ARTICLE

The acute effects of nicotine on corticostriatal responses to distinct phases of reward processing

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Nicotine enhances the reinforcement of non-drug rewards by increasing nucleus accumbens (NAcc) reactivity to anticipatory cues. This anticipatory effect is selective as no clear evidence has emerged showing that nicotine acutely changes reward receipt reactivity. However, repeated rewarding experiences shift peak brain reactivity from hedonic reward outcome to the motivational anticipatory cue yielding more habitual cue-induced behavior. Given nicotine's influence on NAcc reactivity and connectivity, it is plausible that nicotine acutely induces this shift and alters NAcc functional connectivity during reward processing. To evaluate this currently untested hypothesis, a randomized crossover design was used in which healthy non-smokers were administered placebo and nicotine (2-mg lozenge). Brain activation to monetary reward anticipation and outcome was evaluated with functional magnetic resonance imaging. Relative to placebo, nicotine induced more NAcc reactivity to reward anticipation. Greater NAcc activation during anticipation was significantly associated with lower NAcc activation to outcome. During outcome, nicotine reduced NAcc functional connectivity with cortical regions including the anterior cingulate cortex, orbitofrontal cortex, and insula. These regions showed the same negative relationship between reward anticipation and outcome as noted in the NAcc. The current findings significantly improve our understanding of how nicotine changes corticostriatal circuit function and communication during distinct phases of reward processing and critically show that these alterations happen acutely following a single dose. The implications of this work explain nicotinic modulation of general reward function, which offer insights into the initial drive to smoke and the subsequent difficulty in cessation.

INTRODUCTION

Nicotine is a highly addictive naturally-occurring stimulant and the primary psychoactive ingredient in tobacco cigarettes [1]. It is reinforcing due to its ability to potentiate dopaminergic transmission in the nucleus accumbens [NAcc; 2, 3], a key node in the neural reward circuit [4, 5]. In particular, a single acute dose of nicotine can induce an increase in mesolimbic dopamine (DA) activity to the NAcc [3, 6], resulting in increased reward-related learning [7, 8] and reward-seeking behavior [e.g., conditioned placed preference; 9–13]. These findings collectively highlight nicotine's ability to enhance DA function in reward-related brain regions, which subsequently influence how regions such as the NAcc respond to reward.

Prior work suggests that reward processing is separable into two linked but dissociable phases—reward anticipation and outcome [14]. Specifically, reward anticipation is motivated by the incentive salience of a reward-predictive cue or how much a reward is wanted [15–18], whereas reward outcome is associated with the pleasure of reward receipt or how much a reward is liked [19–22]. A recent meta-analysis of human functional magnetic resonance imaging (fMRI) studies confirmed that the NAcc responds to both anticipation and outcome phases [23]. Nicotine can influence such NAcc responding, given that, relative to placebo, acute nicotine induces a robust increase in NAcc reactivity to reward anticipation [24, 25]. Interestingly, how

nicotine influences NAcc reactivity to reward outcome is not well documented and the few studies that have explicitly examined this have reported no significant effect of nicotine on NAcc activity during reward outcome [24, 26], suggesting that nicotine preferentially affects reward anticipation. The focus of nicotine's effect on reward anticipation, but not outcome, is likely driven by how nicotine influences the NAcc, which is to effectively increase DA transmission and the incentive salience encoding of rewarding cues during anticipation [27–29].

This increase in NAcc activity towards reward anticipation under nicotine is in line with animal models showing that nicotine facilitates the shift in the NAcc signal from hedonic encoding of a primary reward to the motivational encoding of the cue associated with the reward [30–33]. This prompts the question of whether the observed increase in NAcc activity during reward anticipation is accompanied by a simultaneous decrease in NAcc activity towards reward outcomes. That is, does a single acute dose of nicotine swing the balance of NAcc activity towards responding to the incentive salience of a reward cue (i.e., anticipation) at the expense of responding to the hedonic drive of the reward itself (i.e., outcome)? If so, a related question is whether this shift in NAcc activity under nicotine could subserve changes in how the NAcc is communicating with other reward-processing foci in the cortex. Prior work has showed that nicotine administration can impact the firing patterns in cortical regions

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and the NAcc [22, 34, 35], thereby diminishing the ability of the cortex to exert top-down influence on the NAcc during reward-seeking behaviors [for review see 36–38]. Given that exposure to nicotine can disrupt the corticostriatal circuit, it is likely that nicotine's influence on the NAcc has a direct consequence on how this particular reward node is functionally connected to key reward-related cortical regions during reward processing.

