Original investigation

The Effects of Nicotine and Tobacco Use on Brain Reward Function: Interaction With Nicotine Dependence Severity

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Abstract

Introduction: This study investigated the effects of nicotine/tobacco on neural activation during performance of a monetary incentive delay task.

Aims and Methods: Prior to each scan, nonsmokers received nicotine or placebo nasal spray, and smokers were smoking satiated or 24-hour withdrawn. During the scan, participants made timed responses to reward-related cues and received feedback. Parameter estimates from cue- and feedback-related activation in medial prefrontal regions and the nucleus accumbens were extracted and underwent within- and between-group analyses. Smokers' nicotine dependence severity was included as a continuous predictor variable for neural activation.

Results: Among smokers ($n = 21$), withdrawal decreased cue-related activation in the supplementary motor area and ventromedial prefrontal cortex, and the difference in activation (satiety > withdrawal) in these regions negatively correlated with nicotine dependence severity (Fagerström Test for Nicotine Dependence). Among nonsmokers ($n = 22$), nicotine increased the difference in nucleus accumbens activation between rewarded and nonrewarded feedback phases. Tobacco withdrawal and acute nicotine also had widespread effects on activation throughout the brain during the feedback phase.

Conclusions: Acute nicotine in nonsmokers may have increased the salience of feedback information, but produced few effects on reward-related activation overall, perhaps reflecting nicotine's modest, indirect effects on reward processing. Conversely, tobacco withdrawal decreased activation compared with satiety, and this difference between conditions correlated with nicotine dependence severity. This suggests that as smokers become more dependent on nicotine, tobacco withdrawal has a more pronounced effect on reward processing.

Implications: Relative to the acute effects of nicotine in nonsmokers, withdrawal from daily tobacco use had more significant effects on reward-related brain activation. This study suggests that the effects of tobacco withdrawal on reward-related brain function interact with subjects' level of nicotine dependence severity. These are potentially important sources of variability that could contribute to smoking cessation outcomes.

Introduction

In the United States, more than 3000 individuals smoke tobacco for the first time every day,¹ and approximately 67.5% will go on to develop tobacco use disorder.² Tobacco is thought to exert its addictive effects by activating nicotinic acetylcholine receptors on dopamine (DA) neurons of the mesolimbic pathway.³ This pathway consists primarily of DA projections from the ventral tegmental area to the striatum and prefrontal cortex, and it is thought to process the reinforcing properties of tobacco and other drugs during the initiation and maintenance of addiction.⁴ Specifically, as initial tobacco use transitions to chronic use, the reinforcement strength of tobacco-related cues increases, and changes in the reinforcement strength of nondrug rewards (eg, money) are also believed to occur. Nicotine's effects on nondrug reward processing are thought to play an important role in addiction for two reasons: First, acute nicotine during initial tobacco use could amplify the reinforcing effects of other nondrug rewards,^{5,6} which could influence the initiation and continuation of tobacco smoking. Second, there is evidence that smokers have less striatal activation to nondrug reinforcers than nonsmokers^{7,8} and smokers' reductions in striatal activation during tobacco withdrawal predicts lapse likelihood.^{9,10} The loss of interest in nondrug reinforcers coupled with an aversion to withdrawal symptoms may help maintain tobacco use among daily smokers.

The influence of nicotine and tobacco use on the reward-related brain response to nondrug rewards could provide a better understanding of the acquisition and maintenance of tobacco addiction. An important paradigm used to investigate reward-related brain responses is the monetary incentive delay (MID) task. This paradigm is based on instrumental conditioning tasks developed for nonhuman primates¹¹ and elicits reward-related activation in the mesolimbic pathway, specifically the striatum (ie, nucleus accumbens [NAcc], caudate nucleus, and putamen) and medial regions of the prefrontal cortex (mPFC).¹² The blood oxygenation-level dependent (BOLD) response to reward cues and feedback information provides an indirect measure of the salience of this information and/or the sensitivity of the neural system to attend to it. Thus, the MID is an excellent measure to test the effects of acute nicotine and daily tobacco use on nondrug reinforcer salience. The MID has been used to investigate the influence of addictive drugs on the neural response to the anticipation and receipt of nondrug rewards.¹³ In particular, previous research has shown differences between smokers and nonsmokers,¹⁴⁻¹⁶ as well as effects of nicotine and withdrawal^{14,15} in reward-related brain activation. While this research demonstrates the sensitivity of the MID to nicotine manipulations, results have been inconsistent. Furthermore, parallel investigations of the acute effects of nicotine in nonsmokers and long-term effects of nicotine in smokers have not been performed. Given the development of tolerance to daily tobacco use, it is highly likely that acute nicotine and tobacco withdrawal will have different, yet complementary effects on reward processing.

