Original investigation

Nicotine Increases Activation to Anticipatory Valence Cues in Anterior Insula and Striatum

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Abstract

Introduction: Smoking is associated with significant morbidity and mortality. Understanding the neurobiology of the rewarding effects of nicotine promises to aid treatment development for nicotine dependence. Through its actions on mesolimbic dopaminergic systems, nicotine engenders enhanced responses to drug-related cues signaling rewards, a mechanism hypothesized to underlie the development and maintenance of nicotine addiction.

Methods: We evaluated the effects of acute nicotine on neural responses to anticipatory cues signaling (nondrug) monetary reward or loss among 11 nonsmokers who had no prior history of tobacco smoking. In a double-blind, crossover design, participants completed study procedures while wearing nicotine or placebo patches at least 1 week apart. In each drug condition, participants underwent functional magnetic resonance imaging while performing the monetary incentive delay task and performed a probabilistic monetary reward task, probing reward responsiveness as measured by response bias toward a more frequently rewarded stimulus.

Results: Nicotine administration was associated with enhanced activation, compared with placebo, of right fronto-anterior insular cortex and striatal regions in response to cues predicting possible rewards or losses and to dorsal anterior cingulate for rewards. Response bias toward rewarded stimuli correlated positively with insular activation to anticipatory cues.

Conclusion: Nicotinic enhancement of monetary reward-related brain activation in the insula and striatum in nonsmokers dissociated acute effects of nicotine from effects on reward processing due to chronic smoking. Reward responsiveness predicted a greater nicotinic effect on insular activation to salient stimuli.

Implications: Previous research demonstrates that nicotine enhances anticipatory responses to rewards in regions targeted by midbrain dopaminergic systems. The current study provides evidence that nicotine also enhances responses to rewards and losses in the anterior insula. A previous study found enhanced insular activation to rewards and losses in smokers and ex-smokers, a finding that could be due to nicotine sensitization or factors related to current or past smoking. Our finding of enhanced anterior insula response after acute administration of nicotine in nonsmokers provides support for nicotine-induced sensitization of insular response to rewards and losses.

Introduction

Tobacco smoking is the leading cause of preventable deaths in the United States, responsible for a 10-year reduction in lifespan among smokers who do not quit.¹ Despite widespread awareness that smoking increases the risk of cancer, cardiovascular, and lung disease, 15% of the general US population smokes tobacco.² This high prevalence of smoking in the face of major public health efforts to decrease smoking speaks to the addictive nature of nicotine. Accordingly, a better understanding of the neurobiological underpinnings of smoking risk is critical to developing new prevention and treatment strategies for nicotine dependence.

Similar to most addictive drugs, nicotine exerts its potential for abuse by activating reward circuits that evolved to increase motivation for natural rewards. Specifically, nicotine acts on nicotinic acetylcholinergic receptors on dopaminergic neurons in the ventral tegmental area that project to the nucleus accumbens, leading to amplification of striatal dopamine release in response to reward-predicting stimuli.³ Striatal dopaminergic activity mediates attribution of incentive salience to drug-related cues in addiction⁴ thought to be associated with a concomitant reduction in salience of nondrug related rewards.⁵

In this study, we used two well-validated tasks to probe the effects of acute nicotine exposure on reward processing using a placebo-controlled crossover design. The use of nondrug, monetary rewards in both tasks allowed for the evaluation of the effects of nicotine on processing of cues that are intrinsically rewarding. Toward these goals, we probed the neural effects of acute nicotine using the monetary incentive delay (MID) task, a well-validated functional magnetic resonance imaging (fMRI) task used widely in the study of incentive processing.⁵ In addition, we utilized a probabilistic reward task in which individuals learn to respond preferentially (ie, develop a response bias) toward a stimulus more frequently associated with monetary reward, as prior studies have shown that nicotine use increases bias toward stimuli more likely to receive monetary reward.