Here, we investigated these questions by taking advantage of the monetary incentive delay (MID) task [39, 40], which allows for the dissociation of reward anticipation and outcome. Using a within-subject study design with healthy non-smoking individuals, we were specifically interested in testing whether acute nicotine administration, relative to placebo, induces a negative correlation between NAcc activity during reward anticipation and outcome and whether nicotine induces changes in task-dependent corticostriatal connectivity.

METHODS

Participants
Seventeen (8 females) participants (mean age: 26.06±6.09) were recruited as part of the healthy control group for another published study [41]. Participants were self-reported non-smokers with less than 20 lifetime uses of nicotine, denied nicotine use in the past year, and had expired carbon monoxide (CO) level of less than 5 ppm at each study visit. Participants were administered the structured clinical interview for DSM-IV-TR [42] to screen for lifetime history or current diagnosis of any of the following psychiatric illnesses: organic mental disorder, schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorders not otherwise specified, bipolar disorder, attention deficit hyperactivity disorder (ADHD), mood congruent or incongruent psychotic features, generalized anxiety disorder and social anxiety disorder. In addition, participants were excluded if they met any of the following criteria: failure to meet MRI safety requirements, lifetime history of electroconvulsive therapy, anticholinergic drug use in the past week, history or current cardiac problems such as known arrhythmia, acute coronary syndromes, or ischemic heart disease, seizure disorder, psychotropic medication or illicit substance use, and breath blood alcohol levels greater than zero. Furthermore, participants provided urine samples to confirm that they were not pregnant or had not engaged in recent drug use, both of which were contraindicative to study participation. Participants provided written informed consent in accordance with the experimental protocol approved by the Partners HealthCare Institutional Review Board upon receiving a complete description of the experiment.

Study drug
Participants were administered nicotine (Nicorette Lozenge, GlaxoSmithKline, Brentford London) and placebo (Tums antacid, GlaxoSmithKline, Brentford London) lozenges on two separate study days roughly 1 week apart. The nicotine lozenge contained 2-mg of nicotine (mean half-life of 2.3 h), which was predicted to reach a peak systemic nicotine concentration of 4.4 ng/ml in approximately 1 h after administration [43]. While pharmacokinetic profiles differ between tobacco smoking and nicotine lozenges, the lozenge dose chosen delivers the total amount of nicotine typically received from smoking a single cigarette [44–46]. Drug administration was conducted in a randomized, counterbalanced, and double-blind manner. In particular, efforts were made to ensure that there were no physical (same size, shape, and color) or gustatory (both mint-flavored) differences between the lozenges. On both study days, 1 h prior to entering the fMRI scanner, participants were instructed to place the lozenge directly into their mouth, next to their cheek and allow it to dissolve without chewing (which took roughly 15 min).

We monitored participants for any potential side effect following ingestion of the lozenges. However, we did not probe for any subjective pleasurable effects. Although we do not preclude the possibility that there are nuanced differences in how the lozenges tasted, no participant reported distinct sensations while taking either lozenge. Systemic nicotine presence in participants on both study days were verified by measuring cotinine, a reliable biomarker for nicotine absorption [47].

MID task
Similar to prior work [39], we used a MID task that features both anticipation and outcome phases. Briefly, each trial was divided into cue anticipation, target response, and outcome presentation phases. The cue anticipation (0.5 s) and target response (0.15 s) phases were separated by a variable inter-stimulus interval (2.25–3.75 s) and the target response and outcome presentation (1.25 s) phases were separated by another inter-stimulus interval (2.4–3.9 s). Each trial ended with a variable inter-trial interval lasting (1.50–4.5 s). Each of the cues presented during the anticipation phase (reward: +$; neutral: 0$; punishment: -$) was, respectively, associated with feedback during the outcome phase denoting whether participants received monetary gain (+$1.96 to +$2.34), monetary loss (-$1.81 to -$2.19) or no-change ($0). During the target response phase, participants were told to respond as quickly as possible to the displayed red square so as to maximize their chances of earning rewards and avoiding punishments. To equalize task difficulty across participants, each participant's 70th percentile reaction time in the practice session was defined as their individual success threshold. The task consisted of five blocks of 24 trials (8 reward, 8 neutral and 8 punishment cues) and participants were not informed of cumulative earnings during the task. Our main conditions of interest were the anticipation and outcome phases for both reward and neutral trials.

