Original Investigation

Altered Reward Processing in Adolescents With Prenatal Exposure to Maternal Cigarette Smoking

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IMPORTANCE Higher rates of substance use and dependence have been observed in the offspring of mothers who smoked during pregnancy. Animal studies indicate that prenatal exposure to nicotine alters the development of brain areas related to reward processing, which might be a risk factor for substance use and addiction later in life. However, no study has examined the effect of maternal smoking on the offspring's brain response during reward processing.

OBJECTIVE To determine whether adolescents with prenatal exposure to maternal cigarette smoking differ from their nonexposed peers in the response of the ventral striatum to the anticipation or the receipt of a reward.

DESIGN An observational case-control study.

SETTING Data were obtained from the IMAGEN Study, a European multicenter study of impulsivity, reinforcement sensitivity, and emotional reactivity in adolescents. The IMAGEN sample consists of 2078 healthy adolescents (age range, 13-15 years) recruited from March 1, 2008, through December 31, 2011, in local schools.

PARTICIPANTS We assessed an IMAGEN subsample of 177 adolescents with prenatal exposure to maternal cigarette smoking and 177 nonexposed peers (age range, 13-15 years) matched by sex, maternal educational level, and imaging site.

MAIN OUTCOME AND MEASURE Response to reward in the ventral striatum measured with functional magnetic resonance imaging.

RESULTS In prenatally exposed adolescents, we observed a weaker response in the ventral striatum during reward anticipation (left side, $F = 14.98$ [$P < .001$]; right side, $F = 15.95$ [$P < .001$]) compared with their nonexposed peers. No differences were found regarding the responsivity of the ventral striatum to the receipt of a reward (left side, $F = 0.21$ [$P = .65$]; right side, $F = 0.47$ [$P = .49$]).

CONCLUSIONS The weaker responsivity of the ventral striatum to reward anticipation in prenatally exposed adolescents may represent a risk factor for substance use and development of addiction later in life. This result highlights the need for education and preventive measures to reduce smoking during pregnancy. Future analyses should assess whether prenatally exposed adolescents develop an increased risk for substance use and addiction and which role the reported neuronal differences during reward anticipation plays in this development.

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About 19% of European women[1] and 14% of US women[2] smoke during their pregnancies despite the strong evidence of its association with pregnancy complications, lower birth weight, higher rates of sudden infant death,[3] and behavioral problems, such as conduct disorder and attention-deficit/hyperactivity disorder (ADHD).[4,5] Several studies also show that maternal nicotine dependence is passed on to the exposed children. They begin to smoke earlier and have a 3.0- to 5.5-fold increased risk for substance dependence compared with nonexposed offspring.[6-10] Kandel and colleagues[9] also showed that the association between exposure and subsequent smoking by the child is independent of the mother's postnatal smoking behavior.

Animal research suggests a direct mechanistic link between prenatal exposure and the offspring's substance use. Nicotinic acetylcholine receptors, when activated, regulate brain development by promoting cell replication, differentiation, and apoptosis. Inappropriate stimulation of these receptors by nicotine disrupts the normal course of development,[11] particularly in parts of the dopamine reward system, including its projections to the ventral striatum and frontal lobe (eg, the orbitofrontal cortex).[12] Adolescent rats with prenatal exposure to nicotine show a lower level of dopamine release in the ventral striatum during a nicotine challenge compared with nonexposed animals,[13,14] indicating that gestational nicotine produces long-lasting changes in the reward circuit. Prenatal nicotine exposure has also been shown to have behavioral consequences: exposed adolescent and adult rodents show less motivation for food rewards but more motivation for and higher intake of cocaine compared with nonexposed rodents.[15,16] An exposure effect on subsequent nicotine consumption has been shown only in female rats after nicotine deprivation.[17] These changes in reward behavior—decreased motivation for natural reinforcement and increased attention to substance-related cues—are characteristic of individuals with substance dependence.[18,19]

The effect of prenatal exposure to maternal cigarette smoking on the reward system of the human brain is sparsely studied. Only structural alterations of the reward circuitry have been reported so far. Prenatally exposed adolescents show lower cortical thickness of the orbitofrontal cortex,[20] which correlates with their drug experimentation.[21] In addition, prenatal exposure to maternal cigarette smoking is associated with structural variation in the white matter, including a large number of prefrontal regions.[22,23] The exposure also interacts with a nicotinic receptor gene polymorphism, influencing the volume of the ventral striatum.[24] Ernst et al[25] provided a detailed overview of the behavioral and neural consequences of prenatal nicotine exposure in animals and humans.

