ARCHIVAL REPORT

Acute Nicotine Differentially Impacts Anticipatory Valence- and Magnitude-Related Striatal Activity

Emma Jane Rose, Thomas J. Ross, Betty Jo Salmeron, Mary Lee, Diaa M. Shakleya, Marilyn A. Huestis, and Elliot A. Stein

Background: Dopaminergic activity plays a role in mediating the rewarding aspects of abused drugs, including nicotine. Nicotine modulates the reinforcing properties of other motivational stimuli, yet the mechanisms of this interaction are poorly understood. This study aimed to ascertain the impact of nicotine exposure on neuronal activity associated with reinforcing outcomes in dependent smokers.

Methods: Smokers ($n = 28$) and control subjects ($n = 28$) underwent functional imaging during performance of a monetary incentive delay task. Using a randomized, counterbalanced design, smokers completed scanning after placement of a nicotine or placebo patch; nonsmokers were scanned twice without nicotine manipulation. In regions along dopaminergic pathway trajectories, we considered event-related activity for valence (reward/gain vs. punishment/loss), magnitude (small, medium, large), and outcome (successful vs. unsuccessful).

Results: Both nicotine and placebo patch conditions were associated with reduced activity in regions supporting anticipatory valence, including ventral striatum. In contrast, relative to controls, acute nicotine increased activity in dorsal striatum for anticipated magnitude. Across conditions, anticipatory valence-related activity in the striatum was negatively associated with plasma nicotine concentration, whereas the number of cigarettes daily correlated negatively with loss anticipation activity in the medial prefrontal cortex only during abstinence.

Conclusions: These data suggest a partial dissociation in the state- and trait-specific effects of smoking and nicotine exposure on magnitude- and valence-dependent anticipatory activity within discrete reward processing brain regions. Such variability may help explain, in part, nicotine's impact on the reinforcing properties of nondrug stimuli and speak to the continued motivation to smoke and cessation difficulty.

Key Words: Functional MRI, incentive salience, nicotine, reward, smoking, striatum

Preclinical and human studies implicate brain regions along the mesocorticolimbic (MCL) and nigrostriatal (NS) dopamine (DA) pathways in processing reinforcing/rewarding stimuli, including drugs of abuse (1–9) (a complete list of abbreviations is also included in Supplement 1). It is hypothesized that DA's role in reward processing involves the attribution of incentive salience to stimuli predicting rewards, rather than the hedonic experience of a reward and/or reward learning (10–12). Human functional imaging investigations partially support this postulation by highlighting the anatomic distinction in activation associated with hedonic versus motivational aspects of rewarding stimuli along MCL and NS DA pathways (13–22). Whereas reward anticipation appears to involve foci in the ventral striatum (VS), reward receipt is consistently associated with ventromedial prefrontal cortex activation (13–16, 23).

Nicotine's central nervous effects are mediated via high-affinity nicotinic acetylcholine receptors (nAChRs) (24). That nAChRs are widely distributed throughout the brain, including in MCL and NS pathways, suggests that they play a role in modulating reward-related activity in dopaminergic (DArgic) pathway regions (25–27). Functional magnetic resonance imaging (fMRI) investigations in smokers support the involvement of these reward-related regions in a range of nicotine-related situational states (e.g., withdrawal, expectation, cue-induced reactivity, craving suppression) (28–35). Moreover, adult and adolescent smokers show reductions in anticipatory striatal activity for nondrug rewards (e.g. money) (36,37). Using a measure of reward learning for nondrug stimuli in a subsample of those included in the current study, we demonstrated nicotine-mediated reductions in learning-related striatal activity (38). Consistent with the notion that nicotine's primary reinforcing properties include enhanced salience for motivational stimuli (39–42), these observations suggest that nicotine-dependent modulation of activity in reward-related regions in smokers likely extends to reinforcing stimuli beyond nicotine itself. However, although reduced anticipatory DArgic/MCL activity may be an antecedent to nicotine dependence (36), the relative impact of trait- and state-specific effects of smoking and nicotine exposure on the neural substrates of distinct reward processes has not been clearly delineated. Furthermore, the consequences of nicotine exposure may differ critically between nicotine-dependent and nondependent or nicotine-naive individuals.

