# Dissociated Effects of Anticipating Smoking versus Monetary Reward in the Caudate as a Function of Smoking Abstinence

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**Background:** Theories of addiction suggest that chronic smoking may be associated with both hypersensitivity to smoking and related cues and hyposensitivity to alternative reinforcers. However, neural responses to smoking and nonsmoking rewards are rarely evaluated within the same paradigm, leaving the extent to which both processes operate simultaneously uncertain. Behavioral evidence and theoretical models suggest that dysregulated reward processing may be more pronounced during deprivation from nicotine, but neuroimaging evidence on the effects of deprivation on reward processing is limited. The current study examined the impact of deprivation from smoking on neural processing of both smoking and monetary rewards.

**Methods:** Two separate functional magnetic resonance imaging scans were performed in 38 daily smokers, one after smoking without restriction and one following 24 hours of abstinence. A rewarded guessing task was conducted during each scan to evaluate striatal blood oxygen level–dependent response during anticipation of both smoking and monetary rewards.

**Results:** A significant reward type by abstinence interaction was observed in the bilateral caudate and medial prefrontal cortex during reward anticipation. The blood oxygen level–dependent response to anticipation of smoking reward was significantly higher and anticipation of monetary rewards was significantly lower during abstinence compared with nonabstinence. Attenuation of monetary reward–related activation during abstinence was significantly correlated with abstinence-induced increases in craving and withdrawal.

**Conclusions:** These results provide the first direct evidence of dissociated effects of smoking versus monetary rewards as a function of abstinence. The findings suggest an important neural pathway that may underlie the choice to smoke in lieu of alternative reinforcement during a quit attempt.

**Key Words:** fMRI, nicotine, reward, smoking, striatum, withdrawal

A core feature of drug dependence is increasing drive to obtain the drug at the expense of available alternative rewards. This change may be due in part to dysregulated reward processing, mediated by neuroadaptations within the mesolimbic dopamine system, particularly the striatum (1–3). According to incentive sensitization theory, repeated exposure to drugs of abuse, including nicotine, results in sensitization of the dopamine response to the drug and related cues, ultimately conferring heightened motivational incentive properties to these stimuli (4). Additionally, opponent process theory posits that chronic drug exposure results in compensatory alterations in reward processing (5), causing nondrug rewards to lose their incentive value and fail to motivate behavior.

Taken together, these theories suggest that drug dependence may be characterized by neuroadaptations contributing to both increased sensitivity to drug reward and a parallel hyposensitivity to nondrug rewards. Human neuroimaging studies comparing drug abusers with control subjects have consistently demonstrated heightened blood oxygen level–dependent (BOLD) response to drug-related versus neutral stimuli in key reward-related regions, including medial prefrontal cortex (mPFC), orbitofrontal cortex, anterior cingulate cortex, and striatum, among individuals dependent on cocaine, alcohol, and nicotine (6–11). Cue-elicited activation within these regions is associated with craving (12) and predicts subsequent relapse (13,14). Conversely, decrements in processing of nondrug-related rewards and positive affective stimuli have been found in the mPFC and striatum among individuals dependent on cocaine (15–17), opiates (18), alcohol (19,20), and nicotine (21–23). Although few studies have evaluated processing of both drug and nondrug reward within the same model, findings generally support the hypothesis that divergent, but complementary, processes co-occur within an individual, contributing to both hypersensitivity to drug reward and hyposensitivity to nondrug reward (15,20,24).

This pattern of dysregulated reward processing may be modulated further by acute drug exposure or withdrawal. For example, smoking self-administration increases when chronic smokers are in a deprived relative to satiated state (25–27), and smokers routinely report lower craving after smoking (28). Thus, when abstinent, smokers may be hypersensitive to smoking-related rewards. Evidence from animal studies also suggests that acute nicotine enhances—whereas withdrawal from nicotine attenuates—the incentive value of other reinforcers (29–34). Nicotine administration lowers intracranial self-stimulation thresholds (35), suggesting that nicotine acutely renders reward systems hypersensitive to nondrug rewards, whereas nicotine withdrawal increases intracranial self-stimulation thresholds (36,37).

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Consistent with these findings, nonsmokers administered transdermal nicotine demonstrated greater response bias to monetary reward compared with nonsmokers administered a placebo patch (38). In other studies, abstinent smokers demonstrated less interference from pleasure-related words during a modified Stroop task than satiated smokers (39) and rated unfamiliar faces as less attractive (40). Behavioral evidence suggests both hypersensitivity to smoking reward and hyposensitivity to alternative rewards may be particularly pronounced when underlying dysregulation is "unmasked" by removal of acute effects of nicotine or emergence of a withdrawal state.