The effects of acute nicotine exposure on brain activation elicited by the MID have been studied in two prior fMRI studies, one in smokers⁶ and one in both smokers and nonsmokers.⁷ In Rose et al.,⁶ anticipation of rewards or anticipation of possible penalties was grouped together as valence, and smokers had reduced activation of the right putamen to anticipating incentives under the nicotine condition compared with placebo. In contrast, Fedota et al.⁷ reported that both smokers and nonsmokers had enhanced activation to anticipating rewards under the nicotine condition compared with placebo in bilateral putamen and dorsal anterior cingulate (dACC), but found no effect of nicotine for anticipating losses. Both studies focused on *a priori* regions of interest (ROIs) that are targets of mid-brain dopaminergic systems: striatal subregions, anterior cingulate, and orbitofrontal cortices. Of note, neither of these studies evaluated the anterior insula.

Although studies using the MID in addiction typically focus on the striatum,⁸ the anterior insula plays an important role in nicotine dependence. Robust activation of the anterior insula and ventral striatum is routinely found in response to anticipatory reward-related signals using the MID task.⁶ The anterior insula, a key node of the salience network,⁷ is activated in both anticipatory and consummatory phases of reward processing to both gains and losses.⁹ Preclinical work in nicotine-naïve rodents demonstrated that of all brain regions activated by nicotine, the insula had increased activation starting at the lowest doses of nicotine tested, suggesting that

the insula is the most sensitive region in the brain to the effects of nicotine.¹⁰ The anterior insula is commonly activated in drug cue reactivity paradigms with positive correlations between insular activation and subjective ratings of craving.^{11,12} Critically, damage to the anterior insula is associated with reduced urge to smoke leading to spontaneous smoking cessation.¹³

Therefore, in addition to focusing on mesolimbic and nigrostriatal regions as in previous research, we evaluated the effects of nicotine on the anterior insula in reward processing. Our study builds upon prior work by evaluating the effects of nicotine on anterior insular activation to anticipation of rewards (MID) and reward-based learning dependent on receipt of monetary reward (probabilistic reward task). The simultaneous use of two reward tasks was primarily undertaken in order to examine correlations between nicotine-induced activation in anticipation of rewards/losses in the anterior insula and response bias. The study sample is comprised of nonsmokers, allowing analyses restricted to nonsmokers to dissociate effects of acute nicotine administration from those due to chronic exposure to nicotine.

We hypothesized that nicotine administration would be associated with increased responses to anticipatory cues in the anterior insula and mesolimbic regions. Because anterior insula activation is found in multiple stages of reward processing,⁹ we also predicted that nicotinic effects on response bias would be positively correlated with anterior insular activation to valence cues from the MID task.

Methods

Participants and Study Design

Fifteen participants (18–55 years old) were recruited from the community. Informed consent approved by local Institutional Review Boards (IRBs) was obtained from each participant prior to study procedures. Participants did not have any Axis I psychiatric illness, as confirmed by the Structured Clinical Interview for DSM-IV,¹⁴ and were required to have negative urine toxicology screens at all study visits. A monitor to measure exhaled carbon monoxide (CO) confirmed self-reported smoking status (CO < 5 for nonsmokers; CO > 10 for smokers). All nonsmokers denied a history of regularly smoking in the past, as defined as having a history of smoking more days than not or smoking ≥ 10 cigarettes daily for more than 1 week.

One nonsmoking participant did not complete the study due to nausea or vomiting and was excluded from analysis. Of the 14 remaining participants, 11 were nonsmokers. Two additional nonsmokers vomited during the nicotine condition after completing the study visit and were included in analyses. Nonsmoking participants included five females and six males and were 41.2 ± 11.0 years old with 15.4 ± 2.1 years of education and received 12.1 ± 3.3 mg of nicotine.

A randomized, placebo-controlled crossover design was used in which each participant was administered transdermal nicotine or placebo on two separate study sessions performed at least 7 days apart. Order of drug was counter-balanced; see Supplementary Methods for details on nicotine patch administration and dosing. The probabilistic reward task was performed 2 hours after initial patch administration. Three hours after patch administration, subjects underwent fMRI while performing the MID task. Participants were compensated with monetary payment for both tasks based on performance after completing the study.