Neuroimaging data collection and preprocessing
Images were collected using a Siemens Trio 3T scanner (Erlangen, Germany) with a 32-channel head coil. Multiecho multi-planar rapidly acquired gradient echo-structural images (MPRAGE) were acquired with the following parameters (TR = 2.1 s, TE = 3.3 ms, slices = 128, matrix = 256, 256, flip angle 7°, resolution $1.0 \times 1.0 \times 1.33$ mm). Slices for the functional images were acquired aligned to the anterior and posterior commissures and the phase encode direction was set from the posterior to anterior direction to prevent prefrontal signal loss. A multi-band acquisition was used for the functional images with the following parameters (TR = 0.72 s, TE = 0.32 s, multi-band acceleration factor = 6, flip angle 66°, slices = 54, voxel size = $3 \times 3 \times 3$ mm).

Images were processed using fMRI of the Brain (FMRIB) Software Library (FSL; www.fmri-b.ox.ac.uk/fsl). In particular, we first brain extracted the images using BET and corrected for motion using MCFLIRT. We subsequently coregistered the mean functional image to the anatomical scan and normalized the anatomical to standard space. The normalized anatomical image was then used to reslice the functional data to standard stereotaxic space defined by the Montreal Neurological Institute (MNI). We also applied slice timing correction and spatial smoothing at full-width half-maximum of 6 mm to the normalized functional data.

Neuroimaging analyses
We conducted two general linear models (GLMs) to examine changes in neural activity in response to acute nicotine administration and to evaluate differences in task-based connectivity. Details pertaining to each GLM are given in subsequent sections. In both GLMs, we included six confound regressors for the x, y, z translational and rotational motion. To further address motion, we identified timepoints representing motion and intensity artifacts (https://github.com/bbfrederick/spikefix) and

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added a regressor to remove these timepoints in the model. All task regressors were convolved with the canonical hemodynamic response function. In the second-level analysis, we combined each participant's five task runs using a fixed-effects model. Finally, in the group-level analysis, we carried out a mixed-effects model with FLAME $1 + 2$ to combine data across all participants. Flame $1 + 2$ fits the model using Bayesian modeling for mixed-effects variance estimation before processing the voxels that were near threshold with Metropolis–Hastings Markov Chain Monte Carlo sampling to obtain a more precise estimation of the mixed-effect variance [48]. Except where noted, all z-statistics images were thresholded and corrected for multiple comparisons using an initial cluster-forming threshold of $z > 3.1$ followed by a conservative whole-brain cluster-extent threshold of $p < 0.05$, as determined by Gaussian Random Field Theory [49, 50]. Images were created using MRIcroGL (https://www.nitrc.org/projects/mricrogl) and overlaid on the MNI152 T1 brain-extracted brain.

Standard GLM
Our first GLM was designed to evaluate nicotine's effects on reward-related activation. We individually modeled the five task runs for each participant in the first-level analysis. Each first-level GLM consisted of six task regressors representing reward cue, neutral cue, punishment cue, reward outcome, neutral outcome, and punishment outcome, respectively. Our main contrasts of interest were between the reward and neutral conditions during both the anticipation (i.e., cue) and outcome phases.

We applied a small-volume correction restricting our region of interest to the bilateral anatomical NAcc. As detailed in the introduction, we focused on the NAcc to determine: (1) if we can replicate prior work showing that, relative to placebo, nicotine increases NAcc activity during reward anticipation and (2) whether nicotine alters the relationship between NAcc activity during reward anticipation and outcome. For the second question, we extracted the NAcc parameter estimates and correlated them between the two reward phases. We then performed a fisher r-to-z transformation on the correlation coefficients for the placebo and nicotine visits, respectively, and directly compared them to assess for significant differences.

Psychophysiological interaction (PPI) GLM
In our second GLM, we implemented a PPI model using an anatomical region of interest in the bilateral NAcc as the seed region to create the physiological regressor. We also added in the same task regressors used for the first standard GLM. To form the PPI regressors, we multiplied the physiological regressor by the convolved task regressor modeling either the reward cue or outcome. In the group-level analysis, we conducted a within-subject two-sample paired t-test to compare the nicotine and placebo PPI regressors for both anticipation (i.e., reward cue) and outcome phases, respectively. In addition, to determine whether NAcc activation to anticipation impacted functional connectivity during the outcome, we also added each participant's mean NAcc parameter estimates for placebo and nicotine visits, respectively, as covariates in the group-level two-sample t-test for the outcome PPI regressor.