The aim of this study was to investigate how reward-related brain function is affected by withdrawal from daily tobacco use in smokers and by the acute effects of nicotine (1 mg) in nonsmokers. Since acute nicotine increases mesolimbic DA activity and withdrawal from daily nicotine decreases this activity,¹⁷ we hypothesized that acute nicotine in nonsmokers would enhance activation to monetary rewards, and withdrawal in smokers would diminish activation to rewards. Among smokers, nicotine dependence severity was included as a continuous predictor (ie, covariate of interest) because tobacco withdrawal symptoms, such as anhedonia, are influenced

by nicotine dependence severity¹⁸ and could play a significant role in neural reward processing. Furthermore, we hypothesized that tobacco-satiated smokers would have less cue-related striatal activation and more feedback-related striatal activation than nonsmokers in the placebo condition, based on previous research.¹⁹

Methods

Participants

Nonsmokers and smokers were recruited from the local community. Participants completed a phone interview and laboratory-based screening session to determine eligibility. To be eligible, participants had to be right handed and aged 18–55 years. Nonsmokers did not smoke more than 50 cigarettes or equivalent nicotine products in their lifetime, did not use any nicotine or tobacco in at least 6 months, and had an expired carbon monoxide concentration of ≤ 5 ppm (Vitalograph, Lenexa, KS) and a urinary cotinine concentration of <100 ng/mL (NicAlert, Nymox Pharmaceutical, Hasbrouck Heights, NJ). Smokers smoked ≥ 10 cigarettes per day for ≥ 2 years, had an afternoon expired carbon monoxide concentration of ≥ 10 ppm, or a morning urinary cotinine concentration of >100 ng/mL. Participants were excluded if they reported significant health problems, including neurological and psychiatric disorders, or used psychoactive medication. Participants were also excluded if they tested positive for drugs (iCup, Alere Toxicology Services, Portsmouth, VA), alcohol (Alco-Sensor III, Intoximeters, St. Louis, MO), or pregnancy (QuickVue+, Quidel Corporation, San Diego, CA) during the screening visit, if they were using smokeless tobacco or nicotine replacement therapy, or if they had any conditions that would make MRI unsafe. During the screening session, participants were placed in a mock MRI scanner to become familiarized with the scanner environment. Participants provided informed consent, and this protocol was approved by Duke University's Institutional Review Board.

Procedure

Participants were scheduled for two scanning sessions between 2 and 14 days apart. The drug condition order was counterbalanced across study days 1 and 2. On arrival to the scan, participants completed the Positive and Negative Affect Scale (PANAS)²⁰ and submitted a breath sample to test for alcohol. Each scan lasted for 1 hour. Following the MRI scan, participants had their blood pressure and heart rate measured.

Smokers completed the Fagerström Test for Nicotine Dependence (FTND)²¹ on the screen visit. Smokers were asked to smoke as usual prior to their arrival on the satiated scan day, and all smokers reported smoking immediately prior to their arrival. They were asked to abstain from smoking for 24 hours prior to their arrival on the withdrawn scan day and to maintain abstinence for a following 24 hours after this scan so that smoking expectancies did not interfere with the scan day performance. Abstinence was verified by carbon monoxide on the scan day and 24-hour postscan. After each scan, smokers completed the Shiffman–Jarvik Withdrawal Scale (SJWS),²² which asked about the severity of cigarette cravings and somatic symptoms on a scale from 1 ("Not at all") to 7 ("Extremely").

Nonsmokers self-administered the drug spray approximately 10 minutes before the scan began. After the scan, nonsmokers completed a side-effect questionnaire, which asked about the severity of potential side effects of the nasal spray on a scale from 1 ("Not at all") to 7 ("Extremely"). At the end of each session, nonsmokers

reported on whether they thought nicotine or placebo was administered that day.

