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Blunted striatal response to monetary reward anticipation during smoking abstinence predicts lapse during a contingency-managed quit attempt

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Abstract

Rationale—Tobacco smoking is associated with dysregulated reward processing within the striatum, characterized by hypersensitivity to smoking rewards and hyposensitivity to non-smoking rewards. This bias toward smoking reward at the expense of alternative rewards is further exacerbated by deprivation from smoking, which may contribute to difficulty maintaining abstinence during a quit attempt.

Objective—We examined whether abstinence-induced changes in striatal processing of rewards predicted lapse likelihood during a quit attempt supported by contingency management (CM), in which abstinence from smoking was reinforced with money.

Methods—Thirty-six non-treatment seeking smokers participated in two fMRI sessions, one following 24-hr abstinence and one following smoking as usual. During each scan, participants completed a rewarded guessing task designed to elicit striatal activation in which they could earn smoking and monetary rewards delivered after the scan. Participants then engaged in a 3-week CM-supported quit attempt.

Results—As previously reported, 24-hr abstinence was associated with increased striatal activation in anticipation of smoking reward and decreased activation in anticipation of monetary reward. Individuals exhibiting greater decrements in right striatal activation to monetary reward during abstinence (controlling for activation during non-abstinence) were more likely to lapse

during CM ($p < .05$), even when controlling for other predictors of lapse outcome (e.g., craving); no association was seen for smoking reward.

Conclusions—These results are consistent with a growing number of studies indicating the specific importance of disrupted striatal processing of non-drug reward in nicotine dependence, and highlight the importance of individual differences in abstinence-induced deficits in striatal function for smoking cessation.

Keywords

smoking; nicotine; reward; ventral striatum; fMRI; relapse; abstinence; withdrawal; cessation; contingency management

Introduction

Despite widespread and longstanding public health efforts, tobacco smoking remains a leading cause of preventable death in the developed world (CDC 2011). As many as 70% of smokers wish to quit, but less than 5% of quit attempts result in abstinence for more than three months (CDC 2002). Identifying mechanisms contributing to lapse and relapse among chronic smokers is critical for improving treatment and prevention efforts, and may ultimately improve interventions for those at greatest risk for relapse.

Disordered reward processing within the mesolimbic dopamine system has been repeatedly implicated in addictive disorders, including nicotine dependence, and may be an important contributor to relapse. According to incentive sensitization theory, repeated exposure to drugs of abuse, including nicotine, results in sensitization of the mesolimbic response to the drug related cues, ultimately conferring heightened motivational incentive properties to these stimuli and leading to increased drug seeking behavior (Robinson and Berridge 1993). At the same time, opponent process theory posits that chronic drug exposure contributes to compensatory alterations in reward processing (Koob and Le Moal 2005), causing non-drug rewards to lose their incentive value and thus fail to motivate behavior. 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 (David et al. 2005; Franklin et al. 2007; Goldstein et al. 2009; Heinz et al. 2004; McClernon et al. 2005; Wrase et al. 2002). At the same time, decrements in response to non-drug rewards and positive affective stimuli have been found in the mPFC and striatum among individuals dependent on cocaine (Garavan et al. 2000; Goldstein et al. 2007; Volkow et al. 1993), opiates (Martin-Soelch et al. 2001), alcohol (Beck et al. 2009; Wrase et al. 2007), and nicotine (Martin-Soelch et al. 2003; Peters et al. 2011; Rose et al. 2012). Together, these findings suggest that chronic smoking is associated with a bias in mesolimbic processing toward smoking reward at the expense of alternative rewards that may contribute to a narrowing of the behavioral repertoire, such that individuals increasingly choose drug over other nondrug reward alternatives.

Importantly, underlying reward dysregulation may be amplified by abstinence from smoking, leading to heightened vulnerability to relapse. Evidence from animal studies suggests that acute nicotine enhances—while withdrawal from nicotine attenuates—the incentive value of other reinforcers (Besheer and Bevins 2003; Chaudhri et al. 2006; Donny et al. 2003; Thiel et al. 2009; Weaver et al. 2012). Abstinent smokers demonstrate increased desire to smoke (i.e. craving) (Shiffman and Jarvik 1976), along with diminished interest in pleasant events, evidenced by decreased attentional bias toward positive stimuli (Dawkins et al. 2006; Freeman et al. 2012; Leventhal et al. 2012; Powell et al. 2002b; Powell et al. 2004); lower ratings of attractiveness for unfamiliar faces (Attwood et al. 2009); lower ratings of anticipated enjoyment in activities; and reduced responsiveness to monetary reward (Dawkins et al. 2006; Geier et al. 2014; Powell et al. 2002a; Powell et al. 2004). Consistent with behavioral evidence, we recently demonstrated that 24 hr abstinence from smoking—compared with smoking as usual—was associated with both heightened response to smoking reward (i.e., puffs of a cigarette delivered after the scan) and attenuated response to monetary reward within the ventral striatum (Sweitzer et al. 2013b)—a key component of reward circuitry thought to encode motivational salience of primary and secondary reinforcers (Bassareo and Di Chiara 1999; Delgado et al. 2000; O'Doherty 2004; Schultz 2000). Furthermore, individual differences were observed in magnitude of abstinence-induced changes in reward processing, suggesting that some smokers may be more vulnerable to these effects and, potentially, at greater risk for resumption of smoking.

