

Investigating the association between smoking, environmental tobacco smoke exposure and reward-related brain activity in adolescent experimental smokers

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Abstract

Reduced anticipatory reward-related activity, especially in the ventral striatum (VS), may underly adolescent vulnerability to develop nicotine dependence. It remains unclear whether nicotine uptake caused by environmental tobacco smoke (ETS) exposure, known to be associated with future smoking, might prompt similar changes in the brain's reward system, rendering adolescents vulnerable for development of nicotine dependence. To address this question, we tested whether current ETS exposure and monthly smoking are associated with VS hypoactivity for non-drug rewards in experimental smoking adolescents. One-hundred adolescents performed a monetary incentive delay task while brain activity was measured using fMRI. To test the hypothesized relationship, we used a variety of approaches: (1) a whole-brain voxel-wise approach, (2) a region-of-interest approach in the VS using frequentist and Bayesian statistics and (3) a small volume voxel-wise approach across the complete striatum. The results converged in revealing no significant relationships between monthly smoking, ETS exposure and reward-related brain activation across the brain or in the (ventral) striatum specifically. However, Bayesian statistics showed only anecdotal evidence for the null hypothesis in the VS, providing limited insight into the (non-)existence of the hypothesized relationship. Based on these results, we speculate that blunted VS reward-related activity might only occur after relatively high levels of exposure or might be associated with more long term effects of smoking. Future studies would benefit from even larger sample sizes to reliably distinguish between the null and alternative models, as well as more objective measures of (environmental) smoking via using devices such as silicone wristbands.

KEYWORDS

environmental tobacco smoke (ETS) exposure, fMRI, MID, monthly smoking, reward, VS activity

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1 | INTRODUCTION

The use of tobacco represents a significant public health problem, which is associated with a wide variety of health risks including dependence.¹ Worldwide, the tobacco epidemic kills more than 8 million people a year.² More than 7 million of those deaths result from direct tobacco use, while around 1.2 million comes from non-smokers being exposed to environmental tobacco smoke (ETS).² The majority of smokers who develop nicotine dependence started smoking during adolescence.^{3,4} Adolescents who are more exposed to ETS, caused by smoking of family and friends, are more likely to start smoking themselves.⁵ In addition, in a cross-sectional study, a higher number of smokers in the child's current social environment are associated with more nicotine dependence symptoms.⁶ On a mechanistic level, it has been suggested that dysfunctional reward-related activity, especially in the ventral striatum (VS), underlies adolescent vulnerability to substance use including nicotine dependence.⁷ More specifically, some studies indicate an association between the amount of smoking and deficits in the processing of rewarding stimuli in individuals at risk for nicotine dependence, including daily smokers.^{8,9} However, it remains unknown whether this association is present in experimental smokers as well. Furthermore, it remains unclear whether nicotine uptake caused by ETS exposure might prompt similar changes in the brain's reward system, rendering adolescents vulnerable for development of nicotine dependence. In order to gain more insight into this question, we investigated whether current ETS exposure and active smoking are associated with abnormal anticipatory reward-related activity within the VS in adolescents in the experimental phase of smoking. Research into experimental smoking is necessary to identify the underlying neural mechanisms that make adolescents susceptible to nicotine dependence.

Dysfunction of cortico-striatal reward pathways, including the VS and the medial prefrontal cortex (mPFC), has been emphasized as a crucial neural mechanism involved in the development and maintenance of addiction.^{10–15} For instance, an image-based meta-analysis showed decreased striatal activation in adults with substance addiction compared with healthy controls during non-drug (i.e., money) reward anticipation.¹⁶ Another recent imaged-based meta-analysis confirmed this pattern of striatal hypoactivation among dependent daily smokers.¹⁷ Furthermore, in daily adult smokers, VS hypoactivity has been associated with higher plasma nicotine levels¹⁸ and a greater number of cigarettes smoked per day,¹⁹ pointing towards a dose-response relationship between striatal hypoactivity and severity of nicotine dependence.

Accumulating evidence suggests comparable reward-related changes in adolescents. More precisely, problematic substance use and even more limited substance use are associated with lower ventral striatal activation during non-drug reward anticipation among adolescents.²⁰ Büchel and colleagues suggest that the relationship between anticipatory VS hypoactivity and substance use might be causal, whereby anticipatory ventral striatal hypoactivity would

be predictive for future problematic drug use.²¹ Patterns of reduced reward-related activity during reward anticipation among adolescents are not only observed for substance use generally but also specifically for smoking.⁸ Peters and colleagues⁸ and Garrison and colleagues²² found evidence for a dose-response dependent relationship between striatal hypoactivity and smoking frequency (including smoking on a daily basis) among adolescents smokers. Furthermore, Peters and colleagues⁸ observed lower ventral striatal responses during reward anticipation of non-drug rewards in a subset of smokers (N = 14) with extremely mild smoking habits (i.e., number of lifetime occasions of smoking ranging from 0–9) while comparing them to controls. Finally, increased smoking frequency in adolescents has also been linked to reduced functional connectivity with the VS and regions associated with inhibition and risk aversion during reward anticipation.⁹ Taken together, these studies indicate that the association between smoking and striatal hypoactivity might be both causal and dose dependent among smoking adolescents during reward anticipation of non-drug rewards and this strengthened the idea that this negative dose-dependent relationship between VS activity for reward anticipation and smoking might be realistic among experimental smoking adolescents as well.