Adolescence, in general, is known as a period of increased reward-seeking and risk-taking behaviors (eg, risky driving or drug consumption).[26] To better understand this phenomenon and its underlying neuronal mechanisms, a number of neuroimaging studies have been conducted. Most of these studies focused on the ventral striatum owing to its major role in reward processing.[27] Two controversial theories have been proposed. Some studies comparing adolescents' and adults' neuronal reward processing reported higher ventral striatum responsivity in adolescents.[28-30] This enhanced response to rewards paired with immature prefrontal areas is thought to lead to an increase in reward-seeking behavior without consideration of the possible risks.[31] In contrast, other studies found that adolescents showed weaker response to rewards in the ventral striatum compared with adults.[32,33] Spear[26] hypothesized that adolescents would search for more intense rewards to compensate for this "hyposensitivity" to reward. Explanations for these contradictory findings included the use of different experimental tasks, focusing more on the anticipation or the receipt of rewards or the age span of the adolescents.[34]

Based on previous research, prenatal exposure to maternal cigarette smoking probably leads to persistent modifications of the reward circuitry. This likelihood may become particularly relevant during adolescence when motivational processes undergo substantial normative alterations. However, no study has examined the effect of maternal smoking on the offspring's brain response during reward processing. Based on findings of decreased dopamine response[13,14] and aberrant volume[24] of the ventral striatum, we predicted a weaker brain response to the anticipation and receipt of a reward in adolescents prenatally exposed to maternal cigarette smoking compared with their nonexposed peers. We tested these hypotheses with functional magnetic resonance imaging (fMRI) in a community-based sample of typically developing adolescents.

Methods

Sample

Participants were enrolled in a large European multicenter study (IMAGEN) on impulsivity, reinforcement sensitivity, and emotional reactivity in adolescents. The total sample consists of 2078 adolescents (age range, 13-15 years) recruited in local high schools in 8 participating sites in Germany, the United Kingdom, France, and Ireland from March 1, 2008, through December 31, 2011. Serious medical conditions (eg, diabetes mellitus, rheumatologic disorders, neurological conditions, and developmental conditions), previous head trauma with unconsciousness, and contraindications for MRI were exclusion criteria. All participants and their parents provided informed written assent and consent, respectively. The study protocol was approved by the local ethics committees. An overview of the study and the entire list of inclusion and exclusion criteria can be found in Schumann et al.[35]

Adolescents' exposure was assessed retrospectively using a questionnaire. Parents were asked about the mother's substance use during pregnancy and general characteristics of the pregnancy, birth, and postnatal care. Two hundred seventy-one of the 1909 families who completed the questionnaire (14.2%) indicated that the mother smoked during pregnancy and stated the number of cigarettes smoked per day for each trimester. The final exposed group (n = 177) consisted of all adolescents who completed the reward task and whose mothers smoked at least 1 cigarette per day throughout the entire pregnancy. Adolescents whose mothers smoked during part of the pregnancy only or less than 1 cigarette per day were not in-

Figure 1. Time Course
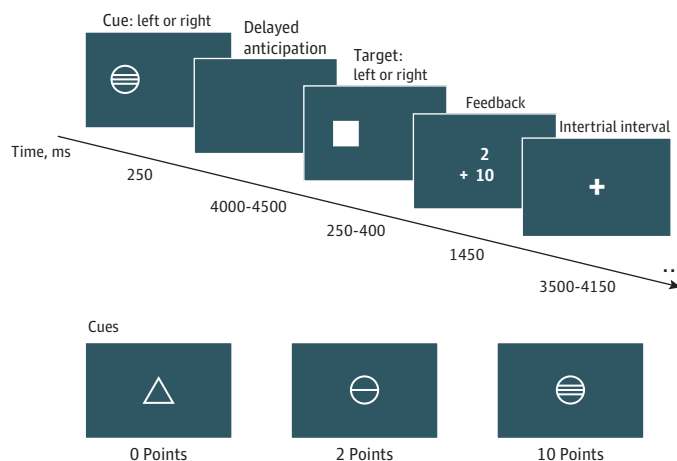
Time course of an example trial of the Monetary Incentive Delay task.

cluded. To those prenatally exposed adolescents, we matched 177 nonexposed adolescents by assessment site, sex, and maternal educational level. Maternal educational level was used as a proxy to control for the potentially confounding effect of socioeconomic status.[36] To explore a possible dose-response relationship, we divided the exposed group by low to moderate exposure (1-10 cigarettes per day [n = 148]) and high exposure (>10 cigarettes per day [n = 29]). This cutoff was based on recent findings.[5,8]

All adolescents underwent screening for psychiatric disorders with the Development and Well-Being Assessment questionnaire.[37] In addition, we analyzed the probability of ADHD as computed automatically by the questionnaire.