RESULTS
Cotinine levels between visits
A paired-sample t-test revealed a significant elevation in participants' serum cotinine levels during the nicotine visit compared to the placebo visits ($t(15) = 2.78$, $p = 0.014$). One participant could not provide a blood sample on the placebo visit and thus was removed from this particular analysis. However, urinalysis was used in this case to confirm the absence of cotinine.

functional magnetic resonance imaging (fMRI)
NAcc activity between placebo and nicotine during reward anticipation. First, we were interested in replicating our prior work in an independent sample [25] where participants showed significantly greater NAcc activity to reward anticipation when they were administered nicotine compared to placebo. We conducted a two-sample paired t-test with a small-volume correction using an anatomical bilateral NAcc mask [41]. Replicating prior findings, participants showed significantly stronger NAcc activation during the nicotine compared to placebo visit (Fig. 1; peak z-stat = 3.78 at $MNI_{x,y,z}$ = 12, 18, −6, $p_{corr} = 0.031$). Also in line with prior reports, no activation was significant when comparing nicotine and placebo during reward outcome.

Relationship between NAcc activity during reward anticipation and outcome under nicotine. Next, we examined whether acute administration of nicotine changed the relationship between NAcc responses to reward anticipation and outcome. In other words, did nicotine alter the association between NAcc activity to anticipation and its activity to outcome? To evaluate this, we applied an anatomical bilateral NAcc mask and extracted the mean parameter estimate (PE) for each participant from both the reward-neutral cue (i.e., anticipation) and reward-neutral outcome (i.e., outcome) contrasts. We correlated participants' anticipation and outcome NAcc activity within each visit (e.g., nicotine or placebo) and found a significant negative relationship in the nicotine visit (Fig. 2b; $r = -0.57$; $p = 0.018$) that was absent in the placebo visit (Fig. 2a; $r = 0.25$, $p = 0.33$). These correlations were significantly different ($Z = -2.39$, $p = 0.017$).

Corticostriatal connectivity during reward anticipation and outcome under nicotine. In our PPI model, we used an anatomical bilateral NAcc as our seed region to identify regions whose connectivity with the NAcc increases during reward anticipation or outcome phases. We directly compared connectivity changes under placebo relative to nicotine administration using a two-sample paired t-test. For the placebo—nicotine contrast, we found a cluster within the anterior cingulate cortex (ACC) extending into the anterior midcingulate cortex (aMCC; Fig. 1b; peak z-stat = 3.15 at $MNI_{x,y,z}$ = 4, −4, 50 $p_{corr} = 0.0029$) exhibited significantly greater connectivity with the NAcc during the outcome phase under placebo relative to nicotine (contrast of placebo—nicotine). No differences in functional connectivity were noted when assessing nicotine administration vs. placebo (contrast of nicotine—placebo). No contrasts for the anticipation phase survived correction.

To further examine the effect of nicotine on corticostriatal functional connectivity during the outcome phase, we included each participant's NAcc PE during anticipation as a covariate into the PPI model. The inclusion of the covariate into the PPI model allowed us to test for regions whose connectivity with NAcc increases during the outcome phase as a function of their NAcc activity during the anticipation phase. For the contrast of placebo—nicotine, after accounting for NAcc anticipation as a covariate, we found a significant cluster in the orbitofrontal cortex (OFC), insula, and ACC (Fig. 1c; peak z-stat = 3.75 at $MNI_{x,y,z}$ = −32, 20, −2, $p_{corr} = 0.0098$).