From previous research, we know that nicotine inhaled from ETS exposure is able to cross the blood-brain barrier, resulting in the occupation of nicotinic acetylcholine receptors (nAChRs) in motivation- and inhibition-related brain regions of adult smokers and non-smokers.²³ This raises the possibility that ETS exposure during adolescence might also result in functional brain changes related to reward processing, such as VS hypoactivity. This is in line with the observation that prenatal cigarette exposure is associated with less anticipatory reward activity within the VS during adolescence,²⁴ indicating that ETS exposure might influence the functionality of the reward circuitry as well.

Identification of vulnerability factors is needed to better understand how adolescents develop nicotine dependence. Insights into the brain mechanisms underlying smoking behaviour in the initial phase of smoking can help to understand the transition from smoking initiation to more frequent smoking and finally nicotine dependence. Therefore, in the present study, we tested whether current ETS exposure and active smoking in experimental smoking adolescents are associated with reduced anticipatory reward-related activity within the VS for non-drug rewards in experimental smokers specifically. To this end, we used fMRI in combination with a Monetary Incentive Delay (MID) task.²⁵ Exploratory associations with reward outcome processing were also tested. One-hundred experimental smoking adolescents with varying levels of ETS exposure participated in the current study. Based on previous studies, we expected to observe a negative association between smoking frequency and anticipatory VS activity for non-drug rewards in experimental smoking adolescents. We also hypothesized a negative association between ETS exposure and anticipatory ventral striatal activity for non-drug rewards.

2 | METHODS

Study methods, procedures and analyses are described in detail on the Open Science Framework website (<https://osf.io/5aypm/>), where we pre-registered our sample size justification and analyses.

2.1 | Participants

One-hundred experimental smoking adolescents aged 14 to 19 years participated in this study ($M_{age} = 16.5$, $SD = 1.13$, 30.0% men). Inclusion criteria were (a) smoking 5 to 500 cigarettes lifetime, (b) having smoked in the past 6 months and (c) being aged between 12 and 18 at time of inclusion. Exclusion criteria were (a) having ever smoked on a daily basis, (b) use of psychoactive medication that could not be stopped for 24 h, (c) fMRI contraindications and (d) history of neurological diseases. Participants received 50 euros in gift vouchers after study completion. Participants and their parents (if participants were younger than 16 years old) provided informed consent. The Medical Ethical Committee of Arnhem-Nijmegen approved the study protocol (#2015-2120).

2.2 | Questionnaires (main predictors)

2.2.1 | ETS exposure

Participants were asked to report on the frequency of ETS exposure in their environment.²⁶ Frequency of ETS exposure was measured with the following question 'How often does X smoke when you are around?', where X were relatives (father, mother and siblings), friends (best friend and friends in general) and 'others' in their environment (i.e., six questions in total). Response items ranged from (0) *X smokes, but not when I am around* to (8) *more than 5 times a day*. If relatives, friends or others did not smoke, a score of zero was assigned. Participants' responses were combined to establish a sum score for current ETS exposure, ranging from 0 to 48.

2.2.2 | Monthly smoking

Monthly smoking was defined as the number of cigarettes smoked on average a month. To establish monthly smoking, we asked participants to indicate which of the following statements would fit best: (1) I smoke at least once a day; (2) I do not smoke daily, but at least once a week; (3) I do not smoke weekly, but at least once a month; (4) I smoke less than once a month; (5) I try smoking every once in a while; (6) I quit smoking, after I smoked at least once a week; (7) I quit smoking, after I smoked less than once a week; (8) I tried smoking every once in a while, but I quit and (9) I never smoked.^{27,28} None of the participants selected 1 or 9, in line with our inclusion criteria. Participants who selected option 2 subsequently indicated how many cigarettes they smoked on average a

week (multiplied by 52 and divided by 12 indicated the amount of cigarettes they smoked on average per month). Participants who selected options 3, 4 or 5 subsequently indicated how many cigarettes they smoked on average per month. The participants who selected options 6, 7 or 8 quit smoking, and therefore, monthly smoking was set at zero.

2.3 | Questionnaires (control variables)

2.3.1 | Pubertal development scale

Confirm earlier work of our group,²⁶ participants were instructed to fill out the Pubertal Development Scale (PDS), containing questions on secondary sexual characteristics.²⁹

2.3.2 | Familial risk

To obtain an estimate of participants' familial vulnerability to develop nicotine dependence, we created a familial risk score.²⁶ The questionnaire, completed by one of the parents, addressed three domains: (1) parents' current smoking behaviour and frequency, (2) the level of nicotine dependence for the period during which parents smoked the most (could either be now or in the past) and (3) smoking behaviour of *their* parents (i.e., grandparents of participants). The scores from the three domains were summed and subsequently averaged for both parents.

