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Dissociated effects of anticipating smoking versus monetary reward in the caudate as a function of smoking abstinence

Maggie M. Sweitzer¹, Charles F. Geier², Danielle L. Joel³, Patrick McGurrin³, Rachel Denlinger³, Erika Forbes^{3,4,5}, and Eric C. Donny^{3,4,5}

¹Department of Psychiatry and Behavioral Sciences, Duke University Medical Center

²Department of Human Development and Family Studies, Penn State University

³Department of Psychology, University of Pittsburgh

⁴Department of Psychiatry, University of Pittsburgh Medical Center

⁵Center for Neural Basis of Cognition, University of Pittsburgh and Carnegie Mellon University

Abstract

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 non-smoking rewards are rarely evaluated within the same paradigm, leaving the extent to which both processes operate simultaneously uncertain. Furthermore, behavioral evidence and theoretical models suggests 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—Thirty-eight daily smokers participated in two separate fMRI scans, one after smoking without restriction and one following 24 hours of abstinence. A rewarded guessing task was conducted during each scan to evaluate striatal BOLD response during anticipation of both smoking and monetary rewards.

Results—A significant reward type X abstinence interaction was observed in the bilateral caudate and medial prefrontal cortex during reward anticipation. BOLD response to anticipation of smoking reward was significantly higher, and anticipation of monetary rewards significantly lower, during abstinence compared with non-abstinence. Furthermore, attenuation of monetary

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Corresponding Author: Maggie M. Sweitzer, Ph.D. Department of Psychiatry and Behavioral Sciences Duke University Medical Center 2608 Erwin Rd., Suite 300 Durham, NC Phone: 919-668-0094 maggie.sweitzer@duke.edu.

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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 alternate reinforcement during a quit attempt.

Keywords

nicotine; fMRI; withdrawal; striatum; reward; smoking

Introduction

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 non-drug 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 non-drug rewards. Accordingly, human neuroimaging studies comparing drug abusers to controls have consistently demonstrated heightened BOLD response to drug-related vs. neutral stimuli in key reward-related regions, including medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and striatum among individuals dependent on cocaine, alcohol, and nicotine (6-11). Furthermore, cue-elicited activation within these regions is associated with craving (12) and predicts subsequent relapse (13, 14). Conversely, decrements in processing of non-drug 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 non-drug 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 non-drug reward (15, 20, 24).

This pattern of dysregulated reward processing may be further modulated 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, smokers may be hypersensitive to smoking-related rewards when abstinent. Evidence from animal studies also suggests that acute nicotine enhances—while withdrawal from nicotine attenuates—the incentive value of other reinforcers (29-34). Furthermore, nicotine administration lowers intracranial self-stimulation

(ICSS) thresholds (35), suggesting that nicotine acutely renders reward systems hypersensitive to non-drug rewards, while nicotine withdrawal increases ICSS thresholds (36, 37). Consistent with these findings, nonsmokers administered transdermal nicotine demonstrated greater response bias to monetary reward compared to placebo patch (38). In other studies, abstinent smokers demonstrate less interference from pleasure-related words during a modified Stroop task than satiated smokers (39) and rated unfamiliar faces as less attractive (40). Thus, behavioral evidence suggests hypersensitivity to smoking reward and hyposensitivity to alternative rewards may both be particularly pronounced when underlying dysregulation is “unmasked” by removal of acute effects of nicotine and/or emergence of a withdrawal state.

Despite rich theoretical background and behavioral evidence, few studies have examined neural response to smoking rewards among smokers tested in both abstinent and non-abstinent 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 non-abstinence versus abstinence (45). Even fewer studies have examined abstinence effects on neural response to non-drug rewards, with similarly mixed findings (23, 44, 46, 47). Thus, despite clear theoretical predictions, effects of smoking abstinence on neural response to reward remain equivocal. Furthermore, even if abstinence does enhance neural processing of smoking rewards, it is unclear whether this heightened response generalizes to other non-drug 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 methodological differences. Most notably, smoking stimuli presented to elicit reactivity to cues are usually divorced from any true predictive relationship with smoking. Thus, presentation of a cigarette is not directly linked with expectancy of actually smoking the cigarette, which may profoundly alter neural processing (48-50). In contrast, studies of non-smoking rewards often involve performance-contingent reward delivery. Thus, comparisons across studies employing different methodological frameworks are insufficient to determine how abstinence from nicotine may differentially affect processing of smoking versus non-smoking rewards.