Relationship between cortical activity during reward anticipation and outcome under nicotine. Given the significant findings from our PPI models, we conducted a post hoc exploratory analysis to probe whether these cortical regions also exhibited the negative relationship between reward anticipation and outcome emerging for the NAcc. For each of the three cortical regions (i.e., ACC, insula and OFC), we created a spherical functional mask extending 5 mm from the peak voxel. Next, we extracted the
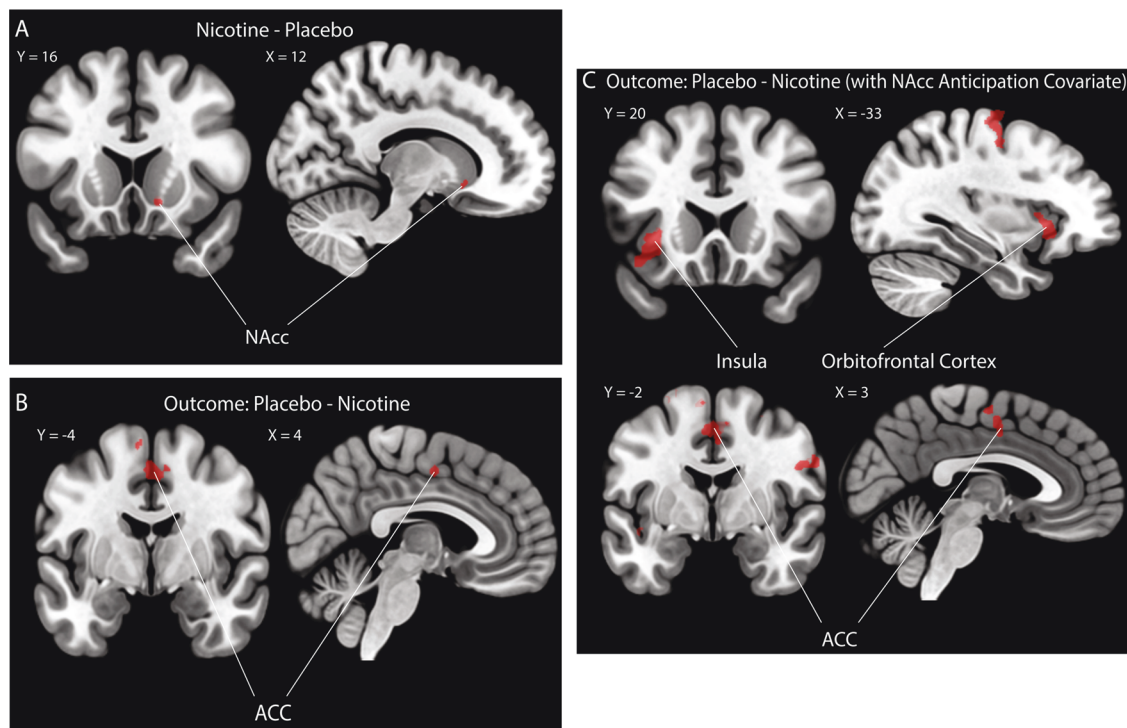
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Fig. 1 Effect of nicotine on corticostriatal activity to reward processing. a NAcc activity between nicotine and placebo visits. Acute nicotine administration significantly increased participants' NAcc activity during reward anticipation. All voxels passed an initial cluster-forming threshold of $z = 3.1$, with small-volume correction within the anatomical NAcc using a cluster-extent threshold of $p < 0.05$. **b** PPI analysis of functional connectivity between NAcc and other brain regions. Acute nicotine administration significantly decreased the functional connectivity between NAcc and the ACC/MCC during reward outcome but not anticipation. **c** After adding in participants' NAcc activation during reward anticipation as a covariate, the PPI model revealed that acute nicotine administration significantly decreased the functional connectivity between NAcc and three cortical regions (i.e., ACC, OFC and insula) during the reward outcome phase. All areas of activation passed an initial cluster-forming threshold of $z = 2.3$, with whole-brain cluster-extent threshold at $p < 0.05$.
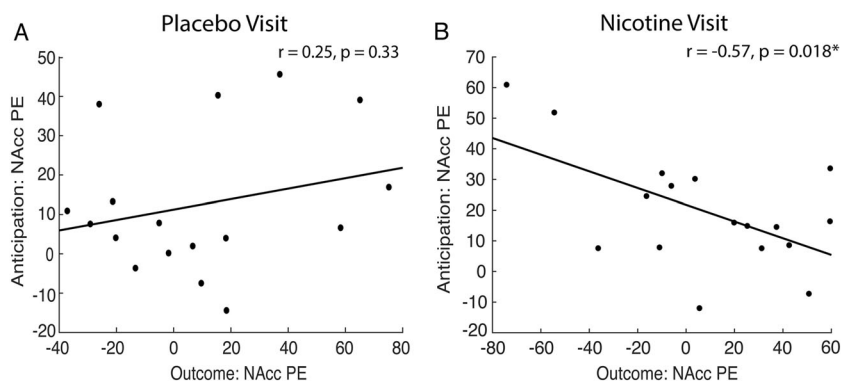

Fig. 2 NAcc anticipation vs outcome relationship between visits. a In the placebo visit, participants' NAcc activity during reward anticipation and outcome did not show any significant relationship. **b** Following acute nicotine administration, participants' NAcc activity demonstrated a significant negative relationship between the reward anticipation and outcome phases. There was a significant difference in the two correlation coefficients for the placebo and nicotine visits.

mean activation from the functional masks for both the anticipation (reward—neutral cue contrast from first GLM) and outcome (reward—neutral outcome contrast from first GLM) phases. We then correlated the activity between the two phases for each ROI.