Consequently, our aim was to determine whether trait (i.e., the combination of chronic nicotine exposure and potential risk factors for smoking) and state (i.e., acute nicotine administration) effects of nicotine would have a differential impact on the functional correlates of distinguishable reward processes in dependent smokers. Reward processing was assessed using a modified monetary incentive delay (MID) paradigm, which has been used to demonstrate regional specificity in DA pathway regions mediating reward anticipation and receipt (13–16). Because nicotine withdrawal is associated with state-specific changes in motivational processing, the relative differences between state- and trait-dependent aspects of nicotine use were considered in the absence of frank withdrawal. We hypothesized that being a chronically exposed, dependent

From the Neuroimaging Research Branch (EJR, TJR, BJS, ML, EAS) and Chemistry and Drug Metabolism (DMS, MAH), National Institute on Drug Abuse, Intramural Research Program, National Institutes of Health, Baltimore, Maryland.

Address correspondence to Emma Jane Rose, Ph.D., Transdisciplinary Science and Translational Prevention Program, Molecular Epidemiology, Genomics, Environment and Health, RTI International, 5520 Research Park Drive, Suite 210, UMBC Main Campus, Baltimore, MD 21228; E-mail: emmajanerose@gmail.com.

Received Dec 13, 2011; revised and accepted Jun 6, 2012.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2012.06.034

Table 1. Summary of Participant Demographics

	Smokers (n = 28)	Control Subjects (n = 28)
Age, Years: Mean (SD)	32.68 (10.02)	30.11 (7.83)
Gender, Male:Female	13:15	16:12
IQ, WASI, Mean (SD)	108.04 (11.63)	107.65 (12.24)
Education, Years: Mean (SD)	12.89 (2.49)	14.00 (2.61)
Ethnicity, AA:C:As	8:20:0	11:14:3
Cigarettes/Day, Min-Max (mean)	18–40 (22.80)	NA
Age at First Use, Years: Min-Max mean	9–31 (15.46)	NA
Years of Use, Min-Max, (Mean)	2.5–38 (16.48)	NA
FTND, Min-Max (Mean)	3–9 (5.89)	NA

There were no significant differences between groups on any demographic measure (see also Table S3 in Supplement 1).

AA, African American; As, Asian/Asian American; C, Caucasian; FTND, Fagerström Test for Nicotine Dependence; Max, maximum; Min, minimum; NA, not applicable; WASI, Wechsler Adult Scale of Intelligence.

smoker would engender reduced anticipatory DArgic/MCL activity (36–38). Following our earlier observation that acute nicotine did not have a differential impact on reward receipt (38), we further hypothesized that acute nicotine would affect motivational but not hedonic aspects of reward processing.

Methods and Materials

Participants

Adult dependent smokers (n = 28) and nonsmoking control subjects (n = 28) were recruited from the general population. Participants were matched for age, IQ, gender, and self-reported race (Table 1). Inclusion and exclusion criteria were as previously described (38).

Procedure

This study was approved by the National Institute on Drug Abuse Intramural Research Program Institutional Review Board. Written informed consent was obtained from participants. Participation involved three visits: task/procedural training in a mock scanner and two MRI sessions. Each session also included a separate reward learning measure described elsewhere (38). Paradigm order was consistent between subjects and sessions, with the MID always conducted first. Experimental sessions were identical across groups, except that smokers had a 21-mg nicotine (Nicoderm; GlaxoSmithKline, Philadelphia, Pennsylvania) or placebo patch applied before scanning. Patch order was random and counterbalanced (n = 13 nicotine first). Participants refrained from consuming alcohol or over-the-counter medications for 24 hours and had no more than a half cup of caffeinated beverages before scanning. Prescanning monitoring of drug and alcohol use was as previously described (38) and included a urine drug test, alcohol breathlyzer, and expired carbon monoxide. Smokers completed a detailed smoking history, including the Fagerström Test for Nicotine Dependence (43) and time of last cigarette.