In the present study, we used a within-subjects design to examine BOLD response to anticipation of both smoking and non-smoking rewards among a relatively large sample of daily smokers during both abstinent and non-abstinent states. We used an 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

Fifty-six daily smokers were recruited as part of a larger study investigating genetic predictors of abstinence during a quit attempt. Inclusion criteria included being between 18 and 65 years old, smoking 5 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 4 or more drinks per day for 10+ days in past 30) or positive urine drug screen or blood alcohol > 0.08 , current use of any psychotropic medication or other tobacco products, interest in using smoking cessation medications, pregnancy/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 provided informed consent in accordance with the University of Pittsburgh Institutional Review Board.

Out of 56 individuals initially recruited, 18 were excluded from analyses for various technical reasons or non-compliance (see supplement). The remaining 38 participants ranged from 18 to 58 years of age ($M = 34.1$ years, $SD = 12.2$); 55.3% were female. Participants smoked between 5 and 30 cigarettes per day ($M = 13.45$, $SD = 6.2$) and had a mean score of 3.5 ($SD = 2.4$) on the Fagerström Test for Nicotine Dependence (FTND) (51). Excluded participants smoked significantly more cigarettes per day [$t(54) = 2.160$, $p < 0.05$] but did not differ on the FTND. Only two participants endorsed 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 upon arrival and after smoking a cigarette in the laboratory. To prevent exclusion of participants who had not smoked recently prior to the visit, the minimum CO inclusion criterion was satisfied if either CO sample was greater than 8 ppm. Participants completed questionnaires assessing demographics, medical and psychiatric history, nicotine use history, and nicotine dependence (FTND).

fMRI Sessions—Participants completed two identical fMRI sessions on two different days (mean of 12.8 days apart), once following smoking *ad libitum* (non-abstinent) and once after 24 hours 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 less than 8 ppm or 50% reduction from baseline. Prior to each scan participants underwent task training and completed subjective measures, including a 4-item version of the Questionnaire on Smoking Urges (QSU-4; (51)) and the Minnesota Withdrawal Scale

(MNWS; (52)). The QSU-4 was repeated immediately after the scans, which lasted approximately 1 hour. During the non-abstinent session, participants smoked a cigarette immediately prior to 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 robustly engage 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 representation of the type of reward they could earn on that trial (\$0.50, a puff of a cigarette, or nothing). After 6 seconds, the actual number was presented, followed by win or no win feedback and a 9-sec inter-trial interval. The task was divided into 4 runs of 18 trials each, with each run lasting 6 minutes, 10 seconds. Reward type and outcome were predetermined and presented in a fixed, pseudorandom order such that each run contained 6 trials of each reward type, each with 50% wins. Participants were informed during training of the amount of reward available for each trial (e.g., \$0.50 or 1 puff) but were led to believe that outcomes were dictated by accuracy of their guesses. Across four runs, subjects won \$6 and 12 puffs, delivered immediately after the scan. To increase salience of the smoking reward, participants were required to remain in the building and refrain from smoking any additional cigarettes for one hour after the scan.

Imaging Acquisition and Preprocessing

BOLD functional images were acquired using a 3.0 Tesla Siemens Allegra scanner with gradient EPI sequence covering 34 interleaved axial slices of 3 mm thickness with the following parameters: TR = 2 sec; TE = 29 ms; flip angle = 90 degrees; 64×64 matrix with FOV = 20×20 cm. A T1-weighted structural image was acquired using a 3-dimensional volume MPRAGE pulse sequence covering 176 axial slices of 1 mm thickness.