We found that neither the ACC (Fig. 3a; $r = -0.22$, $p = 0.39$), insula (Fig. 3c; $r = -0.47$, $p = 0.055$), nor the OFC (Fig. 3e; $r = 0.44$, $p = 0.075$) showed a significant relationship in their activity between the two phases under placebo. Following acute nicotine administration, the ACC (Fig. 3b; $r = -0.71$, $p = 0.0015$) and the OFC (Fig. 3d; $r = -0.49$, $p = 0.045$) both

showed significant negative correlations in their activity between the two phases. The insula did not initially show a significant negative correlation between reward phases ($r = 0.088$, $p = 0.74$) but after removal of a statistical outlier, its relationship became significant as well (Fig. 3f; $r = -0.50$, $p = 0.049$). Comparing the correlation coefficients between visits (i.e., a one-tailed test for nicotine visit coefficient being more negative than placebo visit) for each cortical ROI, we found that the ACC ($z = 1.76$, $p = 0.039$), OFC ($z = 2.67$, $p = 0.0038$), and insula ($z = 2.8$, $p = 0.0026$) all showed significantly different relationships between visits.
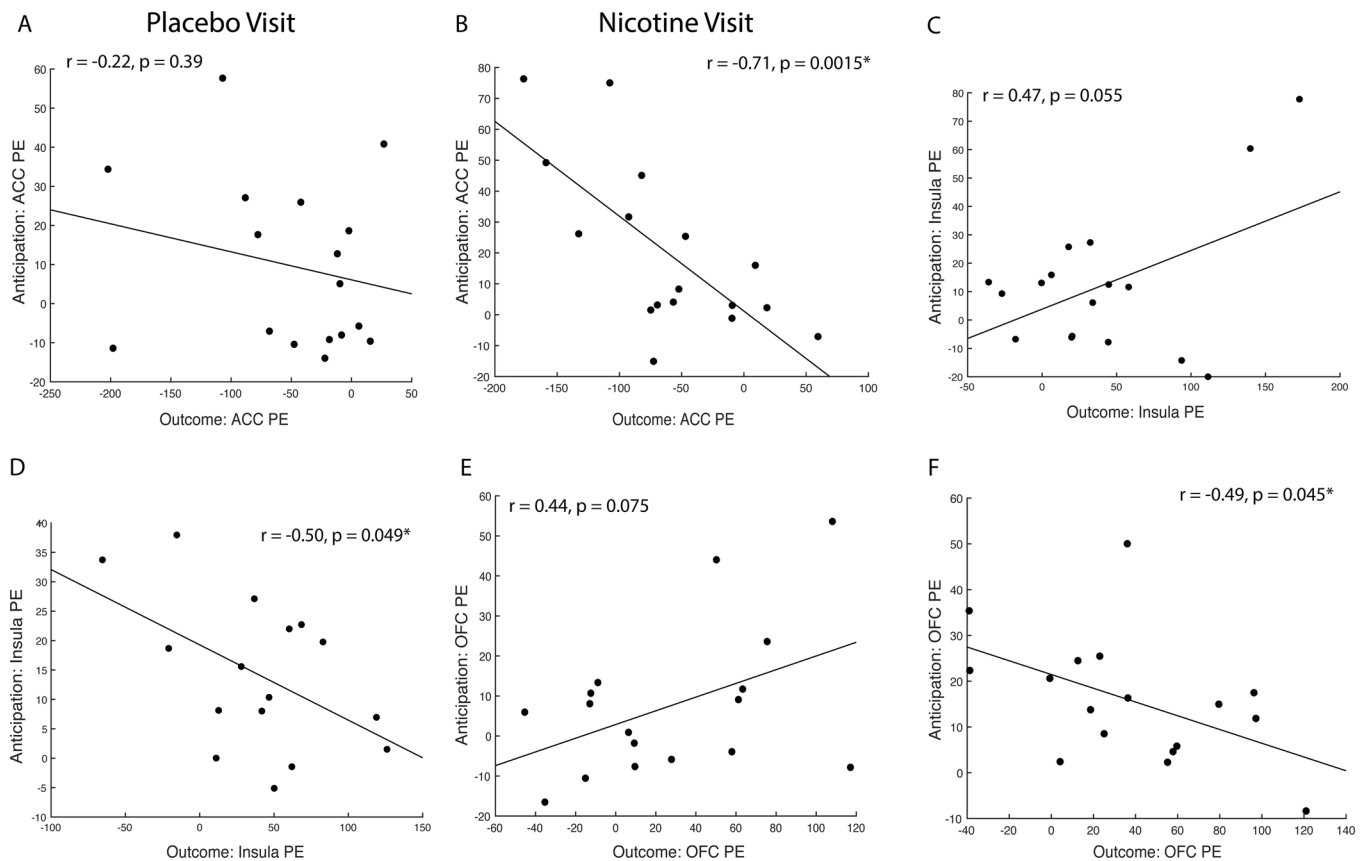
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Fig. 3 **Relationship between anticipation and outcome activity in the cortical regions of interest. a**, **c**, **e** In the placebo visit, none of the three cortical regions of interest (i.e., ACC, insula, OFC) showed a significant relationship between their activity during reward anticipation and outcome. **b**, **d**, **f** Following acute nicotine administration, participants' respective activity in the ACC, insula, and OFC all demonstrated a significant negative relationship between the reward anticipation and outcome phases.