Patch Administration. Patches were affixed to participants' upper back 30 min after their last cigarette and 2 hours before scanning; a delay chosen as optimal for maximizing nicotine plasma concentrations in the nicotine condition and minimizing withdrawal in the placebo condition (44,45). Withdrawal, craving, and mood were queried pre- and postscanning using the Parrott Mood Questionnaire (46) and the Tobacco Craving Questionnaire (TCQ; 12-item short form) (47,48). Participants were debriefed regarding session order after study completion.

The Revised MID (MID-R). In the MID-R (Figure 1) participants attempted to press a button in response to a white cross (TARGET) during its visual presentation. The target's initial duration was 250 msec. However, to ensure a "hit" on approximately two-thirds of trials, the duration was increased or decreased "online" in 25-msec intervals, depending on rate of success/failure.

Trials included four sequential stimuli: PRIME-1, PRIME-2, TARGET, and FEEDBACK. PRIME-1 indicated trial valence: in Figure 1, the blue circle = gain, red square = loss, yellow triangle = neutral. Irrespective of performance, participants won $1 on gain trials and lost $.75 on loss trials. They neither won nor lost on neutral trials. PRIME-2 indicated the magnitude of potential monetary outcome, that is, one of three pseudo-randomly selected magnitudes (small, medium, large). To equate affective responding (22,49), potential losses were smaller than equivalent gains (gain = $2.50, $10, $15;

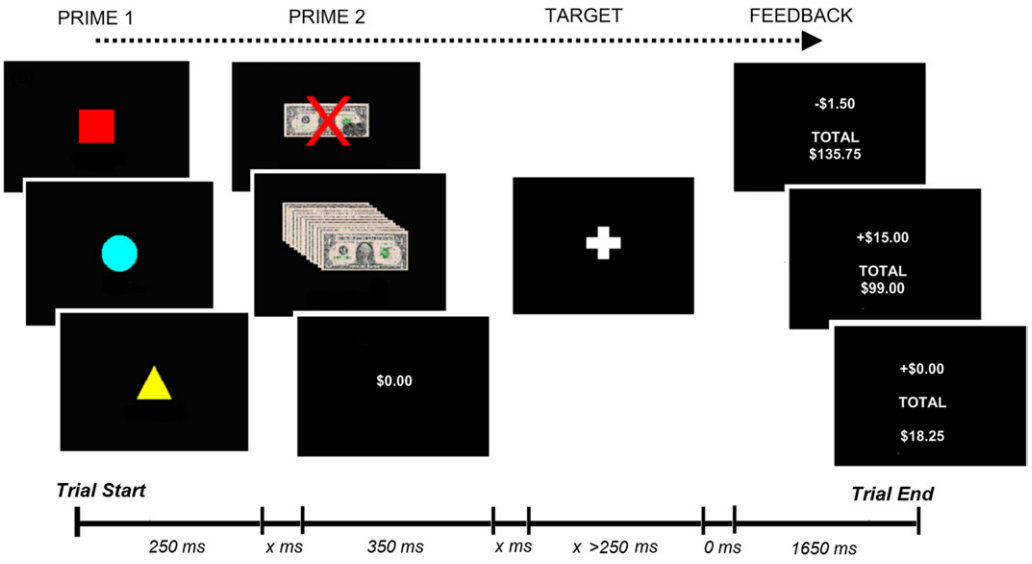

Figure 1. Revised monetary incentive delay task. x, variable presentation time (500–3500 msec), where the two undefined intervals always summed to 4000 msec.