Despite a rich theoretical background and behavioral evidence, few studies have examined neural response to smoking rewards among smokers tested in both abstinent and nonabstinent states, and results have been mixed. Some studies have demonstrated heightened BOLD response to smoking cues (41,42) or in cued anticipation of intravenous nicotine (43) in reward-related areas among deprived versus satiated states. However, other studies have shown minimal effects of abstinence on response to smoking reward (44) or opposite effects, such as greater ventral striatal response to smoking cues during nonabstinence versus abstinence (45). Even fewer studies have examined abstinence effects on neural response to nondrug rewards, with similarly mixed findings (23,44,46,47). Despite clear theoretical predictions, effects of smoking abstinence on neural response to reward remain equivocal. Even if abstinence does enhance neural processing of smoking rewards, it is unclear whether this heightened response generalizes to other nondrug rewards or dissociates based on reward type. Finally, it is unknown whether this potential dissociated response is instantiated in the same or different circuitry depending on type of reward.

Inconclusive findings from existing studies may be due to small sample sizes (average $n = 14$) or methodologic differences. Most notably, smoking stimuli presented to elicit reactivity to cues are usually divorced from any true predictive relationship with smoking. Presentation of a cigarette is not directly linked with expectancy of smoking the cigarette, which may profoundly alter neural processing (48–50). In contrast, studies of nonsmoking rewards often involve performance-contingent reward delivery. Comparisons across studies employing different methodologic frameworks are insufficient to determine how abstinence from nicotine may differentially affect processing of smoking versus nonsmoking rewards.

In the present study, we used a within-subjects design to examine BOLD response to anticipation of both smoking and nonsmoking rewards among a relatively large sample of daily smokers during both abstinent and nonabstinent states. We used a functional magnetic resonance imaging (fMRI) reward paradigm that included the promise of receiving puffs of a cigarette and money after the scan. We hypothesized that following 24-hour abstinence, smokers would exhibit heightened striatal response during anticipation of smoking reward but attenuated striatal response during anticipation of monetary reward compared with smoking as usual.

## Methods and Materials

### Participants

Investigators recruited 56 daily smokers as part of a larger study investigating genetic predictors of abstinence during a quit attempt. Inclusion criteria included age 18–65 years old, smoking five or more cigarettes per day during the past year, expired carbon monoxide (CO) level of ≥8 ppm, and willingness to make a quit attempt. Exclusion criteria included self-reported psychiatric illness or significant medical illness in the past year, current heavy drug or alcohol use as determined by self-report (drug use for ≥10 days or four or more drinks per day for ≥10 days in past 30 days) or positive urine drug screen or blood alcohol >.08, current use of any psychotropic medication or other tobacco products, interest in using smoking cessation medications, pregnancy or lactation, head trauma with loss of consciousness in the past year, claustrophobia, and any known risk from exposure to high-field-strength magnetic fields. Because the parent study involved a genetic component, participation was restricted to Caucasians to minimize population stratification. All participants gave informed consent in accordance with the University of Pittsburgh Institutional Review Board.

Of 56 individuals initially recruited, 18 were excluded from analyses for various technical reasons or noncompliance (Supplement 1). The remaining 38 participants ranged from 18–58 years of age (mean, 34.1 years; SD, 12.2); 55.3% were female. Participants smoked 5–30 cigarettes per day (mean, 13.45; SD, 6.2) and had a mean score of 3.5 (SD, 2.4) on the Fagerström Test for Nicotine Dependence (51). Excluded participants smoked significantly more cigarettes per day [$t_{54} = 2.160$, $p < .05$] but did not differ on the Fagerström Test for Nicotine Dependence. Only two participants admitted illicit drug use in the past 30 days (marijuana and hallucinogens, on two occasions). Results were unchanged when these individuals were excluded from analyses.

### Procedure

**Screening Session.** Eligible participants attended an in-person screening. Breath and urine samples were collected to assess blood alcohol level and illicit drug use and pregnancy, respectively. Expired CO was assessed on arrival and after smoking a cigarette in the laboratory. To prevent exclusion of participants who had not smoked recently before the visit, the minimum CO inclusion criterion was satisfied if either CO sample was >8 ppm. Participants completed questionnaires assessing demographics, medical and psychiatric history, nicotine use history, and nicotine dependence (Fagerström Test for Nicotine Dependence).

**fMRI Sessions.** Participants underwent two identical fMRI sessions on two different days (mean of 12.8 days apart), once following smoking ad libitum (nonabstinent) and once after 24 hours of abstinence (abstinent). Session order was randomly assigned; 17 participants (45%) completed the abstinent session first. Abstinence was verified via self-report and expired CO level <8 ppm or 50% reduction from baseline. Before each scan, participants underwent task training and completed subjective measures, including a 4-item version of the Questionnaire on Smoking Urges (51) and the Minnesota Withdrawal Scale (52). The 4-item Questionnaire on Smoking Urges was repeated immediately after the scans, which lasted approximately 1 hour. During the nonabstinent session, participants smoked a cigarette immediately before the scan to prevent unintended withdrawal.

### Rewarded Guessing Task

During each fMRI scan, participants completed a rewarded guessing task (Figure 1) modified from previous versions shown to engage robustly the ventral and dorsal striatum and other reward-related areas (53–55). Participants earned rewards by "guessing" whether a computer-generated number was higher or lower than 5. For each trial, participants first indicated their guess with a button press and were then presented with a picture