DISCUSSION

The current work shows that acute nicotine administration not only produced a significant increase in NAcc activity during reward anticipation, but more importantly, induced a significant negative relationship in NAcc activity between reward anticipation and outcome. This indicates that greater NAcc response towards anticipation is coupled with lower NAcc response towards reward outcome, indicating a shift in NAcc activity favoring reward anticipation over outcome following a single acute dose of nicotine in non-nicotine users.

Under drug-naïve conditions, the NAcc consistently responds to both reward anticipation and outcome, thereby subserving both the incentive salience of a reward-associated cue and the hedonic properties of the reward itself [23, 51, 52]. In contrast, under the influence of nicotine, the NAcc receives a heightened mesolimbic dopaminergic transmission that results in an increase in its activity towards conditioned cues during reward anticipation [53–56]. Confirming prior work [24, 25], we reported that nicotine significantly increased NAcc activity during anticipation to reward. Building on this observation, we showed that this increase in NAcc activity during anticipation is coupled with a corresponding decrease in NAcc activity during outcome. This significant negative relationship between NAcc activity during reward anticipation and outcome is masked in typical analysis methods since the current and prior work [24] has not observed changes in NAcc activity to outcome when nicotine and placebo visits were directly compared. This significant negative relationship in the nicotine visit suggests that nicotine is facilitating the shift in NAcc responding towards anticipation at the expense of outcome, which parallels the prediction error hypothesis of DA shifting its

firing from the reward to the conditioned stimulus [for review see 57–59] and animal work demonstrating that exposure to nicotine increases the drug-seeking and drug-taking behaviors (i.e., wanting) of other drugs of abuse [60, 61]. It is plausible that nicotine's potentiation of mesolimbic DA transmission to the NAcc subserves the shift in NAcc response from outcome to anticipation, thereby accelerating the cue's acquisition of incentive salience. The association between greater NAcc reactivity to anticipation and lower NAcc connectivity during outcome is reminiscent of the shift from goal-directed to habitual responding typically seen following chronic drug use [62–64]. What is notable is that this shift appears to happen not over repeated nicotine use but following a single 2-mg administration in non-smokers.