Monetary Incentive Delay Task

We used a variant of the MID task identical to the version described in the work of Knutson et al.¹⁵ Anticipatory cues that denoted possible receipt of a monetary reward (circle), avoidance of loss of a monetary reward (square), or no monetary reward or loss (neutral: triangle) were presented for 500 milliseconds. After a jittered delay (2, 4, 6, or 8 seconds), the anticipatory cue was followed by the presentation of a shaded white square target (500 milliseconds). Subjects were instructed to respond using a button press as quickly as possible upon presentation of the target to gain or avoid losing money. Feedback was presented for 1500 milliseconds, indicating the outcome (eg, monetary gains or losses). Each trial was followed by an intertrial interval of 4–10 seconds (in 2-second increments). Fifty trials were presented with 20 reward cues, 20 loss cues, and 10 neutral cues. The total task duration was 12 minutes performed over a single run.

In order to match performance across subjects, the threshold to determine whether a subject responded to the target quickly enough to gain reward or avoid loss was based on individual reaction times, such that subjects succeeded on ~66% of target presentations. Subjects were not informed of the adaptive nature of the task.

MRI Data Acquisition

Subjects were scanned on a 3-T Siemens Trio scanner with a 12-channel head coil at the McLean Imaging Center. High resolution ($1 \times 1 \times 1$ mm³) T1-weighted MPRAGE images were acquired. Functional MR images for the MID task were acquired over 32 axial, interleaving, 4-mm sections by means of a gradient-echo echoplanar imaging sequence (367 volumes; echo time/repetition time 30/2000 milliseconds; flip angle 90°; field of view 384×384 mm²; image matrix 64×64 ; voxel dimensions $3.125 \times 3.125 \times 3.0$ mm) with a tilted slice acquisition (−30° from AC–PC line).

Response Bias Task

A probabilistic reward task described previously was completed during both visits.^{16,17} Each trial began with the presentation of a fixation crosshair for 500 milliseconds. After a delay of 500 milliseconds, a cartoon face without a mouth was presented and a short or long mouth (11.5 vs. 13 mm) flashed briefly (100 milliseconds). Participants were asked to press “c” or “m” on a keyboard to indicate if the face had the short or long mouth. Response key corresponding to mouth length was counterbalanced across sessions and participants. Two blocks of 100 trials each were performed per session. Participants were trained to ensure that they could adequately discriminate between the two stimuli. Unbeknownst to the participants, an asymmetrical reinforcer ratio was used, such that correct responses for one mouth length (“rich stimulus”) were associated with feedback of monetary reward three times more often than for the other mouth length (“lean stimulus”). This differential reinforcement schedule elicits the development of a response bias in favor of the more frequently rewarded (rich) stimulus, which is also manifested as greater accuracy and faster reaction times for the rich compared with the lean stimulus.^{17,18}

Statistical Analyses

Primary analyses of interest were restricted to nonsmokers ($n = 11$). Analyses for the entire sample ($n = 14$) can be found in Supplementary Material.

MID Behavioral Data

A mixed effects repeated measures model was used with median reaction time (RT) as the dependent variable and DRUG, SESSION, and CONDITION (Reward Cue, Neutral Cue, and Loss Cue) and DRUG $\times$ CONDITION as independent variables. DRUG $\times$ CONDITION was removed from the model if not significant ($p < .05$). Because two nonsmokers experienced nausea or vomiting under the nicotine condition, we also included a binary variable for presence or absence of nausea or vomiting (SIDE EFFECTS) in the model.

MID fMRI Task

Analyses were conducted using FSL version 5.0.6. To allow for signal stabilization, the first 4 volumes were removed. Preprocessing steps included motion correction (MCFLIRT), brain extraction, slice time correction, spatial smoothing with a Gaussian kernel full-width half maximum 6 mm, and high-pass temporal filtering. An in-house program was used to detect artifacts due to motion and intensity spiking. Subject fMRI data were spatially normalized to the MNI 152 template. For all subjects, slice SNR values for fMRI data were ≥ 150 (mean relative displacement 0.15 ± 0.06 mm).