Functional images were preprocessed using SPM8 (www.fil.ion.ucl.ac.uk/spm). Images were corrected for slice timing effects and realigned to the mean functional image. Structural images were segmented into native space grey matter and coregistered to the mean of functional images. Functional images were spatially normalized into Montreal Neurologic Institute stereotactic space and resampled to a voxel size of $2 \times 2 \times 2$ mm. Images were smoothed with a Gaussian filter set at 6 mm Full-width at Half Maximum (FWHM), and a high pass filter (128 seconds) was applied. Artifact detection tools implemented in SPM were used to identify and adjust for image artifacts related to intensity spiking and motion (see supplement).

Data Analysis

Preprocessed data were analyzed using the general linear model (56-58). BOLD responses to task events were modeled by convolving stimulus onset times with a canonical hemodynamic response function. Modeled task events included three levels of reward anticipation (money, smoking, or neutral), six possible outcomes (win or no win for each reward type), guessing period, number presentation, and a baseline period encompassing the

last 3 seconds of fixation for each trial. Motion parameters were added as nuisance regressors. Individual participant effects were estimated for each scan using a fixed effects model, and contrast images were created comparing money > neutral and puff > neutral for the anticipation phase. Initial comparisons across the four runs suggested an attenuation of striatal response in anticipation of monetary reward during the second half of the task (see supplement; Figure S1), consistent with previous research (53, 54, 59-61). Consequently, subsequent analyses were restricted to the first two runs.

First-level contrasts were submitted to second-level random effects ANOVA for group analyses. Given limited power during the outcome phase due to fewer trials per outcome type, analyses focused on anticipation. Effects of reward type and abstinence condition on anticipatory activation were modeled with a $2 \times 2 \times 2$ ANOVA. Condition (abstinent, non-abstinent) and reward type (money > neutral, puff > neutral) were entered as within-subjects factors and scan order (abstinent or non-abstinent session first) was entered as a between-subjects factor. Age was included as a covariate. Main effects and interaction effects were tested within *a priori* anatomically defined regions of interest (ROIs) within the striatum and mPFC. Striatal ROIs included bilateral ventral striatum, encompassing the anterior portions of the ventral caudate and putamen, as well as anterior globus pallidus (62), and bilateral dorsal striatum, defined using the WFU_PickAtlas toolbox (www.ansir.wfubmc.edu) to include head, body, and tail of the caudate (63). For mPFC, a 25 mm sphere was created centered on Talairach coordinates $x = 0$, $y = 44$, $z = 18$, in order to encompass BA32 and medial regions of BA9 and BA10 (60). The combined mask encompassed a volume of 73,136 mm³ or 9,142 voxels. Corrections for multiple comparisons were made using a combined cluster size and individual voxel threshold method determined by Monte Carlo simulations implemented in 3dClusterSim (AFNI). A cluster of 25 voxels along with an individual voxel significance level of $p < 0.001$ was required for an overall corrected false positive detection rate of $P < 0.05$. The first eigenvariate was then extracted from clusters within ROIs showing a significant reward type by abstinence condition interaction using SPM8. This approach employs a form of principal component analysis to provide the best estimation of BOLD signal change across all voxels within the cluster without assuming homogeneity of response (64). These values were then exported to SPSS for further analyses. Directionality of significant effects was explored using paired *t*-tests, and correlations between change scores for each reward type and selected behavioral measures were evaluated. Finally, to confirm the regional specificity of observed effects, additional exploratory analyses were conducted across the whole brain using uncorrected $p < 0.001$, with a 25 voxel extent threshold.