2.3.3 | Smoking during pregnancy

To assess smoking during pregnancy, parents were asked: 'Did you/your wife smoke during the pregnancy of your son/daughter?'. Response options were yes or no.

2.3.4 | Alcohol and cannabis use

Alcohol use was measured using the Alcohol Use Disorders Identification Test (AUDIT³⁰). Cannabis use was measured by asking participants to report on the number of lifetime uses.

2.4 | Cotinine measurement

Saliva samples of participants were collected to measure the levels of cotinine, a metabolite of nicotine to validate the amount of smoking/ETS exposure. Cotinine levels were analysed using liquid chromatography coupled with mass spectrometry, with a quantification limit of <1.0 µg/L. Kendall's tau correlations were used to test whether cotinine in saliva was associated with self-reported ETS exposure as well as the monthly smoking variable.

2.5 | Monetary incentive delay task

Reward processing was measured with the MID task.²⁵ The task is displayed and explained in Figure 1.

2.6 | fMRI data acquisition

fMRI data were acquired on a Siemens 3 Tesla Skyra MRI scanner (Siemens Medical system, Erlangen, Germany) using a 32-channel coil. Functional T2*-weighted imaging was obtained using multi-echo echoplanar imaging (EPI) to acquire 39 axial slices in interleaved ascending order (voxel size $3.5 \times 3.5 \times 3.0$ mm; matrix 64×64 ; repetition time (TR) 2,020 ms; echo times (TE) 7, 16.3, 26, 35 and 44 ms; flip angle 80°). A high-resolution weighted anatomical scan was also obtained (MPRAGE; 192 axial slices; voxel size $1 \times 1 \times 1$ mm; matrix 256×256 ; TR 2,300 ms; TE 3.03 ms; flip angle 8°).

2.7 | Data analysis

2.7.1 | Behavioural analyses

Behavioural analyses were performed using SPSS, version 23. Pearson and Kendall's Tau correlations were computed to assess bivariate relationships between current ETS exposure, monthly smoking, pubertal development, familial risk, alcohol use, cannabis use, cotinine and VS activity for anticipation and outcome processing during the MID task. Pearson correlations were used when both variables are parametric, and Kendall's Tau correlations were used when one or both variables are non-normally distributed. For dichotomous variables (gender and smoking during pregnancy [yes/no]), we performed two sample *t* tests

to assess their effect on the predictor variables (ETS exposure and monthly smoking) and outcome variables (VS activity for anticipation and outcome). Results of all these bivariate analyses are included in the supporting information (Table S1). Significant associations with the predictor variables and outcome variables are included in the main text.

Paired-sample *t* test was performed to test the difference in reaction times between rewarded and non-rewarded trials and thus verifies whether the reward task manipulation resulted in the expected behavioural effects. Finally, a hierarchical linear regression analysis was performed to assess the relationship between reaction times (RTs) and current ETS exposure and monthly smoking. Pubertal development, smoking of mother during pregnancy, familial risk, gender, alcohol and cannabis were entered as covariates in the first step. ETS exposure during adolescence and monthly smoking were entered in the second step to test whether these two variables can explain additional variance while controlling for confounding factors. The standard $p < 0.05$ criteria to determine significance was used. An analysis of standard residuals, as part of testing the assumptions for linear regression, was conducted to identify any outliers regarding RTs, which resulted in excluding two participants from the analysis.

2.7.2 | fMRI data preprocessing

Preprocessing steps were conducted in SPM12 (www.fil.ion.ucl.ac.uk/spm). Preprocessing of the functional data included conversion of the MRI data into NIFTI format, followed by realignment to the first image of the time series. Subsequently, 30 volumes, acquired before the start of the actual experiment, were used to estimate weights for a BOLD contrast-to-noise ratio map for each echo. Weighted summation was used to combine all echoes into a single dataset (PAID