Individual subject session data were analyzed using the general linear model with regressors for anticipatory Reward Cue, Loss Cue, Neutral Cue, and five regressors for feedback (neutral trials and successful and unsuccessful trials for anticipatory reward and loss trials) and regressors for six motion parameters and artifactual time points detected by in-house software described elsewhere.¹⁹ Stimulus waveforms were convolved with gamma hemodynamic response functions. The contrasts of interest were for anticipatory cues: Reward Cue–Neutral Cue and Loss Cue–Neutral Cue. Whole-brain group analysis was performed with FLAME using a paired t-test comparing anticipatory cue contrasts for Nicotine–Placebo and Placebo–Nicotine conditions. Control for multiple comparisons was performed using a z -statistic of 2.3 (corresponding to $p = .01$) to define contiguous clusters with a threshold of $p_{\text{corrected}} = .05$ based on a recent study demonstrating that FLAME was associated with an acceptable level of false-positives for event-related designs at this threshold.²⁰ The minimum cluster size was 325 voxels. Given the small sample size, we also planned a priori to use ROI analyses targeting the anterior insula and regions of mesocorticolimbic and nigrostriatal networks implicated in nicotine dependence: ventral striatum, caudate, putamen, and ACC. ROIs from our previous work performed in independent samples were used for the bilateral anterior insula and ventral striatum.^{19,21} For the caudate and putamen, we derived ROIs from the Harvard-Oxford Subcortical Structural Atlas. Since the dorsal region of the anterior cingulate cortex has been implicated in prior studies of nicotine dependence,²² we created a 10-mm sphere around dACC coordinates identified from a meta-analysis of fMRI reward-related tasks (MNI $-2, 28, 28$).²³ Because whole-brain analysis identified clusters involving anterior insula, striatum, and dACC for the Loss Cue–Neutral Cue contrast, ROI analyses were restricted to the Reward Cue–Neutral Cue contrast. Mean parameter estimates were extracted from each ROI (averaged over each ROI). We used repeated measures mixed models with DRUG, SESSION, and SIDE EFFECTS in each model.

Response Bias Task

The main variable of interest was response bias, as it indexes reward responsiveness. After removing outlier reaction times,¹⁷ response bias (log b) was calculated as

$$\log b = \frac{1}{2} \log[(\text{Rich}_{\text{correct}} * \text{Lean}_{\text{incorrect}}) / (\text{Rich}_{\text{incorrect}} * \text{Lean}_{\text{correct}})].$$

To allow calculation of response bias in cases without incorrect responses, 0.5 was added to each cell in the 2×2 contingency table for correct and incorrect responses for the rich and lean stimuli.²⁴ To determine whether nicotine administration was associated with a change in response bias, a repeated measures mixed effects model was used with RESPONSE BIAS as the dependent variable and DRUG, SESSION, BLOCK, and SIDE EFFECTS as independent variables.

The main purpose of measuring response bias was to probe possible relationships between total response bias (averaged across blocks) and nicotine effects on activation for anticipatory cues in the anterior insula for the MID. (We used the anterior insula ROIs for both the gain and loss contrasts since anterior insula clusters derived from whole-brain cluster analysis also included striatal regions.) To this end, we used repeated measures mixed effects models with MID anticipatory reward cue- or loss cue-related activations in the anterior insula as dependent variables and DRUG, SESSION, RESPONSE BIAS, SIDE EFFECTS, and DRUG $\times$ RESPONSE BIAS interaction as predictor variables. The primary variable of interest was the DRUG $\times$ RESPONSE BIAS interaction. We performed Pearson correlations between anterior insula activation and RESPONSE BIAS for each drug condition separately and compared the two correlation coefficients with r -to- z transformation using a method that accounts for nonindependence of correlations.²⁵

For ROI and response bias analyses, tests of hypotheses were two-sided with a significance level of 0.05 (uncorrected for multiple comparisons).

Results

MID Behavioral Data

For median RT, there was a significant CONDITION effect owing to significantly faster RT for both Reward Cue and Loss Cue trials relative to Neutral Cue trials (Reward Cue: $\beta = -0.03$, $p = .003$; Loss Cue: $\beta = -0.02$, $p = .03$; Supplementary Table 1), confirming that this version of the MID elicited the intended effects. For the nicotine condition, median RT was 44 milliseconds faster for Reward Cue and 40 milliseconds faster for Loss Cue trials compared with Neutral Cue trials, whereas for the placebo condition, median RT was 16 milliseconds faster for the Reward Cue and 5 milliseconds for Loss Cue trials; however, there were no significant DRUG, DRUG $\times$ CONDITION, or SESSION effects. There was a significant effect of SIDE EFFECTS associated with increased RT for those who experienced nausea or vomiting ($\beta = 0.08$, $p = .001$).