Results

Subjective Measures

Repeated-measures ANOVA was used to evaluate changes in subjective measures during abstinence, with session order entered as a between-subjects factor. As expected, main effects of abstinence were observed for CO level [$F(1,34) = 79.883$, $p < 0.001$], craving [$F(1,35) = 44.127$, $p < 0.001$], and withdrawal [$F(1,36) = 13.807$, $p < 0.001$]. CO was significantly lower during abstinence versus non-abstinence, while craving and withdrawal

were both significantly higher during abstinence (Table 1). In addition, a significant abstinence by timing interaction was observed for craving [$F(1,35) = 17.525, p < 0.001$], such that craving during non-abstinence increased from pre- to post-scan [$t(37) = 5.49, p < 0.001$], while craving during abstinent sessions remained unchanged [$t(36) = 0.55, ns$]. There were no interactions with session order for any variable.

fMRI Reward Anticipation

Main Effects of Task Conditions—Anticipation of reward (money or puffs) compared with neutral trials, collapsed across conditions, produced robust activation throughout expected ROIs. Significant activation was observed in the bilateral striatum, including caudate and anterior putamen, and in the mPFC extending to the anterior cingulate cortex (Figure S3). There were no significant main effects of abstinence condition or reward type within the striatum or mPFC. No significant interactions with scan order were observed, suggesting minimal learning or habituation effects between scans in these regions.

Reward by Condition Interaction—We tested our primary hypothesis of a reward X condition interaction within *a priori* ROIs of the striatum and mPFC. As expected, a significant reward X condition interaction was observed bilaterally in the caudate head and in the mPFC (Figure 2a). Consistent with our central hypothesis, pairwise comparisons conducted within SPSS indicated that abstinence from smoking was associated with a significant decrease in anticipatory activation to monetary rewards in the bilateral caudate [$t(37) = 3.434$ and 3.279 , both p 's < 0.01] and a parallel increase in anticipatory activation to smoking rewards [$t(37) = 5.287$ and 4.732 , both p 's < 0.001] relative to non-abstinence (Figure 2b). Within the mPFC, abstinence was associated with a significant increase in anticipatory activation to smoking rewards [$t(37) = 4.001, p < 0.001$]; change in anticipatory activation to monetary reward was not significant [$t(37) = 1.745, ns$]. Abstinence-induced decreases in anticipatory activation to monetary reward were not significantly correlated with increases in anticipatory activation to smoking reward. Within the abstinent condition, however, anticipatory activation to monetary and smoking rewards were inversely correlated in the mPFC ($r = -.336, p < 0.05$), but not in the striatum.

Exploratory Whole Brain Analyses—Exploratory analyses conducted across the whole brain at an uncorrected threshold of $p < 0.001$ revealed additional activation clusters related to the condition X reward interaction in the right insula and right brainstem (Figure S4). Only small areas of activation were associated with main effects of abstinence state (Figure S5) or reward type (Figure S6).

Correlations with Subjective Measures

Given the significant reward $\times$ condition interaction within the bilateral caudate head and mPFC, we explored whether abstinence-induced changes in anticipatory activation to each reward type were correlated with changes in craving or withdrawal. We computed difference scores characterizing the change in anticipatory activation to monetary and puff rewards during abstinence using values extracted from significant interaction clusters in the right and left caudate head and mPFC (Figure 2a). We further computed difference scores for subjective measures taken before each scan; for craving we used the average of pre and post-

scan QSU-4 scores. In the left caudate, larger abstinence-induced decreases in anticipatory activation to monetary reward were associated with greater increases in craving ($r = .322, p < 0.05$; Figure 3a) and withdrawal ($r = .353, p < 0.05$; Figure 3b). The association between decreased activation to monetary reward and increased withdrawal during abstinence was bilateral (right caudate: $r = .370, p < 0.05$; Figure 3d); association with craving was also observed in the mPFC ($r = .433, p < 0.01$; Figure 3c). Surprisingly, the increase in anticipatory activation to smoking reward was unrelated to both measures.