This procedure was part of a longer scan session that included a measure of classical conditioning administered after the MID.²³

Drug Administration (Nonsmokers)

Drug nasal sprays were provided by a local compounding pharmacy. The nicotine spray contained Nicotrol (Pfizer, New York, NY), and the placebo spray contained saline and a weak concentration of capsaicin oil. The nasal spray pumps and bottles (MedWestVaco, Richmond, VA) delivered 0.5 mg/spray. Participants self-administered two puffs from the spray pump, one in each nostril, delivering 1 mg of nicotine or placebo; administration was double blinded. One milligram of nicotine is similar to the amount of nicotine absorbed from smoking a single cigarette.²⁴ Previous studies have reported cognitive effects at this dose without subjective effects.^{25,26}

Monetary Incentive Delay Task

The MID task was a modified version based on Knutson et al.¹² This version has been previously described in Murty and Adcock.²⁷ Briefly, each trial began with a 500-ms cue indicating whether a reward (\$2) or nonreward (\$0) could be earned for a speeded button press to a target image. Following a variable delay between 5.5 and 6.5 seconds, a target appeared onscreen. Participants responded to the target by pressing a button on an MR-compatible response box with the index finger of their right hand. The target response time for earning the reward was determined by an adaptive algorithm, which estimated the response-time threshold at which each participant would be successful approximately 65% of trials. Thresholds were calculated independently for each drug condition to ensure that reinforcement rates would be similar. Following the target image, feedback appeared onscreen (1 s) indicating whether the participant responded fast enough, in addition to the reward earned for the current trial and the accumulated reward. The intertrial interval between feedback and cue was 1–4.5 seconds (mean = 2.8 s). Participants performed two runs of this task; each run consisted of 20 reward trials and 20 nonreward trials. Participants were told that they would receive points for each rewarded, on-time response that went toward a \$10 bonus each scan day. At the end of the study, all participants were awarded a \$20 bonus.

Immediately prior to the first run of the MID, participants completed a 20-trial practice version to familiarize them with the paradigm and to calibrate response-time thresholding.

Image Acquisition

Images were acquired on a 3T General Electric MR750 scanner (Milwaukee, WI) equipped with 50 mT/m gradients. A high-resolution anatomical image was collected using a 3D fast spoiled gradient-recalled echo (3D-SPGR) sequence (repetition time [TR] = 8.156 ms, echo time [TE] = 3.18 ms, field of view = 25.6 cm², matrix = 256 × 256, flip angle = 12°, 166 slices, and slice thickness = 1 mm).

Blood oxygen level-dependent signal was measured using a gradient-recalled inward spiral pulse imaging sequence (SENSE spiral) (TR = 1500 ms, inversion time [TI] = 0, TE = 30 ms, flip angle = 60°, acquisition matrix = 64 × 128, field of view = 25.6 cm², number of slices = 30, and slice thickness = 3.8 mm resulting in 4 × 4 × 3.8 mm voxels, 294 volumes for a duration of 7 min 27 s per run). The first four image volumes were removed to allow for stabilization of the magnetic

resonance (MR) signal. An infrared camera attached to the head coil was used to monitor alertness.

Image Preprocessing

Functional images were preprocessed and analyzed using the Functional MRI of the Brain (FMRIB) Software Library (FSL Version 6.00 FMRIB, Oxford, United Kingdom). Functional images were skull stripped, temporally realigned, motion corrected, smoothed with a 4-mm smoothing kernel, and high pass filtered (cutoff = 100 s). Functional images were registered to the high-resolution anatomical images and then normalized to the Montreal Neurological Institute 152 template. A first-level general linear model analysis was conducted for each participant using two explanatory variables (EVs) for the cue phase: (1) reward and (2) nonreward and four EVs for the feedback phase: (1) reward cue/on-time response, (2) reward cue/late response, (3) nonreward cue/on-time response, and (4) nonreward cue/late response. EVs were convolved with double-gamma hemodynamic response functions with the temporal derivative added. In the first-level analysis, contrasts were defined for each outcome EV in addition to (1) cue phase: reward cue > nonreward cue, (2) feedback phase: reward cue/on-time response > reward cue/late response, and (3) nonreward cue/on-time response > nonreward cue/late response. As described in Murty and Adcock,²⁷ serial presentations of color object images were presented during the delay between the cue and the target to test subsequent memory, and object images were modeled orthogonal to the cue presentation. These EVs are not the subject of the present investigation and are not discussed. Motion outliers were identified and included as confound EVs in the first-level analysis. A second-level fixed-effect analysis combined the two runs of the MID for each scan session.

