processing have also demonstrated effects on anticipation but not outcome (32). One speculative possibility would therefore be that anticipatory responses may be more sensitive to interindividual differences.

There are a few limitations of the present study. As would be expected, both alcohol and cannabis use were more frequently observed in the smokers. However, we accounted for these differences in the neuroimaging analyses, and the results remained significant after the exclusion of cannabis-using smokers and after the inclusion of alcohol use scores as a covariate. Second, nicotine use was assessed by using self-report questionnaires only. Because of the extensive behavioral testing and structural neuroimaging, the smokers were abstinent for at least 2 hours before completion of the monetary incentive delay task, but future studies may benefit from controlling for abstinence more directly, for example through the measurement of breath carbon monoxide concentration. Third, additional variance might be introduced through the use of different scanners and the possibility for site-specific differences in instructions or procedures. However, we controlled for site effects in the data analyses, and extensive quality control measures were taken to ensure that data acquisition followed exactly the same procedures at all sites (see also the standard operating procedures of the IMAGEN study, available elsewhere [12]). Finally, because of scanning time constraints, the modified monetary incentive delay task did not include loss cues, and thus valence cannot be dissociated from saliency.

FIGURE 3. Results of a Triple Conjunction Analysis Formally Testing for a Low But Present Neural Response to Reward Anticipation in Adolescent Smokers[a]



[a] The display threshold was set to p<0.005, uncorrected. Only the left ventral striatum showed reward-anticipation-related activity in both the smokers and comparison subjects plus a lower response in the smokers (A). Ventral striatal activity was negatively correlated with the average reaction time for successful trials ("hits") in the smokers (r=–0.37, N=39, p=0.03), and the correlation for the comparison subjects approached significance (r=–0.27, N=41, p=0.10) (B).

In summary, we have shown behaviorally that adolescent smokers exhibit greater temporal discounting and novelty seeking than do nonsmoking comparison subjects. At the neural level, our data reveal smaller reward-anticipation responses in the bilateral ventral striatum in adolescent smokers, which may reflect a risk factor for the development of early substance abuse.

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