Adolescents' history of substance use was assessed by a questionnaire based on the European School Survey Project on Alcohol and Drugs.[38] Nicotine dependence was measured with the Fagerström Test for Nicotine Dependence[39]; alcohol abuse, with the Alcohol Use Disorder Identification Test.[40] Personality traits were assessed with the Neuroticism Extraversion Openness Five-Factor Inventory[41] and the Novelty Seeking subscale from the Temperament and Character Inventory.[42] A measure of impulsivity, delay discounting, was obtained with the Kirby questionnaire.[43]

Monetary Incentive Delay Task

Participants performed a modified version of the Monetary Incentive Delay task (MID),[44] a reward task, while their brain response was measured with fMRI. The trials consisted of the following 4 parts: cue presentation, an anticipatory delay, a response phase with target presentation, and an outcome (**Figure 1**). Cues signaled the amount of reward participants could win in a given trial (none, small, or large) and the side on which the target would appear. For every reward level, half the cues appeared on the left side and half on the right side of the screen. This part was followed by a variable anticipation interval (4000-4500 milliseconds). During the response phase, participants were instructed to press the left or the right button as fast as they could while a target was presented on the right or the left side of the screen. To achieve correct re-

sponses (ie, participants responding while the target was on the screen) in 66% of all trials for each participant, the duration of the target presentation varied from 250 to 400 milliseconds and was adjusted in every trial to the participants' performance by subtracting 10 milliseconds if the success rate was greater than 66% and adding 10 milliseconds if the success rate was less than 66%. If the success rate was at exactly 66%, the target time remained unchanged. During the outcome phase, participants received feedback on the amount of points they had won in the respective trial and an update of the total cumulative gain (1450 milliseconds). Trials were separated by an intertrial interval (3500-4150 milliseconds). Overall winnings were converted to chocolate candies after completion of the task. The MID task consisted of 66 trials (22 for each reward level) and had a duration of 11 minutes. Data were acquired in a single run. Before scanning, participants had a short training session to ensure that they learned the association between cues and their corresponding wins. Compared with other versions of the MID task,[44] we did not include loss trials owing to time constraints related to other assessments in this large-scale study.

fMRI Data Acquisition

Scanning was performed with 3-T magnetic resonance scanners from different manufacturers (Siemens, Philips, General Electric, and Bruker). Scanning parameters were chosen to be compatible with all scanners.[35] However, to ensure that results were not biased by scanner type or other site-specific factors, exposed subjects were matched to nonexposed participants by imaging site.

Functional images were acquired with a gradient-echo planar sequence (repetition time, 2.2 seconds; echo time, 30 milliseconds; flip angle, 75°). For each subject, 300 volumes were obtained. They consisted of 40 slices aligned to the anterior commissure–posterior commissure line (2.4-mm thickness; 1-mm gap; voxel size, $3.4 \times 3.4 \times 3.4$ mm³).

To exclude structural abnormalities and for anatomical references, T1-weighted images were acquired from each participant using a modified protocol based on the Alzheimer's Dis-

Figure 2. Response to Reward Anticipation and Feedback in the Ventral Striatum (VS) in Adolescents With Prenatal Exposure to Maternal Cigarette Smoking and Their Nonexposed Peers
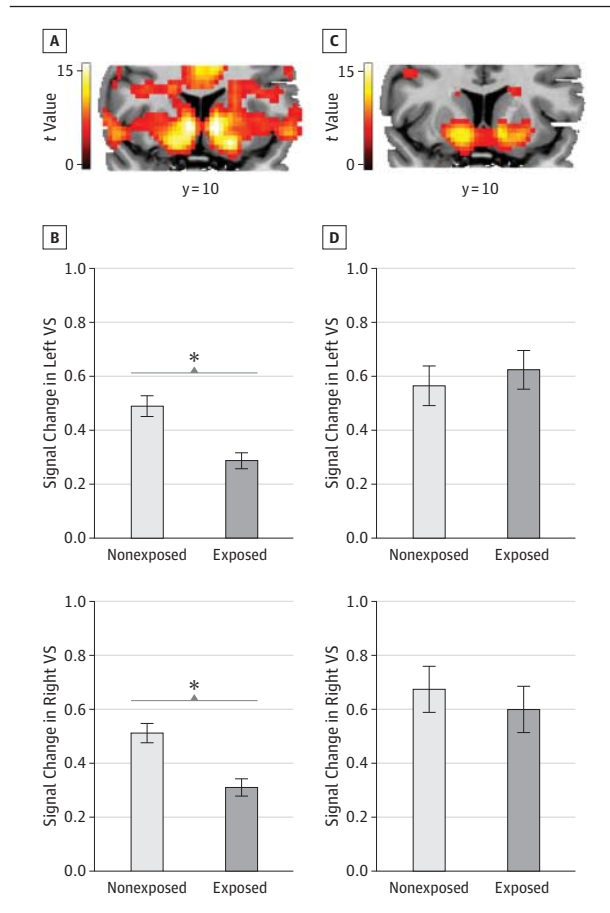
A, Response of the VS in all participants to anticipation of any reward vs no reward. The display is set to threshold $t = 4.88$ ($P < .05$, familywise error [FWE] corrected with ≥25 contiguous voxels). B, Differences between nonexposed and exposed adolescents in signal change in the left and right VS to anticipation. Error bars indicate SEM. *$P < .01$. C, Response of the VS in all participants to feedback of win vs no win. The display is set to threshold $t = 4.88$ ($P < .05$, FWE corrected with ≥25 contiguous voxels). D, Differences between nonexposed and exposed adolescents in signal change in left and right VS to feedback. Error bars indicate SEM.