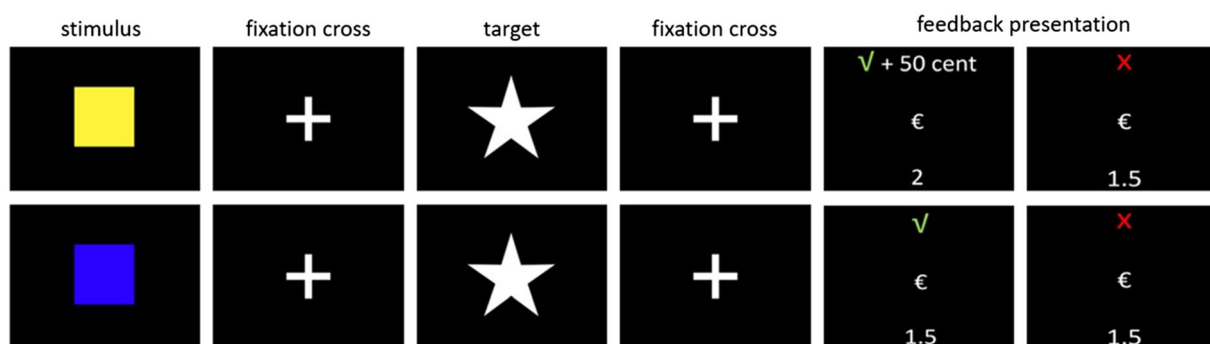


FIGURE 1 Monetary incentive delay task. A blue or yellow square (counter-balanced across participants) was presented for 500 ms as a cue announcing a rewarding trial or non-rewarding trial. Cue presentation was followed by a delay during which a fixation cross was presented (jittered between 2,500 and 8,500 ms). Next, a target (white star) appeared on the screen. Participants were instructed to press as fast as possible upon presentation of the target. Eight practice trials preceded the task. Reaction times during the practice trials were used to tailor task difficulty to each individual resulting in an individually determined time window in which participants can respond. This time window was continuously adjusted to ensure a hit rate of 66%. After target presentation, a fixation cross was presented (jittered between 1,500 and 3,000 ms), followed by the feedback (1,500 ms) about whether they were fast enough (✓, +50 cent in case of rewarded trials) or not (✗, in case of non-rewarded trials) and cumulative earnings (total amount of money gained so far). In total, 60 rewarding and 60 non-rewarding trials were presented in a randomized order. Participants were told that the monetary gains accumulated during the task would be added to their final compensation, and in practice, this compensation was always rounded up to 50€

method³¹). Further steps included coregistration of functional and anatomical data, normalization into MNI space and smoothing with a FWHM of 8 mm. After preprocessing, an independent component analysis (ICA)-based automatic removal of motion artefacts was applied using FSL (www.fmrib.ox.ac.uk/fsl; ICA-AROMA^{32,33}).

2.7.3 | fMRI data analyses

Our first-level GLM included two regressors modelling the anticipation phase: 'reward anticipation' (50 cent cue) and 'non-reward anticipation' (0 cent cue). It further included four regressors modelling the outcome phase: two regressors for trials on which subjects responded fast enough ('reward hit' and 'non-reward hit') and two regressors for trials on which subjects responded too late ('reward too late' and 'non-reward too late'). Finally, one 'miss' regressor was included if subjects failed to respond or responded within 100 ms. The anticipation phase was modelled with a boxcar function as the combination of the cue and delay periods (duration 3,000–9,000 ms) time-locked to the onset of the cue. The outcome phase was modelled with a boxcar function (duration 1,500 ms) time-locked to the onset of the outcome. All regressors were subsequently convolved with the canonical hemodynamic response function. High-pass filtering (128 s) was applied to the time series of the functional images to remove low-frequency drifts.

First, we computed the contrast reward anticipation > non-reward anticipation and performed a whole-brain one-sample *t* test across all participants to check whether the task activated the expected brain network. The resulting T-map was thresholded with a voxel level uncorrected $p < 0.001$, combined with a cluster level family-wise error (FWE) corrected $p < 0.05$, accounting for multiple comparisons across the whole brain.^{34,35}

Second, whole-brain multiple linear regressions across all participants were performed for the reward anticipation > non-reward anticipation contrast, with current ETS exposure and monthly smoking as covariates of interest. Pubertal development, smoking during pregnancy, familial risk, alcohol use and cannabis use were included as additional covariates of no-interest. Resulting T-maps were thresholded with a voxel level uncorrected $p < 0.005$, combined with a cluster level family-wise error (FWE) correction $p < 0.05$.

To test the robustness of our findings, we performed the whole-brain multiple linear regression analyses again while excluding eight participants. For these eight participants, we initially assumed the amount of cigarettes smoked a month to be zero. Since there was some uncertainty as to whether this amount was exactly zero for these participants, we performed a sensitivity analysis without these participants. See preregistration for more details (<https://osf.io/5aypm/>).

Given our a priori hypothesis about the VS, we performed a ROI analysis using an a priori mask of this region.³⁶ Percent signal change was extracted using the *rfxplot* toolbox.³⁷ To test the effect of monthly smoking and current ETS exposure on extracted VS activation during anticipation, the same hierarchical regression

analysis was performed as described for the MID reaction times, including the extra sensitivity analysis. To examine whether the assumptions for hierarchical regression were met, an analysis of standard residuals was conducted to identify any outliers regarding VS activity during reward anticipation and reward outcome. This resulted in the exclusion of one participant from the analysis for reward anticipation. Additionally, Bayesian statistics with default priors in JASP³⁸ were performed in order to quantify evidence for the null and alternative hypothesis.