MID fMRI Task

Whole-Brain Analysis

Whole-brain analysis comparing nicotine and placebo conditions revealed increased activation in regions encompassing the right frontopolar/anterior insula with nicotine administration (Nicotine–Placebo) for the Loss Cue–Neutral Cue contrast. We also identified regions in bilateral superior frontal gyri, caudate, putamen, and dACC for the Loss Cue–Neutral Cue contrast, all with increased activation with nicotine (Table 1; Figure 1).

There were no significant whole-brain findings for the Reward Cue–Neutral Cue contrast. There were no significant findings for either contrast for Placebo–Nicotine comparison.

ROI Analyses: Reward Cue–Neutral Contrast

We found a significant DRUG effect with increased nicotine-induced activation in the right anterior insula ($\beta = 217.9$, $p = .03$). We also found significant nicotine-induced activation in the right caudate ($\beta = 197.9$, $p = .01$), right ventral striatum ($\beta = 150.6$, $p = .03$), left putamen ($\beta = 97.1$, $p = .01$), and dACC ($\beta = 254.6$, $p = .001$; Figure 2; Supplementary Table 2). There were no significant DRUG effects for the left anterior insula, left caudate, left ventral striatum, and right putamen. There were significant effects of SESSION for the right anterior insula, right caudate, left putamen, and dACC associated with relatively decreased activation in the second scan. There was a significant effect of SIDE EFFECTS only for the left putamen, associated with decreased activation in individuals who experienced nausea or vomiting.

Analyses for the entire sample ($n = 14$) that included three smokers are presented in Supplementary Material and were consistent with results for nonsmokers (Supplementary Table 3 and Figure 1).

Response Bias Task

There were no significant effects of DRUG, BLOCK, or SIDE EFFECT for response bias. There was a significant effect of SESSION associated with increased response bias for the second scan ($p = .001$). However, when evaluating relationships between total response bias and anterior insula MID activations, using the right anterior insula ROI for the Reward Cue–Neutral Cue contrast, we found a significant DRUG $\times$ RESPONSE BIAS interaction ($\beta = 1816.9$, $p = .003$). There was a significant positive correlation between RESPONSE BIAS and right anterior insula activation for the nicotine condition ($r = 0.63$, $p = .04$; Figure 3A), but no significant correlation for the placebo condition ($r = -0.37$, $p = .26$). Correlation for the nicotine condition was significantly greater than correlation for the placebo condition (DRUG comparison of correlations: $z = 2.30$, $p = .02$).

Table 1. Nicotine–Placebo Effects for Anticipatory Loss Cue–Neutral Cue Contrast From the Monetary Incentive Delay Task in Nonsmokers

Brain area	Side	Volume (No. of voxels)	Z value	Peak activity: MNI coordinates		
				x	y	z
Loss Cue–Neutral Cue						
Fronto-insular cortex	R	1847	3.7	56	22	20
Superior frontal gyrus	R	1029	3.9	36	50	26
Superior frontal gyrus	L	982	3.9	–50	42	26
Fronto-insular cortex, caudate, putamen	L	382	3.2	–38	14	8
Dorsal anterior cingulate cortex	Bilateral	364	3.4	4	24	40

Identified from whole-brain analysis ($p_{\text{corrected}} < .05$). There were no significant whole-brain findings for the Reward Cue–Neutral Cue contrast.

Figure 1. Brain areas identified by whole-brain analysis with significant DRUG effects (Nicotine-Placebo) for the anticipatory Loss Cue-Neutral Cue contrast from the monetary incentive delay task in nonsmokers ($p_{\text{corrected}} < .05$).