ease Neuroimaging Initiative project (http://adni.loni.ucla.edu /methods/documents/mri-protocols/). The images consisted of 160 slices with $1.1 × 1.1 × 1.1$-mm^3 voxel size.

fMRI Preprocessing and Data Analysis

All imaging preprocessing steps and statistical analyses were performed with statistical parametric mapping software (SPM8; Wellcome Trust Centre for Neuroimaging). Preprocessing was performed using an automated pipeline. Individuals' fMRI images were time corrected by slice using the first slice as the reference. The slices were then spatially realigned, resliced, and nonlinearly warped on Montreal Neurological Institute space using a custom echoplanar imaging template. This custom-made template was created on the mean of a set of echo planar images of 240 randomly selected subjects (30 for each imaging site). Data were smoothed with a 5-mm gaussian isotropic kernel.

A first-level model was constructed for each subject using the following regressors: anticipation of large, small, and no rewards and feedback for large, small, and no rewards. These regressors were entered twice into the model (once for success [win] and once for no success [no win] in this specific trial), resulting in a total of 12 regressors. Trials with no responses were modeled as error trials, and 2 additional regressors (no response for anticipation and for feedback) were included. The baseline was implicitly modeled and constituted the intertrial interval. These modeled events were convolved with SPM's canonical hemodynamic response function. Movement parameters were included as covariates for each subject (3 translation and 3 rotation parameters). Contrast images were created for each subject.

For the second-level statistic, we focused our analysis on the following 2 contrasts: (1) anticipation of any reward (small and large) vs no reward and (2) feedback of win vs no win in all trials with any reward. The main effects of anticipation and feedback were tested with 2-sample t tests, thresholded at $t = 4.88$ ($P < .05$) with familywise error correction of at least 25 contiguous voxels (**Figure 2**). Because the exposed and nonexposed groups differed in their lifetime smoking history (**Table 1**), we included the reported number of cigarettes smoked as a covariate in these analyses.

Because of our a priori hypotheses of differences in the ventral striatum between the exposed and nonexposed groups and its consistent recruitment by the MID task,[44-48] we tested our hypothesis solely in these regions of interest. Masks of the ventral striatum were created by using coordinates from a meta-analysis on fMRI reward tasks.[27] We applied a 12-mm sphere centered at x, y, z values of −12, 10, −6 and 12, 10, −6 (Montreal Neurological Institute coordinates) for the left and right ventral striatum, respectively. We extracted individuals' mean signal change in these regions of interest and processed data with commercially available software (PASW Statistics 19; SPSS Inc). Differences in brain response of the ventral striatum to reward anticipation and feedback between groups were tested using a multivariate analysis of variance, with exposure status as the independent variable and signal change in the left and right ventral striatum as the outcome variable. A second multivariate analysis of variance was conducted to test for a dose-response relationship, with nonexposure, low to medium exposure, and high exposure as independent variables. The adolescents' lifetime frequency of cigarette smoking was entered as a covariate in these analyses.

To explore possible group differences outside the ventral striatum region of interest, we also conducted exploratory 2-sample t tests for the anticipation and the feedback contrasts, respectively. To exclude false-negative results, these whole-brain analyses were thresholded at $P < .001$ with familywise error correction at the cluster level. These analyses were also corrected for the adolescents' smoking frequency.

To test for an association of ventral striatum response and adolescents' smoking frequency, bivariate correlation analyses were conducted. Because the adolescents' smoking frequency was non–gaussian distributed, we conducted a nonparametric correlation analysis (Spearman rank correlation [ρ]). The significance level for these analyses was set to $P < .05$ (2-tailed).