The regression analysis for reward anticipation as performed on the whole brain level was performed for a small volume of interest (striatum) as well to investigate anatomical specificity across the striatum. This analysis was performed for both the complete sample and the sensitivity sample. The small volume was defined as the bilateral putamen, caudate and nucleus accumbens using the Hammers-smith atlas.³⁹ The significance threshold was set at $p < 0.005$, voxel-level uncorrected combined with a cluster level family-wise error (FWE) correction $p < 0.05$.

2.7.4 | Exploratory fMRI analyses

All the above described fMRI analyses were also applied for the outcome phase: to the reward hit > reward too late contrast and reported in the main text. Furthermore, for the sake of completeness and transparency, all whole-brain linear regression analyses in the complete and sensitivity samples for both contrasts were also performed without covariates. Results of these analyses are reported in the supporting information.

3 | RESULTS

3.1 | Descriptive statistics

Table 1 includes a summary of participants' demographics as well as information on the predictors, covariates and cotinine values.

3.2 | Behavioural results

3.2.1 | Correlational analyses

See Table S1 for results of all bivariate analyses. For ETS exposure, a significant correlation was observed with familial risk ($r = 0.470$, $p < 0.001$), suggesting that adolescents with a higher risk of familial nicotine dependence are more likely to experience exposure to ETS. Monthly smoking was positively associated with cannabis use ($r_T = 0.263$, $p < 0.001$) and cotinine levels ($r_T = 0.365$, $p < 0.001$). Furthermore, adolescents with mothers who smoked during pregnancy were more exposed to ETS in their current life than adolescents with mothers who had not smoked during pregnancy ($t[89] = -3.28$, $p = 0.001$).

TABLE 1 Demographics

	Experimental smokers (N = 100)				
	Mean	SD	Range	Median	IQR
Gender, n (% male)	30 (30%)				
Education					
Low, n (%)	57 (57%)				
Middle, n (%)	20 (20%)				
High, n (%)	23 (23%)				
Age	16.5	1.13	14–19	17	1
ETS exposure	9.03	6.91	0–33	7.0	10.75
Monthly Smoking	7.23	0.95 ^a	0–43.33	3.0	10.5
PDS score <i>female</i>	2.53	1.69	0–4	3.4	3.8
<i>male</i>	0.97	1.53	0–3.8	0.0	2.7
Familial risk ^b	1.99	2.35	0–8.5	1.0	4.0
Smoking during pregnancy n (% yes) ^b	12 (13.2%)				
AUDIT	8.33	4.96	0–21	8.0	6.0
Cannabis lifetime use	15.59	2.90 ^a	0–145	2.0	15
Cotinine	6.56	1.55 ^a	0–74.10	0.5	4.55
Cigarettes lifetime	90.97	10.91 ^a	2–500	42.5	91.25
Age of first cigarette	14.59	1.26	11–17	15	2

^aFor non-normally distributed variables, standard error is given instead of standard deviation.

^bN = 91 instead of 100 due to nine missing values on these variable, because not all parents filled out the questionnaires that were meant for them.

3.2.2 | MID reaction times

The paired-sample *t* test showed faster reaction times for rewarding (290 ms) than for non-rewarding (328 ms) trials ($t[99] = -12.135$, $p < 0.001$). The hierarchical regression analysis examining the association between ETS exposure, monthly smoking and reaction times (RT_{reward} minus RT_{non-reward}) showed a non-significant step one model ($F[6,91] = 0.660$, $p = 0.682$). ETS exposure and monthly smoking did not explain additional differences in reaction times ($\Delta R^2 = 0.019$, $p = 0.414$), suggesting that these two variables are not associated with reaction times during MID performance in experimental smoking adolescents.

3.3 | Imaging results

All results referred to in this section can be accessed online (at <https://neurovault.org/collections/8977/>), where we uploaded the corresponding T-maps.

3.3.1 | Whole brain one-sample *t* test

First, we examined whether the task activated the expected brain network for both the anticipation phase and the outcome phase. For anticipation (i.e., reward anticipation > non-reward anticipation), brain activity was observed in reward-related regions such as the bilateral

striatum (both dorsal and ventral), pallidum, insula and the ACC (Figure 2A). For outcome (i.e., reward hit > reward too late), brain activity was observed in the orbitofrontal cortex (OFC), ventro-medial prefrontal cortex (vmPFC), caudate and the posterior cingulate cortex (PCC) as well as the inferior and middle frontal gyrus (Figure 2B). Activity in these brain regions for the anticipation and outcome phases are in line with previous literature (see, e.g., recent neuroimaging meta-analysis of the MID task by Oldham et al.⁴⁰).

3.3.2 | Whole brain regression analyses

Second, we examined whether there were significant associations between current ETS exposure, monthly smoking and brain activity during the reward anticipation phase and the reward outcome phase. We did not observe any significant associations during the reward anticipation phase. During the reward outcome phase, we only observed a significant association between ETS exposure and activity in the cerebellum, such that higher ETS was associated with increased reward-outcome related activity within the cerebellum.