Discussion

The present study found that abstinence contributed to both heightened activation in anticipation of smoking rewards and attenuated activation in anticipation of monetary rewards. This interaction was robust and specific to reward-related regions, including bilateral caudate head and ventral striatum, and mPFC. The striatum and mPFC have been previously shown to be activated by similar monetary reward tasks (53, 55, 65) and are known to be important for encoding reward prediction, salience attribution, and subjective value of rewards (1, 2, 66). Furthermore, these regions have been previously implicated in studies of smoking cue reactivity (41, 42, 67, 68), demonstrating the capacity for smoking stimuli to engage reward-related circuitry. Although a few previous studies have observed abstinence-induced changes within reward-relevant circuitry for monetary reward or smoking cues separately (41-43, 47), this study is the first to demonstrate parallel, dissociated effects of abstinence on processing of both types of rewards within the same paradigm. These findings support theoretical predictions and suggest that abstinence contributes to increased bias toward anticipation of smoking rewards at the expense of other rewards, which could be an important motivator of continued smoking behavior.

These results differ from a previous study that examined effects of smoking withdrawal on motivation to obtain both monetary and smoking rewards but failed to find significant changes beyond a small cluster in the mPFC showing heightened activation in anticipation of both reward types during abstinence (44). Although lack of a comparable interaction effect to that seen here is somewhat surprising, the increased power from the larger sample size in the present study may have enabled detection of effects missed in other studies.

The dissociated effects observed here raise important questions about potential underlying mechanisms. One possibility is that the pattern of results during abstinence may be the result of altered top-down prefrontal modulation of striatal reward processing. Neurons of the prefrontal cortex are known to project to the head of the caudate (69), and recent studies have demonstrated altered activation in several prefrontal regions during affective processing or cognitive control tasks among smokers (70-72). Further evidence suggests that activation in these regions, including the anterior cingulate and dorsolateral prefrontal cortex, may be heightened during abstinence (73-75), possibly reflecting state-based inefficiency in inhibitory control networks. Thus, diminished prefrontal cognitive control during abstinence may exacerbate bottom-up reward dysregulation favoring smoking at the expense of other rewards. Future studies incorporating connectivity analyses could be used to explore these hypotheses.

The fMRI paradigm used here focused primarily on reward anticipation rather than outcome. The robust abstinence by reward type interaction evident during anticipation is consistent with the central role of incentive motivational processes in drug dependence and with theories proposing increased “wanting” of drug reward at the expense of hedonic “liking” (4). Thus, it is possible that reward dysregulation modulated by smoking abstinence preferentially involves incentive motivational processes driving expectation of reward rather than the impact of reward delivery. Additional studies explicitly separating reward anticipation from outcomes are needed to fully test this hypothesis.

Several caveats related to task design and interpretation should be noted. First, it is possible that smoking reward simply functioned as a cue exposure manipulation, particularly since effects were observed during reward anticipation. However, the decrease in monetary reward anticipation during abstinence is not likely driven by heightened cue reactivity, particularly since both reward types were offset with neutral trials, providing a no-reward condition for comparison. Second, no behavioral response was required during reward anticipation, so behavioral data cannot confirm that participants were engaged and processing different reward types. However, imaging results suggest strong differences in activation between rewarded and neutral trials, supporting that participants were alert and attentive. Third, subjective value of puffs was not standardized and likely varied from person to person. Although this prevents direct comparison of smoking versus monetary reward processing, the within-subjects comparison conducted here suggests the *relative* balance of incentive properties of these rewards shifted during abstinence in favor of heightened incentive motivation for smoking. A final consideration is that smoking and monetary rewards differed in their capacity as primary versus secondary reinforcers, respectively. Evidence suggests substantial overlap in reward circuitry activated by different reward types (76), but the possibility remains that money could have been perceived as an additional means of obtaining smoking reward, or that its subjective value was differentially affected by the imposed 1-hour post-scan delay (wherein puffs could be consumed but money could not be spent). Future studies incorporating additional non-drug, primary rewards (such as food) could address these discrepancies.