Table 1. General Group Characteristics

	Group[a]		Difference Between Groups	
	Exposed (n = 177)	Nonexposed (n = 177)	Statistical Finding	P Value
Age, y[b]	14.65 (0.37)	14.63 (0.39)	0.40[c]	.69
Adolescents' pubertal maturation[d]	3.68 (0.63)	3.69 (0.69)	0.08[c]	.94
Maternal educational level[e]	4.62 (1.61)	4.62 (1.62)	0.00[c]	>.99
Probability of having ADHD, DAWBA score	2.31 (7.33)	2.00 (7.88)	13 687.5[f]	.046
Female sex, No. (%)	103 (58.2)	103 (58.2)	0.00[g]	>.99
Right-handed, No. (%)[h]	158 (89.8)	154 (89.5)	0.01[g]	.99
Substance use				
Lifetime frequency of alcohol drinking	8.21 (10.88)	7.05 (10.47)	14 551.0[f]	.23
Lifetime frequency of cigarette smoking	6.34 (12.78)	4.40 (10.46)	13 698.5[f]	.02
Frequency of cigarette smoking during past 30 d	1.35 (4.66)	0.78 (3.57)	15 136.0[f]	.44
FTND score	0.18 (0.79)	0.05 (0.38)	15 043.5[f]	.048
Lifetime frequency of illicit drug use	0.03 (0.14)	0.02 (0.05)	14 961.5[f]	.22
Adolescents with potential alcohol abuse, No. (%)[i]	15 (8.5)	9 (5.1)	1.61[g]	.21
Adolescents who smoked ≥1 cigarette in their life, No. (%)	81 (45.8)	58 (32.8)	6.27[g]	.02
Personality measures				
TCI score				
Exploratory excitability	33.66 (4.15)	33.85 (4.15)	0.44[c]	.66[j]
Impulsivity	27.30 (4.58)	27.33 (4.74)	0.05[c]	.96[j]
Extravagance	30.68 (5.86)	29.11 (6.34)	2.41[c]	.02[j]
Disorderliness	22.54 (3.55)	22.73 (4.35)	0.45[c]	.65[j]
NEO-FFI score				
Neuroticism	2.04 (0.68)	1.88 (0.59)	2.44[c]	.02[j]
Extraversion	2.49 (0.49)	2.52 (0.43)	0.54[c]	.59[j]
Openness	2.08 (0.45)	2.15 (0.47)	1.42[c]	.16[j]
Agreeableness	2.26 (0.46)	2.39 (0.45)	2.52	.01[j]
Consciousness	2.27 (0.60)	2.32 (0.60)	0.71[c]	.48[j]
Impulsivity, delay discounting k value, log transformed[k]	−3.90 (1.42)	−4.49 (1.46)	3.56[c]	<.001

Abbreviations: ADHD, attention-deficit/ hyperactivity disorder; DAWBA, Development and Well-Being Assessment; FTND, Fagerström Test for Nicotine Dependence; NEO-FFI, Neuroticism Extraversion Openness Five-Factor Inventory; TCI, Temperament and Character Inventory.

[a] Unless otherwise indicated, data are expressed as mean (SD).

[b] Includes 173 in the exposed group and 172 in the nonexposed group.

[c] Calculated by the 2-sample t test.

[d] Ranges from 1 for prepubertal to 5 for postpubertal and includes 174 participants for the exposed group.

[e] Ranges from 1 for professional qualification (eg, doctorate, doctor of medicine, or master's degree) to 7 for did not go to school or completed primary school education only.

[f] Calculated by the Mann-Whitney test.

[g] Calculated by the χ² test.

[h] Includes 176 for the exposed group and 172 for the nonexposed group.

[i] Indicates Alcohol Use Disorder Identification Test score of greater than 7.

[j] The significance level was corrected for multiple comparisons (for multiple subscales from the same questionnaire).

[k] Represents the subjective discounting parameter, higher values represent higher delay discounting (eAppendix in Supplement).

Analysis of Nonimaging Data

Group comparisons regarding all nonimaging parameters were performed using a 2-sample t test or, for non–gaussian-distributed variables, the nonparametric Mann-Whitney test. The significance level for all analyses was set to P < .05 (2-tailed). In case of testing multiple subscales from the same questionnaire, the significance level was Bonferroni corrected.

Results

Characteristics of the exposed and nonexposed groups are provided in Table 1. The 2 groups did not differ in sex, age, pubertal maturation, handedness, or maternal educational level. We found no group differences in the number of mothers with alcohol or illicit drug consumption during pregnancy, the duration of pregnancy, or pregnancy complications (Table 2). Mothers who smoked during pregnancy smoked a mean of 7 (range, 1-30) cigarettes per day. Those mothers were also more exposed to secondhand smoking during their pregnancy

(χ^2 = 86.67 [P < .001]). Consistent with previous findings of reduced birth weight in prenatally exposed children,[3] the exposed adolescents had a significantly lower birth weight (by 130 g, corrected for the duration of the pregnancy; $F_{2,287}$ = 4.07 [P = .045]; η^2 = 0.01) than their nonexposed peers.

Regarding the personality measures (Table 1), after correcting the significance level for multiple comparisons, we did not find differences between the groups except for higher impulsivity (delay discounting) in the exposed adolescents (eAppendix in Supplement).

None of the adolescents met the criteria of the *DSM-IV* or *International Classification of Diseases, 10th Revision*, for a psychiatric disorder in the self-report or the parent report. The exposed adolescents showed a slightly higher mean probability for ADHD (U = 13 687.5 [P = .046]).