Figure 2. (A) ROIs: violet = anterior insula. (B) red = caudate, blue = putamen, and yellow = ventral striatum. (C) green = dorsal anterior cingulate (dACC). (D) Nicotine was associated with significantly greater activation in the right anterior insula, right caudate, right ventral striatum, left putamen, and dACC for the anticipatory Reward Cue-Neutral Cue contrast in nonsmokers using mixed effects models controlling for DRUG, SESSION, and SIDE EFFECTS (* $p < .05$).

Figure 3. Positive correlations between total Response Bias (averaged across both blocks) from the probabilistic reward task and activation in the right anterior insula region of interest in the monetary incentive delay task for the anticipatory. (A) Reward Cue-Neutral Cue ($r = -0.63$, $p = .04$) and (B) Loss Cue-Neutral Cue contrasts ($r = 0.89$, $p < .001$) during the nicotine condition. Correlation between response bias and right anterior insula activation was significantly greater in the nicotine compared with placebo condition for both contrasts (Reward Cue-Neutral Cue: placebo $r = -0.37$, $p = .26$; difference between nicotine and placebo: $z = 2.30$, $p = .02$; Loss Cue-Neutral Cue: placebo $r = -0.42$, $p = .20$; difference between nicotine and placebo: $z = 4.03$, $p < .001$).

For the Loss Cue–Neutral Cue contrast, we found a significant DRUG $\times$ RESPONSE BIAS interaction ($\beta = 1570.6$, $p \leq .001$). There was a significant positive correlation between RESPONSE BIAS and right anterior insula activation for the anticipatory loss contrast in the nicotine condition ($r = 0.89$, $p < .001$; Figure 3B), but not for the placebo condition ($r = -0.42$, $p = .20$). Correlation for the nicotine condition was significantly greater than correlation for the placebo condition (DRUG comparison of correlations: $z = 4.03$, $p < .001$). There were no significant DRUG $\times$ RESPONSE BIAS interactions for the left anterior insula ROI for either contrast.

In summary, we found significant DRUG $\times$ RESPONSE BIAS effects for right anterior insula activation for both the Reward Cue–Neutral Cue and Loss Cue–Neutral Cue contrasts and significant positive correlations between response bias and right anterior insula activation in anticipation to both rewards and losses associated with nicotine.

Control Analyses

Given the small sample size, to determine whether findings were influenced by outliers, outliers were defined using the median rule (median $\pm 2.3 \times$ interquartile range).²⁶ No outliers were identified for ROI findings or response bias.

To evaluate whether whole-brain clusters for the Loss Cue–Neutral Cue were influenced by nausea or vomiting, we extracted mean contrast parameter estimate from each of the five clusters. For each cluster, we used repeated measures mixed models with DRUG, SESSION, and SIDE EFFECTS as independent variables. Controlling for SIDE EFFECTS, the DRUG effect remained significant in all clusters.

Discussion

Acute nicotine administration was associated with increased activation to cues anticipating rewards and losses in the right anterior insula, striatum, and dACC in a cohort of nonsmokers. The novel finding of our study was enhanced nicotine-induced activation of the right anterior insula in response to anticipatory valence cues. A second novel finding was the significant DRUG $\times$ RESPONSE BIAS interaction for right anterior insula activation, indicating a positive relationship between response bias and activation of the anterior insula in response to anticipating potential rewards and avoiding losses associated with nicotine administration. We replicated the finding of nicotine-induced increased striatal activation to anticipatory gains found in a prior study using the MID in nonsmokers.²⁷ In addition, we also found nicotine-induced activations to losses in the striatum.

Rich in nicotinic acetylcholine receptors,²⁸ the anterior insula plays an important role in nicotine dependence due to its prominent response to smoking cues and its influence on smoking cessation¹³ and relapse.²⁹ The anterior insula is thought to represent interoceptive awareness of salient events³⁰ and serves as a critical hub of the salience network.⁷ Thus, the nicotinic effect on insular activation to anticipatory cues for both gains and losses suggests that nicotine is associated with enhanced processing of salient cues regardless of valence, possibly by modulating interoceptive states associated with anticipating rewards and losses.