Data Analysis

Smoker and nonsmoker demographics were analyzed using independent-sample *t* tests and chi-square tests. PANAS mood scores were analyzed with 2 (drug condition) × 2 (valence) repeated-measures analyses of variance (ANOVAs) for within-subject effects and 2 (valence) × 2 (group) mixed ANOVAs for between-subject effects. SJWS (scores for 'arousal' were reverse-scored), side effects, blood pressure, and heart rate were analyzed with 2 (drug condition) multivariate repeated-measure ANOVAs for within-subject tests and 2 (group) multivariate ANOVAs for between-subject tests. FTND score was included for smokers as a continuous predictor variable. Follow-up analyses consisted of Pearson's correlation coefficient.

To determine regions of interest (ROIs) that were significantly affected by the task-related reward and response-time manipulations, imaging data underwent an initial, whole-brain one-sample *t* test of the cue phase (reward cue > nonreward cue) and a paired-sample *t* test of the feedback phase (reward cue [on-time > late response] > nonreward cue [on-time > late response]). These analyses consisted of all subjects and all drug conditions. Results of the whole-brain analyses were considered significant if they passed a statistical threshold of *z*-score > 3.1, with clusterwise *p* < .05 using Gaussian random field theory.²⁸ ROI data were created by extracting parameter estimates from functional clusters that overlapped with the ventral striatum (ie, NAcc) and medial portions of PFC based on visual inspection from all participants in all drug conditions and converted to percent BOLD signal. These ROI values were used to investigate the effects of the nicotine/placebo and satiated/withdrawn conditions using repeated-measures ANCOVAs for smokers

and nonsmokers, separately, for the cue phase (2 drug condition $\times$ 2 reward) and the feedback phase (2 drug condition $\times$ 2 reward $\times$ 2 response time). Smokers' satiated condition and nonsmokers' placebo condition were compared using mixed between/within repeated-measures ANOVAs. These measures were analyzed in SPSS (Version 21.0.; IBM, Chicago, IL). Since education level differed between groups (see Results), education level was tested as a covariate of interest in the ROI analyses; education did not covary with any dependent variables and was thus excluded from analyses. Last, whole-brain analyses of drug condition effects in the cue and feedback phases were explored for nonsmokers and smokers, separately. Results of these whole-brain analyses were considered significant if they passed a statistical threshold of z -score > 2.58 , with clusterwise $p < .05$ using Gaussian random field theory. Figures were created using MRIcron (www.mccauslandcenter.sc.edu/mricron/).

Results

Participants

Twenty-three nonsmokers and 21 smokers completed the study; however, one nonsmoker was removed due to falling asleep in the scanner. The final sample consisted of 43 participants. There were no differences between smokers and nonsmokers in age, sex, or race; however, nonsmokers had more years of education ($t(41) = 3.1$, $p = .003$). Participant characteristics are shown in Table 1. Among smokers, FTND scores were normally distributed.

Mood and Side-Effect Ratings

Nonsmokers' mood ratings on the PANAS did not differ by drug condition, nor did condition interact with positive/negative valence. Among smokers, the extent to which drug condition interacted with valence (increased negative mood and decreased positive mood from satiety to withdrawal) positively correlated with FTND scores ($r = .54$) (drug condition $\times$ valence $\times$ FTND: $F(1,19) = 8.0$, $p = .011$). PANAS mood scores did not differ between groups.

Overall, smokers' SJWS scores tended to increase from satiety to withdrawal but were not significantly affected by drug condition, except for craving (drug condition: $F(1,18) = 11.1$, $p = .004$). (There were incomplete SJWS scores for one smoker during withdrawal.)

Nonsmokers' side-effect ratings did not differ between drug conditions. Blood pressure and heart rate were not affected by condition for either smokers or nonsmokers. There were no group differences in blood pressure or heart rate.