Regarding adolescents' substance use (Table 1), the 2 groups did not differ in lifetime alcohol and illicit drug consumption or in the number who reported alcohol abuse. However, the exposed group showed a higher lifetime frequency of cigarette smoking (U = 13 698.5 [P = .02]), but no differences in smoking frequency during the last 30 days (15 136.0

Table 2. Pregnancy Characteristics

	Group[a]		Difference Between Groups	
	Exposed (n = 177)	Nonexposed (n = 177)	Statistical Finding	P Value
Duration of pregnancy, wk[b]	39.27 (2.15)	39.32 (3.55)	0.31[c]	.88
Birth weight, g[d]	3341 (625)	3472 (527)	4.07[c]	.045
Mothers				
Smoking during pregnancy, No. (%)	177 (100.0)	0	354.00[e]	<.001
Exposure to second-hand smoking, No. (%)	107 (60.5)	23 (13.0)	86.67[e]	<.001
Consumption of alcohol during pregnancy	49 (27.7)	37 (20.9)	2.13[e]	.17
Consumption of illicit drugs during pregnancy	5 (2.8)	0	5.04[e]	.06
Medical problems/neurological diseases during pregnancy[f]	9 (5.1)	13 (7.3)	0.78[e]	.51
No. of cigarettes smoked per day during pregnancy	6.96 (4.70)	0	0[g]	<.001
No. of drinks consumed during pregnancy[h]	5.26 (12.04)	4.89 (26.37)	11 339.5[g]	.11

[a] Unless otherwise indicated, data are expressed as mean (SD).

[b] Birth weight was corrected for the duration of pregnancy. Includes 147 for the exposed group and 150 for the nonexposed group.

[c] Calculated by the F test.

[d] Includes 144 for the exposed group and 146 for the nonexposed group.

[e] Calculated by the χ^2 test.

[f] Includes diabetes mellitus, hypertension, and convulsions.

[g] Calculated by the Mann-Whitney test.

[h] Includes 157 for the exposed group and 162 for the nonexposed group.

Table 3. Performance Data of the Monetary Incentive Delay Task

	Group, Mean (SD)[a]		Difference Between Groups	
	Exposed (n = 174)	Nonexposed (n = 175)	t Value	P Value
Success, %				
Overall	62.84 (5.31)	62.59 (5.26)	0.45	.66
No-reward trials	51.58 (15.29)	53.01 (14.64)	0.92	.36
Small-reward trials	67.87 (10.32)	66.90 (9.80)	0.91	.36
Large-reward trials	68.91 (9.56)	67.66 (9.10)	1.25	.21
Reaction time for success, ms				
No-reward trials	241.31 (25.33)	244.58 (26.73)	1.16	.25
Small-reward trials	235.36 (35.65)	238.03 (30.58)	0.75	.45
Large-reward trials	231.75 (33.81)	234.57 (29.25)	0.83	.41
Reaction time for no success, ms				
No-reward trials	367.12 (91.34)	365.42 (95.16)	0.17	.87
Small-reward trials	329.07 (78.15)	335.18 (99.43)	0.64	.53
Large-reward trials	310.83 (74.59)	306.87 (68.73)	0.51	.61

[a] Owing to technical problems, behavioral data were not available for 3 adolescents from the exposed group and 2 from the nonexposed group.

[P = .44]). The significant difference in lifetime smoking was a result of the higher number of adolescents who smoked at least 1 cigarette in their life in the exposed group (χ^2 = 6.27 [P = .02]). The exposed group showed a slightly higher score on the Fagerström Test for Nicotine Dependence[39] (U = 15 043.5 [P = .048]). Performance data of the MID task are provided in **Table 3**. We found no differences in success rates or reaction times between the 2 groups. We detected substantial responses for both groups in the ventral striatum for the main effects of anticipation of rewards compared with no rewards (peak at coordinates 9, −11, −2; t_{1351} = 17.62 [P < .001]) and feedback of win compared with no win (peak at 9, 14, −5; t_{1351} = 12.36 [P < .001]) (Figure 2). Lists of all brain regions are given in eTable 1 and eTable 2 in Supplement.

Comparisons of the brain response to reward anticipation in the ventral striatum between the exposed and nonexposed adolescents revealed the following group differences (Figure 2). The exposed group showed a weaker response in the left ($F_{1,351}$ = 14.98 [P < .001]; η^2 = 0.04) and right ($F_{1,351}$ = 15.95 [P < .001]; η^2 = 0.05) ventral striatum. Response of the ventral striatum to the feedback of a reward did not differ between groups (left ventral striatum, $F_{1,351}$ = 0.21 [P = .65]; right ventral striatum, $F_{1,351}$ = 0.47 [P = .49]). The test for a dose-response relationship showed no significant linear decrease in brain response from nonexposed to highly exposed adolescents. The reported main effects and group differences in ventral striatum response were unbiased by the adolescents' smoking frequency because we included it as a covariate in our analysis. When tested for an association with the ventral striatum response, the adolescents' lifetime frequency of smoking correlated negatively with reward anticipation in the right ventral striatum (r = −0.11 [P = .049]), and correlation of smoking frequency and signal in the left ventral striatum approached significance (r = −0.10 [P = .08]). No association was found between lifetime frequency of smoking and signal in the ventral striatum during feedback.