The present study found correlations between increased withdrawal symptoms and cigarette craving during abstinence and decreased anticipatory activation to monetary reward. Consistent with previous findings (20), these results highlight the importance of individual differences and suggest that some individuals may be more susceptible to abstinence-induced changes in reward processing than others. While it is surprising that craving and anticipation of puff reward were not correlated, the association between reported craving and anticipatory activation to monetary reward suggests that these alternate rewards may be in competition within common reward-related neural circuitry. Although causation cannot be inferred, the intriguing possibility exists that increasing salience of alternative rewards could actually diminish motivation to smoke. Indeed, one recent study found that manipulating increased social reward in the context of romantic love lead to diminished smoking cue reactivity among abstinent smokers (77).

Although the present findings established strong effects of abstinence versus acute exposure on anticipatory activation to monetary and smoking rewards, further work is needed to

clarify whether this is due to effects of deprivation or recent smoking. To the extent that deprivation does contribute to observed effects, it would also be interesting to examine the duration of effects beyond a single 24-hour time point to determine whether reward dysregulation recovers after a period of protracted abstinence. Furthermore, future studies could employ a placebo-control design to differentiate effects of smoking and non-nicotine factors from pharmacological effects of nicotine.

The present findings may have important implications for smoking cessation. Deprivation from nicotine during early stages of a quit attempt may lead to increased bias toward smoking reward, contributing to greater likelihood of relapse for individuals most susceptible to these changes. This reward dysregulation may be particularly problematic for smokers with depression or other psychiatric disorders and may help to explain high comorbidity between smoking and depression. Future studies should explore these possibilities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Schematic of events within each trial of the fMRI reward task. Trials began with a 4-sec presentation of a question mark, during which participants indicated their guess via button press. Next, an image was presented for 6 sec depicting the reward that would be won if the guess was correct (stack of dollar bills = \$0.50, cigarette = a puff of a cigarette, or blue notebook = no reward). The “actual” number was then presented for 500 msec, followed by 500-msec win or no win feedback (up arrow or yellow circle, respectively). The feedback phase was followed by a 9-second inter-trial interval (ITI), marked by a white fixation cross.

Figure 2.

A. Striatal activation associated with reward anticipation trial type (money > neutral or smoking > neutral) X condition (abstinent or non-abstinent) interaction, masked within ventral and dorsal striatum and medial prefrontal cortex ROIs. Slices shown at $x = 0$, $y = 10$, $z = -2$, with threshold of $p < 0.001$, 25 voxel extent. Right caudate head: 6, 4, 2; $F = 23.95$, 169 voxels. Left caudate head: -4, 6, -2; $F = 20.18$, 121 voxels. Medial prefrontal cortex: 2, 40, 12; $F = 20.60$, 194 voxels. **B-D.** BOLD response by group and condition, based on eigenvariate extracted from clusters showing significant interaction above within the left striatum (**B**), right striatum (**C**), and medial prefrontal cortex (**D**). Error bars reflect standard error.

A.

C.

B.

D.

Figure 3.

Associations between increase in subjective measures (craving or withdrawal) during abstinence and decrease in BOLD response to monetary > neutral anticipation during abstinence, relative to non-abstinence. Decrease in BOLD response is expressed as eigenvariate extracted from non-abstinent scans minus abstinent scans. Increased craving is associated with decreased anticipatory activation to monetary reward in the left caudate (A.) and medial prefrontal cortex (C.) as a function of abstinence. Increased withdrawal is associated with decreased anticipatory activation to monetary reward in the left (B.) and right (D.) caudate as a function of abstinence.

Table 1

Mean values for smoking-related measures during abstinence and non-abstinence.

Variable	Mean (SD) Non- Abstinent	Mean (SD) Abstinent
Carbon Monoxide	20.18 (14.69)	3.82 (2.62)
Pre-scan QSU-4	16.28 (20.70)	56.62 (29.57)
Post-scan QSU-4	41.22 (25.28)	58.75 (28.73)
Average QSU-4	28.54 (18.12)	57.99 (27.81)
MNWS	119.61 (102.80)	214.76 (159.18)

Abbreviations: QSU-4-Questionnaire of smoking urges, 4 item version (51); MNWS-Minnesota Withdrawal Scale (52).