Thus, abstinence-induced dysregulation of reward processing may represent an important mechanism contributing to the choice to smoke in lieu of alternative reinforcement during a quit attempt. In support of this hypothesis, Wilson and colleagues recently found that blunted ventral striatal response to monetary outcomes during an fMRI reward paradigm predicted higher likelihood of smoking during a laboratory delay of smoking reinforcement task (Wilson et al. 2014). However, findings were limited by a restricted range of smoking outcomes (i.e., only 5 participants chose to smoke during the reinforcement task), lack of a smoking as usual condition, and examination of only one reward type. Furthermore, it is unclear whether results extend beyond the laboratory setting to a real-world quit attempt.

In the present study, we evaluated whether abstinence-induced changes in striatal responsivity to smoking and monetary rewards, previously reported for this sample, predicted smoking lapse outcomes during a three-week quit attempt supported by contingency management (CM). CM, in which smokers are provided with monetary incentives for periods of biochemically-verified abstinence, has been widely demonstrated to be effective for improving abstinence rates, particularly while incentives remain in place (Alessi et al. 2004; Dallery et al. 2007; Dunn et al. 2008; Higgins et al. 2004; Roll and Higgins 2000; Roll et al. 1996; Tidey et al. 2002). Importantly, the procedure provides a real-world corollary for assessing the trade-off between monetary and smoking rewards. We focused our investigation on the striatum because this region is central to reward processing, activation within the striatum is strongly elicited by the rewarded guessing task used here, and previously identified dissociated effects of abstinence on anticipation of smoking and monetary reward within this sample were restricted to this region. We hypothesized that smokers exhibiting greater abstinence-induced dysregulation in striatal processing of

rewards, characterized by increased responsivity to smoking reward and decreased responsivity to monetary reward, would be most likely to lapse during CM.

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 conditions putting them at 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 as approved by the University of Pittsburgh Institutional Review Board.

Out of 56 individuals initially recruited, 11 withdrew from the study prior to completion of fMRI sessions (nonattendance, $n = 5$; inability to achieve abstinence for fMRI session, $n = 3$; alcohol intoxication, $n = 1$; claustrophobia, $n = 1$; size constraints of scanner, $n = 1$); and 9 were excluded from analyses due to technical issues. The 36 participants included in analyses ranged from 18 to 58 years of age ($M = 34.1$ years, $SD = 12.4$); 53% were female. Participants smoked between 5 and 30 cigarettes per day ($M = 13.6$, $SD = 6.2$) and had a mean score of 3.5 ($SD = 2.4$) on the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al. 1991). Excluded participants smoked significantly more cigarettes per day [$t(54) = 2.16$, $p < 0.05$] 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 24hrs abstinence (abstinent). Session order was randomly assigned; 16 participants (44.4%)

completed the abstinent session first. Abstinence was verified via self-report and expired CO < 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; (Toll et al. 2006)), and the Minnesota Withdrawal Scale (MNWS; (Hughes and Hatsukami 1986)). 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.