When testing for an effect of the heightened impulsivity in the exposed adolescents, the differences during reward anticipation remained significant after correcting for it (eAppendix in Supplement). The exploratory whole-brain analyses for the anticipation of rewards revealed the following brain areas that responded less in the exposed compared with the nonexposed adolescents: the right and left ventral striatum, consistent with our a priori hypotheses, and the right middle frontal gyrus (Brodmann area [BA] 10), left superior parietal cortex (BA 7), left lingual gyrus (BA 18), left inferior occipital gyrus (BA 19), and left middle temporal gyrus (BA 21) (eTable 3 in Supplement). We found no brain regions where the nonexposed adolescents showed less responsivity during anticipation than the exposed adolescents. The exploratory analyses of the feedback contrast revealed no group differences.

Discussion

This report is, to our knowledge, the first to describe reduced reactivity of the ventral striatum to reward anticipation in adolescents with prenatal exposure to maternal cigarette smoking compared with nonexposed peers. Our finding is in line with previous animal studies reporting structural alterations in the brain reward system and lower levels of dopamine release within the ventral striatum after prenatal nicotine exposure.[11-15] Our exploratory analysis revealed some additional areas that were less responsive during reward anticipation in the exposed adolescents. The middle frontal gyrus and superior parietal cortex are known to be part of the reward circuit.[27] We also found areas that are responsible for visual perception (the lingual gyrus, occipital gyrus, and middle temporal gyrus). Increased signaling in these areas is thought to encode the saliency of a stimulus.[49,50] Thus, the exploratory analysis supports our hypothesis and shows that prenatally exposed adolescents differ from their peers mainly in the neuronal reward system and related visual areas. Although recent studies reported thinner orbitofrontal cortices in exposed adolescents,[20,21] we did not find functional differences in these areas in our exploratory analyses. This finding may be related to the fact that the MID task engages the medial orbitofrontal cortex,[27] whereas structural differences were observed in the lateral orbitofrontal cortex. Despite our expectation of differences in the ventral striatum in response to feedback of win compared with no win, we found no differences between the 2 groups. Therefore, our results do not support the idea of a general hyposensitivity of the ventral striatum in prenatally exposed adolescents but rather an attenuated responsiveness to a specific phase of the reward process, namely, the anticipation of rewards. This finding is in line with several other studies investigating reward processing in specific groups (ie, substance users,[45,46] children of alcoholics,[51] and adolescents vs adults[52]) and the effect of genotypes on reward processing,[53] which also reported differences in ventral striatum response exclusively during the anticipation phase. One could therefore speculate that the anticipation and the receipt of a reward are distinct processes that engage the ventral striatum differently. Support for this assumption comes from studies showing that, during anticipation, the signal in the ventral striatum increases with the magnitude of a win, probably encoding the incentive salience of a reward.[18,54] During the receipt of a reward, however, the response of the ventral striatum is decreased when a reward is omitted or the received gain is lower than expected, and the response is increased when the gain is higher than expected.[55,56] This finding indicates that during this phase the signal in the ventral striatum encodes the match between reward expectation and the actual outcome (ie, the prediction error). The coding of the prediction error is discussed as the essential principle for prediction-outcome learning.[55] With regard to our results, this principle suggests that the incentive value of the same reward stimulus is reduced in exposed compared with nonexposed peers, whereas the match between reward prediction and outcome remains unchanged.

The observed weaker reactivity to anticipatory rewards in the exposed adolescents may have serious consequences. As recently shown in a previous study by Schneider et al and the IMAGEN Consortium,[47] adolescents with lower ventral striatum response to reward anticipation are more likely to engage in risky behavior. We have suggested that these adolescents seek more intense rewards to compensate for the blunted neural response to conventional incentives.[47] Research in rodents has demonstrated that reduced activation of the dopaminergic reward system in drug-naive animals predicts their drug intake.[57] Adolescent smokers also display less ventral striatum responsivity during reward anticipation than do age- and IQ-matched nonsmokers. This effect was still observed when analyzing a subgroup of adolescents who smoked fewer than 10 cigarettes in their life, suggesting that a low response of the ventral striatum during reward anticipation represents a vulnerability factor for the initiation of substance use and later development of addiction.[46]

We replicated that finding in our sample; the responsivity of the right ventral striatum to reward anticipation was negatively associated with the frequency of smoking. However, this association was rather small and became significant only because of the large sample size. The low proportion of smokers and therefore the small variance in our sample might explain why this correlation was so small compared with the report by Peters et al.[46] However, other studies have reported positive associations between ventral striatum responsivity toward rewards and self-reports of the likelihood of risk taking[58] or impulsivity, a trait that is also discussed as a risk factor for substance use.[59,60] Galvan et al[58] used a reward-learning paradigm in their study that might engage the ventral striatum differently. Also, impulsivity in the later studies was assessed with a psychopathic tendency questionnaire, and this impulsivity measure captured different features than conventional impulsivity questionnaires or tasks.[60] These differences limit the comparability with our results.