In a recent study using the MID (without drug challenge), smokers and ex-smokers had increased activation of the anterior insula in anticipation of both rewards and losses compared with never smokers.³¹ Enhanced insular activation to anticipatory cues in smokers

and ex-smokers may reflect nicotine sensitization versus inherent vulnerability to develop addiction^{32,33} or chronic effects of nicotine.³⁴ Our finding of enhanced nicotine-induced insular activation to valenced cues in nonsmokers is more consistent with a model that nicotine sensitizes insular response to salient stimuli.

Prior studies of acute nicotine administration using the MID task have shown inconsistent results in the striatum. One study reported reduced ventral striatal activation for anticipatory valence cues in response to nicotine in smokers; nonsmokers were not administered drug in this study.³⁵ A second study examined the effect of nicotine patch administration in both smokers and nonsmokers. Nicotine administration was associated with increased striatal activation (dorsal putamen) in both groups in response to anticipating rewards but not losses.²⁷ We replicated the finding of nicotine-induced increases in activation for cues anticipating possible monetary gain in the striatum (including putamen) in nonsmokers. Our study is distinct in also finding nicotine-induced increases of bilateral striatal activation for cues anticipating possible monetary loss. Preclinical research suggests that mesolimbic dopamine signaling occurs not only to rewards, but also to salient aversive stimuli.^{36,37} A meta-analysis of fMRI studies of subjective value found ventral striatal activation to stimuli denoting both positive and negative valences.²³

The absence of a significant DRUG effect for the probabilistic reward task contrasts previous findings of increased response bias in nonsmokers exposed to acute nicotine,¹⁶ which may be due to the smaller sample size and decreased power of the current study. In our previous study, we observed enhanced response bias with nicotine compared with placebo with an effect size of $d = 1.0$ in a larger sample. A minimal sample size of 18 participants is required to detect an effect size of $d = 1.0$ with 80% power at a significance level of $\alpha = 0.05$. However, we did find significant DRUG $\times$ RESPONSE BIAS interactions between response bias and right anterior insula activation for both rewards and losses with significant correlations between right anterior insula activation in anticipation of valenced cues and response bias for the nicotine condition. The finding of a positive correlations between response bias and insular activation in response to both rewards and losses speaks to the prominent role of the anterior insula at various stages in reward processing and responding to salience irrespective of direction of valence.⁹

The major study limitation is the small sample size. Our results should therefore be considered as preliminary and require replication. However, the MID task produces robust effect sizes allowing for significant striatal findings in small samples, cited as needing six subjects for power of 0.80.³⁸ Moreover, consistency between increased nicotine-induced activation in the striatum in nonsmokers and anterior insula activation in smokers in previous work^{27,31} supports the validity of our findings. Another limitation is that we did not correct for multiple comparisons in our ROI analyses for the Reward Cue–Neutral Cue contrast, increasing the risk of false positives. In addition, nicotine administration was associated with nausea or vomiting in two participants. The influence of side effects on our analyses was mitigated by controlling for nausea or vomiting. We also did not control for socioeconomic status, which may influence reward reactivity in paradigms using monetary rewards. Finally, participants received different doses of nicotine. Future research should therefore entail evaluation of the effects of nicotine on anterior insula activation in anticipation of valenced cues in a larger cohort of nonsmokers using standardized doses of nicotine (perhaps using lower doses to avoid side effects as available in nicotine lozenges).

Conclusions

We report novel findings of enhanced insular activation to anticipatory valence cues with nicotine and enhanced striatal responses to losses using the MID task. Critically, the current findings emerged in nonsmokers, allowing us to conclude that effects on anticipatory valence activation are specific to acute nicotine exposure and not due to factors related to chronic or past smoking.

Supplementary Material

Supplementary data are available at *Nicotine and Tobacco Research* online.

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Declaration of Interests

Over the past 3 years, Pizzagalli has received consulting fees from Akili Interactive Labs, BlackThorn Therapeutics, Boehringer Ingelheim, Pfizer, and PositScience. Evins has received research grant awards to her institution from Pfizer, Forum Pharmaceuticals, and GlaxoSmithKline and has received consulting fees from Pfizer and Reckitt Benckiser. All other authors declare no conflicts of interest.

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DAP and AEE contributed equally as senior authors.

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