Drug Blind

Nonsmokers were not able to correctly guess which spray they had received better than by chance; 68% correctly guessed placebo spray (one-sided binomial t test: $p > .10$) and 50% correctly guessed nicotine spray (one-sided binomial t test: $p > .10$).

Number of Responses

Due to the adaptive algorithm, approximately 65% of trials had on-time responses (mean = 24 on-time response and 16 late responses). There were no differences in the number of on-time responses between smokers' satiated condition and nonsmokers' placebo condition, nor were there main effects of condition within smokers or nonsmokers.

ROI Imaging Results—Cue Phase

Across all subjects and conditions, reward cues elicited more activation than nonreward cues in the bilateral mPFC (including the anterior supplementary motor area [SMA] extending into the paracingulate/anterior cingulate, and the ventromedial prefrontal cortex [VMPFC]), the bilateral posterior cingulate, precentral gyrus, occipital cortex, cerebellum, as well as the left middle temporal gyrus, and frontal pole (Figure 1a and Supplementary Table 1). Parameter estimates from the SMA and VMPFC clusters were extracted for analysis of drug condition effects.

Smokers showed greater SMA activation during satiety compared with withdrawal (drug condition: $F(1,19) = 20.0$, $p < .001$) (Figure 1b). The difference in activation between conditions (satiety $>$ withdrawal) negatively correlated with FTND scores ($r = -.65$) (drug condition $\times$ FTND: $F(1,19) = 14.0$, $p = .001$) (Supplementary Figure 1a). Smokers also showed a larger difference in reward (reward $>$ nonreward) during satiety than during withdrawal (drug condition $\times$ reward: $F(1,19) = 11.7$, $p = .003$). This drug condition $\times$ reward interaction effect negatively correlated with FTND scores ($r = -.54$) (drug condition $\times$ reward $\times$ FTND interaction: $F(1,19) = 7.6$, $p = .012$). In other words, as FTND scores increased, the difference

Table 1. Participant Characteristics

	Nonsmokers	Smokers	Significance level
<i>n</i>	22	21	
Men/women	11/11	8/13	<i>ns</i>
Age, mean $\pm$ SD	31.6 $\pm$ 11 (range: 18–55)	34.5 $\pm$ 10 (range: 20–50)	<i>ns</i>
Years of education	16.4 $\pm$ 2	14.1 $\pm$ 3	$t(41) = 3.1$, $p = .003$
Race C/N/A/AA/O	9/0/1/10/2	7/1/1/10/2	<i>ns</i>
CO at screening	1.2 $\pm$ 0.6 ppm	16.0 $\pm$ 10 ppm	$t(41) = 6.9$, $p < .001$
CO satiated		20.3 $\pm$ 10 ppm	Satiated $>$ withdrawn
CO withdrawn		3.7 $\pm$ 3 ppm	$t(20) = 7.7$, $p < .001$
Cigarettes per day		14 $\pm$ 5	
Years of smoking		16 $\pm$ 10	
FTND score		4 $\pm$ 2 (range: 0–8)	
Postscan blood pressure, heart rate	Placebo: 119 $\pm$ 17/77 $\pm$ 11, 72 $\pm$ 10 bpm Nicotine: 119 $\pm$ 13/75 $\pm$ 13, 72 $\pm$ 15 bpm	Satiated: 119 $\pm$ 12/80 $\pm$ 12, 74 $\pm$ 12 bpm Withdrawn: 120 $\pm$ 16/79 $\pm$ 13, 69 $\pm$ 12 bpm	<i>ns</i>

bpm, beats per minute; C/N/A/AA/O, Caucasian/Native American/Asian/African American/Other; CO, carbon monoxide; FTND, Fagerström Test for Nicotine Dependence; *ns*: nonsignificant.

in both the condition and condition $\times$ reward interaction effects changed from satiety > withdrawal to withdrawal > satiety.

Smokers showed greater VMPFC activation during satiety compared with withdrawal (drug condition: $F(1,19) = 7.6$, $p = .012$) (Supplementary Figure 2a). The difference in activation between conditions (satiety > withdrawal) negatively correlated with FTND scores ($r = -.56$) (drug condition $\times$ FTND: $F(1,19) = 8.6$, $p = .008$) (Supplementary Figure 1b). In other words, as FTND scores increased, the difference in the condition effect changed from satiety > withdrawal to withdrawal > satiety.