Our results also fit well with findings that individuals with ADHD show a hyposensitivity of the ventral striatum to reward anticipation.[48] This population is also characterized by increased sensation seeking and a heightened risk for substance abuse.[25,48] Maternal smoking during pregnancy is a known risk factor for the development of this disorder,[4,5] and

alterations in brain function are discussed as key candidates mediating the association between maternal smoking and subsequent ADHD in the exposed offspring.[61] One could speculate that the reported lower anticipatory ventral striatum response in prenatally exposed adolescents might be a common underlying mechanism of ADHD and substance use.[25] None of our participants met the criteria for ADHD, but the exposed adolescents showed a slightly higher probability for it. One could suspect that the lower brain response during anticipation resulted from inattention to the task. Because the mean probability for having ADHD, although different, was fairly low (approximately 2%), and because no group differences were found regarding the behavioral data, we regard this possibility as unlikely.

Several limitations of this study should be noted. First, we assessed the exposure status retrospectively via self-report by a parent. Therefore, the data could be biased by memory and/or social desirability, particularly for the reported number of cigarettes smoked per day during pregnancy. We could not check these data against medical records. However, the plausible rate of maternal smoking during pregnancy in our study (14.2%)[1,2] and the finding of lower birth weight in the exposed group, which is a consistent finding in prenatally exposed children,[2,3] supports the reliability of the parents' reports.

Second, the groups differed in the adolescents' smoking behavior. We accounted for this difference by including the adolescents' number of cigarettes smoked during their lifetime as a covariate in our statistical model.

Third, owing to the nature of observational studies, we are not postulating a causal link between prenatal exposure to maternal cigarette smoking and the (weaker) brain response to anticipatory rewards. A recent review[62] supports the notion of a causal relationship between smoking during pregnancy and heightened risk for substance abuse and addiction in the offspring. However, the authors also state that confounding risk factors and genotype (the exposed offspring have a first-degree relative with nicotine dependence) might play a role and conclude that most likely a combination of all these factors contributes to the observed relationship. By balancing potential confounders (eg, maternal educational level and prenatal exposure to alcohol or other substances) we tried to make the groups as similar as possible except for the exposure of interest. Because our data point in the same direction as experimental animal studies, a direct physiological effect of the prenatal nicotine exposure seems at least plausible. Nevertheless,

other explanations for the reported difference—for instance, a genetic variation that enhances mothers' smoking and is inherited by the child—are also possible.

Fourth, our version of the MID task has some limitations. Owing to time constraints, we did not include losses; this might have weakened our ability to detect group differences, especially during the feedback phase.[28] Also, because of the constraints imposed by local ethics committees, we used abstract points that were converted to candies instead of the monetary rewards used in most other studies.[28,29,32,52] However, we find that our version of the task recruited similar brain regions of the reward circuit, which others have reported[28,32,44,48]; therefore, we believe that the reinforcing properties of the task were still intact (which can also be seen in the decrease in reaction times with increasing reward). Nevertheless, we cannot rule out that these modifications might have influenced our results. Future studies should also include losses to analyze whether exposed and nonexposed adolescents would react differently to the modifications.

In summary, we showed that adolescents prenatally exposed to maternal cigarette smoking exhibit weaker brain response to anticipatory rewards in the ventral striatum than their nonexposed peers. No differences were found during the feedback of a reward in the ventral striatum. The lower response of the ventral striatum during reward anticipation might reflect a risk for the initiation of substance use and the development of addiction later in life. A longitudinal pursuit of the development of these adolescents could give a detailed insight into the risk of maternal smoking during pregnancy and the development of addiction. The IMAGEN study is planning to follow up these adolescents at 16 and 18 years of age. Future analyses of these data will provide a great opportunity to assess whether prenatally exposed adolescents develop an increased risk for substance use and addiction and which role the reported neuronal differences during reward anticipation plays in this development.

The current finding of lower reactivity of the ventral striatum in prenatally exposed adolescents and the potentially heightened risk for addiction highlights the need for education and preventive measures to reduce smoking during pregnancy. Education of the mother about this specific risk may enhance her motivation to stop smoking. In addition, knowledge of existing prenatal exposure in adolescents suggests increased attention for the development of substance dependence and counseling of those at risk.

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