Sensitivity analyses in the reduced sample ($N = 92$) did not reveal new significant associations during reward anticipation. For the reward outcome phase, sensitivity analyses were unable to replicate the significant association between ETS exposure and cerebellum activity observed in the complete sample; however, significant positive associations were observed between ETS exposure and activity in the middle temporal and superior frontal gyri.

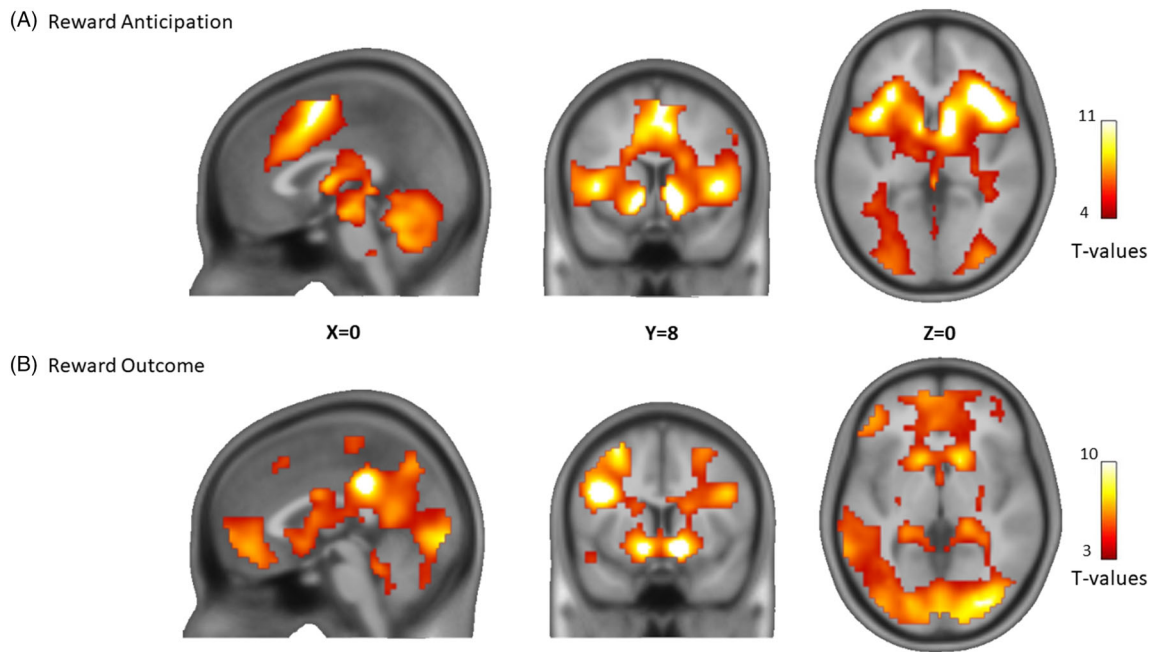


FIGURE 2 Reward-related brain activity in MID task (N = 100). (A) Whole-brain activations for reward anticipation: reward anticipation > non-reward anticipation. (B) Whole-brain activations for reward outcome: reward hit > reward too late. T-maps are overlaid on a MNI brain template (display threshold: voxel-level uncorrected $p < 0.001$, combined with a cluster-level family-wise error [FWE] corrected $P < .05$)

3.3.3 | ROI analyses

Results of the ROI analyses showed non-significant step 1 regression models for both anticipation ($F[6,92] = 0.797$, $p = 0.574$) and outcome ($F[6,93] = 0.607$, $p = 0.724$) in the complete sample as well as in the sensitivity sample (i.e., $F[6,85] = 0.652$, $p = 0.688$ and $F[6,85] = 0.705$, $p = 0.646$ for anticipation and outcome, respectively). Current ETS exposure and monthly smoking did not explain additional variance in ventral striatal activity for both anticipation ($\Delta R^2 = 0.023$, $p = 0.344$) and outcome ($\Delta R^2 = 0.019$, $p = 0.408$) in the complete sample as well as in the sensitivity sample (i.e., $\Delta R^2 = 0.034$, $p = 0.224$ and $\Delta R^2 = 0.025$, $p = 0.335$ for anticipation and outcome, respectively). We further examined these null findings using Bayesian statistics on the extracted percent signal change values. Using standard priors as implemented in JASP, Bayes factors for anticipation and outcome in the complete sample were $BF_{01} = 1.754$ and $BF_{01} = 1.962$, while in the sensitivity sample, they were $BF_{01} = 1.227$ and $BF_{01} = 1.648$, respectively, reflecting anecdotal evidence for the null-hypotheses.

3.3.4 | Small volume corrections

The results for both the complete sample and the sensitivity sample did not reveal any significant associations between current ETS exposure or monthly smoking and reward anticipation and outcome activation in the striatum using a small volume correction while correcting for covariates of no interest.