Nonsmokers showed no drug condition effects in SMA or VMPFC activation.

Between-group analyses revealed that smokers showed greater VMPFC activation during the satiated condition than nonsmokers during the placebo condition (between-group: $F(1,40) = 10.2$, $p = .003$) (Supplementary Figure 2a). There were no between-group differences in the SMA activation.

ROI Imaging Results—Feedback Phase

Across all subjects and conditions, on-time responses elicited more feedback activation than late responses following reward cues compared with nonreward cues in the bilateral VMPFC and the NAcc,

as well as in the left middle frontal gyrus, left superior occipital cortex, bilateral posterior cingulate, precuneus, and occipital cortex (Figure 2a and Supplementary Table 1).

Smokers showed a trend toward greater NAcc activation during satiety compared with withdrawal (drug condition: $F(1,19) = 4.2$, $p = .054$) (Figure 2b).

Nonsmokers showed greater difference in NAcc activation from on-time (ie, rewarded) to late (ie, nonrewarded) responses after nicotine compared with placebo (drug condition $\times$ response time: $F(1,21) = 5.3$, $p = .032$) (Figure 2b). Nonsmokers showed no drug condition effects in VMPFC activation.

There were no between-group differences in the NAcc or VMPFC activation during the feedback phase.

Exploratory Whole-Brain Analysis of Drug Condition Effects

Among nonsmokers, nicotine increased activation compared with placebo during the feedback phase bilaterally in the precuneus, frontal pole, superior occipital cortex, precentral gyrus, superior frontal gyrus, temporal pole, as well as in the left supramarginal gyrus. Nicotine decreased activation bilaterally in the occipital cortex and

Figure 1. (a) Whole-brain activation from the cue phase (reward cue > nonreward cue). Color bar indicates Z score. (b) Percent BOLD signal extracted from the SMA/anterior cingulate cluster (circled in (a)) for smokers and nonsmokers across conditions. *Smokers showed a larger difference in reward (reward > nonreward) during satiety than during withdrawal ($p = .003$). Shown are the estimated marginal means, controlling for nicotine dependence severity (smokers only). Error bars are SEM. BOLD, blood oxygenation-level dependent; SMA, supplementary motor area.

Figure 2. (a) Whole-brain activation from the feedback phase (reward cue [on-time > late response] > nonreward cue [on-time > late response]). Color bar indicates Z score. (b) Percent BOLD signal extracted from the right NAcc cluster (circled in (a)) for smokers and nonsmokers across conditions. *Smokers showed a trend toward greater NAcc activation during satiety compared with withdrawal ($p = .054$). #Nonsmokers showed greater NAcc activation (on-time > late response) after nicotine compared with placebo ($p = .032$). Shown are the estimated marginal means, controlling for nicotine dependence severity (smokers only). Error bars are SEM. BOLD, blood oxygenation-level dependent; NAcc, nucleus accumbens.

the right superior parietal lobule (Supplementary Figure 3a and Supplementary Table 2). Drug condition effects did not interact with reward or response-time effects.

Among smokers, withdrawal decreased activation compared with satiety during the feedback phase bilaterally in the paracingulate gyrus, temporal lobe, parietal lobe, left angular gyrus, and right inferior frontal gyrus. Withdrawal increased activation bilaterally in the occipital cortex (Supplementary Figure 3b and Supplementary Table 2). Drug condition effects did not interact with reward or response-time effects.

There were no within-group drug condition effects during the cue phase.

Discussion

In summary, we investigated the acute and long-term effects of nicotine/tobacco on neural activation during performance of the MID task. Prior to each scan, nonsmokers received nicotine or placebo nasal spray, and smokers were smoking satiated or 24-hour withdrawn. Overall, there were more consistent, robust effects of withdrawal among smokers than that of acute nicotine among nonsmokers. Furthermore, this study suggests that the effect of tobacco withdrawal on reward-related brain function interacts with smokers' nicotine dependence severity. This is a potentially important source of variability that could contribute to smoking cessation outcomes.