Further probing of NAcc activity revealed that acute nicotine significantly decreased the functional connectivity between NAcc and ACC specifically during the outcome phase (discussed in detail in the next paragraph). Intriguingly, after accounting for NAcc anticipatory activation, two additional cortical regions (i.e., OFC and insula) also showed decreased functional connectivity with the NAcc during the outcome phase. These cortical regions have all been implicated as key players in the reward-processing circuit [for review see 65] and in particular, the OFC and insula are proposed as hedonic hotspots in the brain [14]. The role of these two cortical regions during reward processing is to monitor the stimulus features of the reward and translate this into a hedonic value that can be passed onto the NAcc for behavioral updates [66–68]. In other words, while acute nicotine does not blunt NAcc reactivity to reward outcome, it is plausible, with evidence from prior work reporting that participants pre-exposed to nicotine reported lower subjective "liking" of potent rewards such as

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cocaine [69], that nicotine may disrupt the hedonic drive of a rewarding stimulus (i.e., how pleasurable is the reward) by reducing communication within the reward pathway. As such, this ability for nicotine to acutely disrupt corticostriatal connectivity towards reward outcomes showcases nicotine's potent ability to perturb the reward-processing circuitry that can compound into long-term behavioral consequences. The extent of how nicotine alters the hedonic drive can be probed in future studies exploring nicotine-induced changes in the pleasurable sensation of consuming other drugs and rewards.

Of the three cortical regions showing nicotine-induced decrease in functional connectivity with NAcc, the most notable is ACC because it exhibited the same negative relationship as NAcc in its response to reward anticipation and outcome. Although the OFC and insula also showed this negative relationship, ACC had the strongest negative relationship that was comparable to that demonstrated by NAcc. Prior animal work has demonstrated that the ACC and NAcc are functionally connected during reward processing [70–73] and that nicotine reduces the communication between ACC glutamatergic neurons and NAcc-bound VTA DA neurons [37, 74, 75]. In the same vein, our current finding in humans also points to a nicotine-induced reduction of ACC-NAcc connectivity during reward outcome that may contribute to both regions showing a similar shift in their responses from reward outcome to anticipation. This latter observation is important given that both ACC and NAcc are recipients of heavy dopaminergic projections from the ventral tegmental area that increases DA signaling under nicotine [76–80] and that both regions display response profiles matching the generation of prediction error during cue-outcome associative learning [81–86]. Therefore, it seems likely that the disruption of the functional connectivity between ACC and NAcc during reward outcome is related to the negative relationship that both regions exhibited towards anticipation and outcome. Whether the former engenders the latter remains an open question for future research.

The current work includes the following limitations. First, even though our current sample size is comparable with previously published datasets applying similar methodology [e.g., 87], future studies should recruit a larger sample to replicate and extend our reported findings into domains such as sex differences. Second, our current study was designed to measure brain activation during the anticipated peak nicotine levels estimated across the population. However, it is plausible that nicotine's effect on this shift may differ between individuals depending on their rate of nicotine metabolism [88], suggesting the need for future research evaluating how metabolism influences the currently-presented data. It is also likely that nicotine's neural effect on general reward function and in particular, its abuse potential and transition to chronic use, is dependent on the route of intake and the associated pharmacokinetics. Thus, future studies should also evaluate how variance in pharmacokinetics due to different consumption methods (smoked vs. oral) influence the shift observed in the ACC and NAcc. Despite these limitations, the current work employed a rigorous design, which not only replicated the nicotine-induce facilitation of NAcc reactivity to reward anticipation, but revealed other strong effects supported by the existent literature.

Overall, our findings provide a more nuanced perspective on how nicotine impacts reward processing beyond its ability to enhance the motivational drive of anticipatory reward cues. The observation that a single acute dose of nicotine creates a shift in NAcc activity from outcome to anticipation expands on the traditional view of nicotine heightening incentive salience. Further, these findings were noted in non-smokers using a task involving monetary rewards, not stimuli previously associated with nicotine, thus fitting with the idea that nicotine has a global influence on reward processing [53]. Such influences on reward processing may not only contribute negatively towards smoking cessation but could also increase the susceptibility to dependence and difficulty quitting of other abused substances used concurrently with nicotine [89]. In addition, nicotine's ability to disrupt the corticostriatal communication specifically during the hedonic-driven outcome phase of reward processing hints at potential mood-related consequences, consistent with the high comorbidity between nicotine use and mood disorders [90] as well as the observed mood improvements following smoking cessation [91]. In short, these findings showcase the potent acute effect of nicotine on altering both the activity and the communication between key nodes in the reward-processing circuitry to powerfully drive adaptive behaviors.

AUTHOR CONTRIBUTIONS
A.C.J. conceptualized and designed the study with DAP. M.Z. recruited and collected the data. K.S.W. conducted all analyses and wrote the initial draft with A.C.J. and E.M. L.V.M. and D.O. provided clinical expertise and served as study physicians. All authors reviewed and edited the final manuscript.

ADDITIONAL INFORMATION
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