4 | DISCUSSION

In this study, we investigated the relationship between current ETS exposure, monthly smoking and VS reward-related activity in a sample of 100 experimental smoking adolescents, using a variety of pre-registered analyses approaches: (1) a whole-brain voxel-wise approach, (2) an ROI approach with the VS as ROI using frequentist as well as Bayesian statistics and (3) a small volume voxel-wise approach across the complete striatum. The results converged in revealing no relationship between monthly smoking, current ETS exposure and reward-related brain activation across the brain or in the (ventral) striatum specifically. Additionally, Bayesian statistics showed only anecdotal evidence for the null hypothesis in the VS, limiting our ability to draw firm conclusions about the hypothesized relationship between monthly smoking, ETS exposure and VS activity.

With regard to monthly smoking, current results showed anecdotal evidence for the lack of an association with VS anticipatory reward-related activation in experimentally smoking adolescents. This is in contrast with previous work from Peters and colleagues,⁸ who observed a relationship between anticipatory VS reward-related activity and smoking frequency in adolescents, so that the VS response was lowest in those who smoked more frequently. The discrepancy between these and the current results may originate from differences in sample size and composition; unlike our study, the study by Peters and colleagues⁸ included adolescents with more established patterns of smoking, including daily smoking. Furthermore, while Peters and colleagues⁸ observed lower VS responses during reward anticipation in a subset of smokers with extremely

mild smoking habits (<10 cigarettes lifetime), it should be noted that this study was based on only 14 participants. Our inability to replicate this result in a larger sample of ($N = 100$) suggests that the relationship between monthly smoking and anticipatory VS reward-related hypoactivity may be weak at best or that changes in anticipatory reward-related VS activity do not yet occur in the very early phases of smoking when smoking is limited and adolescents are still experimenting. It might suggest that anticipatory reward-related VS hypoactivity arises as a consequence of smoking rather than as a predisposition to start smoking. Large longitudinal studies will be needed to further investigate this hypothesis. With regard to ETS exposure, our study found no conclusive evidence for an association with VS anticipatory reward-related activation, given that the frequentist statistics found no significant association and the Bayesian statistics revealed anecdotal evidence for an absence of association. The idea that ETS exposure during adolescence may result in reward-related functional brain alterations is partly based on a previous study focusing on the effects of intra-uterine cigarette smoke exposure.²⁴ Adolescents prenatally exposed to tobacco showed less activity within the VS during reward anticipation of non-drug rewards compared with adolescents who were not exposed to tobacco prenatally.²⁴ Although it has been shown that the acetylcholine receptors within the brain in reward-related regions can be occupied by nicotine as a result of ETS exposure,²³ our results, although inconclusive, tend to suggest that ETS exposure during adolescence is not associated with changes in brain functioning related to anticipatory reward processing. This difference with the study of Müller²⁴ may arise from the fact that the levels of nicotine exposure for the foetus are higher if the mother smoked during pregnancy in comparison to the levels of nicotine exposure derived from ETS exposure for experimentally smoking adolescents. This might suggest that brain-related responses might occur only after relatively high levels of exposure, whereas in this study, relatively low levels of exposure during adolescence may not have (yet) resulted in anticipatory reward-related brain changes. Within our sample, we observed a relatively low mean level of ETS exposure, as well as a limited between-subject variability. Although we aimed to include participants at the low and high end of ETS exposure (i.e., from 0–48, respectively), we only managed to include participants with a mean ETS exposure score of 9 with a range of 0–33. Future studies should therefore focus on including more participants at the high end of ETS exposure to be able to better establish the association with anticipatory reward-related brain activity, if there is any.

Within this study, inconclusive evidence for the absence of association between anticipatory reward-related brain activity and monthly smoking as well as current ETS exposure was found among experimental smoking adolescents. Potentially, this could be related to the fact that reward-related activity patterns may differ by gender. A recent longitudinal study⁴¹ showed that anticipatory reward-related brain activity predicted future alcohol use differently for male and female adolescents. For boys, higher VS activity during reward anticipation predicted increases in alcohol use 2 years later, while in girls, blunted VS activity was found to be associated with increases in

alcohol use. Such opposite profiles between boys and girls could potentially explain the lack of an association in our study, which enrolled a boy/girl ratio of 30/70. However, additional exploratory analyses comparing boys and girls showed no evidence for significant gender differences in how anticipatory reward-related brain activity patterns are associated with monthly smoking and current ETS exposure (although one must keep in mind that these sub-group analyses may be underpowered).

With regard to reward outcome, current results showed anecdotal evidence for a lack of an association between current ETS exposure, monthly smoking and striatal responsivity. This observation is somehow consistent with previous findings which did not find evidence for significant difference in striatal responses to reward outcomes between smokers and control subjects.^{8,42} Across the whole brain, we did observe significant activity within the cerebellum for higher levels of ETS exposure in the complete sample. However, sensitivity analyses were unable to replicate this result. Given the low reliability of these results, no strong conclusions can be formulated regarding the activity observed in the cerebellum. Overall, no notable evidence for a relationship between monthly smoking, ETS exposure and reward related outcome activation was found. Replication is needed to confirm these findings.