Effects of Withdrawal From Daily Tobacco Use

Among smokers, the 24-hour smoking abstinence condition increased self-reported craving, and higher FTND scores were associated with a greater extent of decreased positive mood, and increased negative mood, from satiety to withdrawal. During the cue phase of the MID task, withdrawal decreased mPFC activation (SMA and VMPFC) overall. Additionally, the difference in activation between conditions negatively correlated with FTND scores. As FTND scores increased, the difference in activation changed from satiety > withdrawal to withdrawal > satiety. A similar trend toward decreased activation during withdrawal was shown during the feedback phase. In the whole-brain analysis, withdrawal decreased activation in the frontal, temporal, and parietal lobes and increased activation in the occipital lobe.

Tobacco withdrawal symptoms such as negative and/or depressed mood begin within 24 hours of the last cigarette and can last for 2–3 weeks.²⁹ Nicotine/tobacco withdrawal increases anhedonia³⁰ and decreases reward responsivity,³¹ brain reward function,³² and striatal DA release.³³ The striatal response to nondrug (ie, monetary) rewards is particularly relevant to smoking cessation because withdrawal-induced decreases in this striatal response corresponds to an unwillingness to refrain from smoking for monetary reinforcement¹⁰ and predicts the likelihood of lapse during a contingency management-supported quit attempt.⁹ Furthermore, according to the incentive-sensitization theory of drug addiction, drug-related cues acquire heightened incentive salience compared with nondrug cues, which can decrease the likelihood of nondrug-related behavior.³⁴

The BOLD response elicited by reward cues has been interpreted to reflect increases in attention to salient stimuli, and the salience of the stimuli may be related to the motivational value of the reward (eg, ^{35,36}). Many studies on reward-related processing in tobacco smokers have administered smoking cues during a smoking satiated compared with a withdrawn state; a meta-analysis suggests that

smoking cues during withdrawal increase activation in the extended visual system and the dorsal PFC.³⁶ Compared with smoking cues, smokers may be expected to have diminished BOLD response to monetary cues based on the incentive-sensitization theory; however, a study by Bühler et al. reported no difference between cue types and reported increased cue-related activation in the PFC during tobacco withdrawal compared with satiety.³⁵ Overall, the effects of withdrawal on nondrug reward cue-related activation have been mixed. Previously, we reported that withdrawal increased anticipation-related activation in the PFC and decreased activation in the putamen.³⁷ Alternatively, withdrawal-induced decreases in anticipation-related activation in the striatum and PFC have also been shown.¹⁵

The present study suggests that the effects of withdrawal on cue-related PFC activation are negatively related to nicotine dependence severity, perhaps reflecting an increased recruitment of attentional resources to offset the negative effects of withdrawal on mood and cognition. Nicotine dependence severity was also used as a covariate by Sweitzer et al., who reported positive reward > negative reward feedback activation in the ventral striatum positively correlated with nicotine dependence severity (measured with the Nicotine Dependence Syndrome Scale³⁸); as nicotine dependence severity increased, the difference in activation changed from withdrawal > satiety to satiety > withdrawal.³⁹ The reasons for the difference between positive and negative correlations with nicotine dependence severity are unclear, but there are some notable differences between studies. For instance, the study by Sweitzer et al. consisted of 10 smokers with FTND scores of ≥ 4 , while the FTND scores in our study ranged from 0 to 8. Alternatively, the positive correlation in the striatum reported by Sweitzer et al., and the negative correlation in the PFC reported here, could be co-occurring in a compensatory manner. Altogether, these studies suggest that nicotine dependence severity moderates the interaction between tobacco withdrawal and the BOLD response to nondrug rewards. However, both studies had small sample sizes and additional research is warranted, but accounting for dependence severity may help reduce discrepancies across similar studies in the future. Furthermore, there may be other sources of variability influencing nondrug reward-related brain activation in smokers, for instance, genetic variations in the hepatic enzyme cytochrome P450 (CYP2A6), which is responsible for nicotine inactivation and clearance from the body.⁴⁰

A limitation of the study is that the covariations with FTND score were tested post hoc, and the study was not optimally designed to measure the influence of this variable. In addition, our smoker sample smoked 10–22 cigarettes/d. Among smokers, cigarettes per day tends to correlate with nicotine dependence severity, but the extent of exposure to tobacco smoke may have its own brain-related effects. Future studies can control for this confound by recruiting smokers within a narrower range of cigarette use.

Effects of Nicotine in Nonsmokers

Compared with the effects of tobacco withdrawal on smokers, there were fewer effects of acute nicotine on nonsmokers. During the feedback phase, nicotine increased the difference in NAcc activation from on-time (ie, rewarded) to late responses (ie, nonrewarded) compared with placebo. This is at least partially due to a larger difference in the nicotine condition between on-time and late responses following the nonreward cue. In these trials, no money was awarded, but feedback indicated whether the individual responded on time. Nicotine may have increased the salience of this feedback. Alternatively, the

omission of expected rewards results in the inhibition of DA neuronal firing¹¹ and decreased BOLD activation in the NAcc.⁴¹ The condition $\times$ response-time interaction may have occurred because nicotine enhanced an inhibitory effect on NAcc activation during late responses. No other effects were found in the ROIs. In the whole-brain analysis, nicotine increased activation during the feedback phase in the frontal, temporal, and occipital cortices and decreased activation in the occipital cortex and right parietal lobule.

Acute nicotine has been shown to increase BOLD activation throughout the brain, in particular the striatum and orbitofrontal cortex,⁴² as well as enhance brain reward function³² and reward sensitivity.^{43,44} There is also extensive evidence using animal models that nicotine acutely increases behavior reinforced by nondrug rewards,⁶ although similar work in humans has been mixed with the most consistent evidence occurring in nicotine-dependent smokers.⁴⁵ Other studies have shown that nicotine increases anticipation-related activation in the putamen and PFC of nonsmokers.¹⁵ Previously, we published the results of acute nicotine effects on nonsmokers during a classical conditioning task administered during this same scan session. In the reward feedback phase, nicotine increased activation in the anterior insula, and inferior frontal gyrus, temporal lobe, and occipital cortex, and decreased activation in the caudate nucleus.²³ Overall, these results suggest that nicotine has a net positive effect on brain activation, although not all of these effects may be reward related. Although highly addictive, acute nicotine does not appear to have strong direct effects on the mesolimbic reward system. Perhaps nicotine indirectly affects reward processing by enhancing the salience of reinforcing information or improving attentional performance.

A limitation is that all of the nonsmokers in our sample had tried smoking in the past, but never used cigarettes regularly. Their neural response to nicotine may be different from individuals who are at high risk of developing tobacco addiction. Another potential limitation is that the nicotine concentration–time curve for nasal nicotine differs from cigarette smoking, with the average concentration after 1-mg nasal spray being 1.5–2 $\times$ smaller than that of cigarette smoking.⁴⁶ Future studies should also test more than one dose of nicotine and measure plasma nicotine levels.

Differences Between Smokers and Nonsmokers

Although differences could have been related to the effects of nicotine on smokers' brain function, we compared nonsmokers' placebo condition with smokers' tobacco-satiated condition because this represents smokers' typical brain function, given their daily use of cigarettes. Smokers showed more cue-related VMPFC activation during the satiated condition than nonsmokers during the placebo condition, although the hypothesized differences in striatal activation were not found. Previous studies that compared MID reward-related activation between smokers and nonsmokers have shown that smokers have less activation in the frontal cortex,^{14,15} NAcc,^{14,15} and caudate,¹⁵ or more activation in the frontal cortex¹⁶ and caudate.¹⁴ Greater activation has been interpreted to represent stronger reward-related motivation or salience for nondrug rewards, which may be diminished in smokers,¹⁴ or enhanced by nicotine exposure.¹⁶ It is also possible that group differences reflect pre-existing individual differences in reward processing that relate to one's risk for developing tobacco addiction. Overall, our results do not provide evidence of diminished reward processing of nondrug rewards in tobacco-satiated smokers.

In conclusion, our results indicated that both acute nicotine and withdrawal from daily tobacco have widespread effects on the brain, although withdrawal produced more task-related effects in the mPFC and striatum. Smokers' responsiveness to nondrug rewards has been linked to lapses during cessation attempts; however, more prospective studies are needed to determine how nicotine dependence severity interacts with reward-related brain function. Furthermore, the present study was limited to measuring neural correlates of reward gain, and future studies should also investigate the effects of nicotine and withdrawal on reward loss.

Supplementary Material

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

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Declaration of Interests

None declared.

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