To our knowledge, this is the first (pre-registered) study that addresses the role of current ETS exposure and monthly smoking with regard to reward-related brain activity using fMRI in the very early phases of smoking in a large sample of adolescents. In addition, we succeeded to recruit a sample in which half of the participants were in a relatively lower educational track. Given that lower educational levels are associated with higher smoking rates in the environment,⁴³ these individuals are at increased risk for developing a nicotine dependence as well as relatively high levels of ETS exposure. Nevertheless, the present results should be interpreted in the context of some limitations. First, we found only anecdotal evidence in favour of the null-hypotheses. This indicates that the results are inconclusive and that the performed study was not sensitive enough to distinguish between the null and the alternative model. Our pre-registered power analysis was conducted to allow the detection of medium effect sizes ($f^2 > 0.15$); however, it is possible that the effect size of the relationship between monthly smoking, ETS exposure and striatal reward-related brain activation is even smaller in reality. Consequently, to ensure that the study has acceptable power to distinguish between the null and alternative model and is able to detect or exclude a small effect, we possibly need an even larger sample size. Recent studies have actually suggested that the identification of reliable brain-behaviour correlations requires larger sample sizes than are typically used, partly due to the limited test-retest reliability of fMRI measures.^{44–46} Even though our study is more powered than the vast majority of previous studies, it may remain underpowered for that purpose.

Second, the adolescents in the current study showed a relatively large age range, thereby possibly increasing the variance in brain development across participants. It could be that normal brain development across adolescents, characterized by increases in striatal

engagement,⁴⁷ interferes with our hypothesis of reduced ventral striatal activation. To control for this, we included the pubertal development scale (PDS) as a covariate in all our analysis; however, it appeared that there was not much variance within this PDS measure (see Table 1), while it is known that behavioural, emotional and cerebral development can still widely differ among adolescents.^{48–50} To better quantify brain development, future research could use measures of salivary testosterone that are sensitive to interindividual differences^{51,52} and are mechanistically involved in mediating brain development.^{53–55}

Third, the ETS exposure measure in this study is a subjective measure based on self-report. In order to obtain a more detailed measure of the actual exposure in the current environment, future studies could include silicone wristbands measuring the nicotine exposure in the environment⁵⁶ as well as more elaborate questionnaires distinguishing between indoor versus outdoor smoking. Moreover, future studies could also take into account lifetime ETS exposure, in addition to current exposure, to better determine the long-term effects on reward-related brain activity during adolescence.

Finally, ideally future studies could include an extra control condition. This could either be a group of never-smoking adolescents or a group of regularly smoking adolescents. This could help in better interpreting the results of the current study in which we tested the dose-response relationships with monthly smoking and ETS exposure. On the one hand, comparing experimental smoking adolescents with never-smoking adolescents could help identify the role of ETS exposure specifically while ruling out effects of smoking itself. On the other hand, comparing experimental smoking adolescents with regularly smoking adolescents could help to test whether reward-related changes in brain activity can be replicated in a group of regular smokers and in addition test whether there are reward-related changes in experimental smokers in the same direction as previously observed in regular smokers.

In summary, the frequentist analyses did not show evidence for the hypothesized dose-response relationship between current ETS exposure, monthly smoking and VS hypoactivity during reward anticipation and outcome among experimentally smoking adolescents. Bayesian statistics provided only anecdotal evidence supporting the null hypothesis. This study therefore offers inconclusive evidence for the absence of association between reward-related brain activity and monthly smoking as well as current ETS exposure. Larger sample sizes are therefore needed to reliably distinguish between the null and alternative model. Although only anecdotal, the results of this study tend to support the null-hypotheses and thus suggest that blunted reward-related brain responses may only occur after relatively high levels of exposure—such as prenatal exposure instead of ETS exposure during adolescence—or are associated with the more long term effects of smoking behaviour. In order to test this hypothesis, future research will benefit from larger sample sizes, as well as from an increased pools of participants at the high end of ETS exposure and the use silicone wristbands to measure (environmental) smoking.

AUTHORS CONTRIBUTION

JD designed the study, recruited participants, collected data, performed the fMRI measurements and data analysis, and wrote the manuscript. ML wrote the grant for this project, designed the study, contributed to the data analysis and edited the manuscript. GS contributed to the data analysis and edited the manuscript. MK and RO wrote the grant for this project, designed the study and edited the manuscript.

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CONFLICT OF INTEREST

The authors declared that no competing interest exists.

DATA AVAILABILITY STATEMENT

T-maps can be accessed online (at <https://neurovault.org/collections/8977/>). The SPSS datasets and syntax are available via data archiving and network services of DANS: <https://doi.org/10.17026/dans-z8s-p6ke>.

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