Contingency Management (CM)—Following completion of both fMRI sessions, participants made a smoking quit attempt using an adapted internet-based CM procedure (Dallery et al. 2007; Glenn and Dallery 2007), allowing for mobile biochemical verification of smoking abstinence. Participants were provided with computer equipment, including a netbook with webcam and a Bedfont piCO⁺ CO monitor (<http://bedfont.com/smokerlyzer>), and were instructed on how to use this equipment. Participants selected a quit date and were provided with brief smoking cessation counseling prior to beginning the procedure. During CM, participants were instructed to log in to the study website and record and submit CO samples twice daily (at least 8 h apart) throughout a 3 day baseline period and subsequent 18 day quit attempt. During the baseline period, participants smoked *ad libitum* and were paid \$3.00 for each submitted sample; during the abstinence incentive period only samples meeting criteria for abstinence (self-reported abstinence and CO < 8 ppm or a 30% drop from the previous sample) were reinforced. In cases where technical problems prevented video verification (5.5% of total samples), self-reported abstinence was accepted. Reinforcement was provided according to an ascending schedule: participants received \$3.00 for the first abstinent sample, and this amount increased by \$0.25 for each consecutive abstinent sample. Participants also received a \$5.00 bonus for every 3rd consecutive abstinent sample. Non-abstinent samples were not reinforced and resulted in resetting of the payment schedule to \$3.00. Following a lapse, reinforcement was returned to the highest previously earned level after submission of three consecutive abstinent samples. Missing samples (7.0% of total) were not reinforced, but data were imputed based on self-report and surrounding samples for the purpose of analyses (i.e., missing samples were coded as abstinent when preceded and followed by four abstinent samples and < 2 ppm increase in CO was observed following the missing sample). After achieving an initial 24 hrs abstinence following the quit date (i.e., two consecutive abstinent samples), participants who self-reported smoking or submitted a CO sample above the required cutoff were deemed to have lapsed. These criteria for classification of lapsed versus abstainers is consistent with previous studies and the Society for Research on Nicotine and Tobacco's working group definition of a slip (Hughes et al. 2003; Janes et al. 2010). Subsequent analyses were aimed at differentiating those who lapsed from those maintaining continuous abstinence. In cases where coding of missing samples affected lapse classification ($n = 1$), analyses were rerun with that participant dropped from analyses.

Functional Neuroimaging

Reward Guessing Task—During each fMRI scan, participants completed a rewarded guessing task (Fig 1), during which they could earn monetary reward and puffs of a cigarette by “guessing” whether a computer-generated number would be higher or lower than 5. This

task has been previously described in detail, and effects of abstinence on striatal response to monetary and puff rewards within this sample were previously reported (Sweitzer et al. 2013b). Briefly, 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 the 6 second anticipation phase, 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. Rewards (\$6 and 12 puffs) were delivered during a 1-hr waiting period after the scan, during which participants were required to abstain from smoking cigarettes other than the puffs earned in the scanner.

Imaging Acquisition and Preprocessing—BOLD functional images were acquired using a 3.0 Tesla Siemens Allegra scanner (Erlangen, Germany) 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. Image preprocessing was conducted 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 as previously reported (Sweitzer et al., 2013b).

Data Analysis—As in our previous report which found habituation of the striatum to monetary reward anticipation during the second half of the task (Sweitzer et al. 2013b), and consistent with prior research (Forbes et al. 2012; Forbes et al. 2009; Forbes et al. 2010; Forbes et al. 2011), analyses were restricted to the first two runs of the task to minimize habituation effects. In our previous report, first-level contrasts for the reward anticipation phase (money > neutral and puff > neutral) were submitted to a second-level random effects 2 (reward type) X 2 (abstinent vs non-abstinent condition) X 2 (scan order) ANOVA. We previously reported a significant reward type X abstinence interaction within *a priori* regions of interest (ROI's) of the ventral and dorsal striatum, such that abstinence was associated with heightened anticipatory activation to smoking reward and attenuated anticipatory activation to monetary reward (Sweitzer et al. 2013b). Here, we extracted the first eigenvariate from these previously identified clusters (encompassing 169 and 121 voxels for the right and left caudate head, respectively; Fig 2) showing a significant reward type by abstinence condition interaction. This process yielded an estimate of the overall activation across voxels within each ROI (i.e., left and right striatum) for anticipation of each reward type (money, puffs) within each abstinence condition (abstinent, non-abstinent). Extracted values were exported to SPSS, and logistic regression was used to examine whether individual differences in striatal activation during abstinence, relative to non-abstinence, were predictive of lapse outcomes. Age and sex were included as covariates for all analyses.

Results

Contingency Management Outcomes

All 36 participants achieved an initial period of 24 hr abstinence following the quit date. Thirteen (36.1%) subsequently maintained continuous abstinence throughout the procedure (including one participant for whom a missing data point was imputed as abstinent); the remaining 23 (63.9%) lapsed during the quit attempt. Demographic predictors of lapse are presented in Table 1. Age, sex, and FTND were not significant predictors of lapse during CM. There was a trend toward smoking higher cigarettes per day associated with greater likelihood of lapse, but this difference did not reach statistical significance [Odds Ratio (*OR*) = 1.138, $p = 0.06$, 95% Confidence Interval (*CI*): .993 – 1.305].

Subjective Effects

As previously reported for this sample, smoking abstinence was associated with significant increases in self-reported craving ($t = 6.5$, $p < 0.001$) and withdrawal ($t = 3.5$, $p < 0.005$). During 24 hrs abstinence, higher levels of self-reported craving and withdrawal were positively correlated with anticipatory activation to puff reward in both the right caudate ($r = .387$ and $.384$, respectively, both p 's < 0.05), and in the left caudate ($r = .402$ and $.411$, respectively, both p 's < 0.05). No associations were seen for monetary reward or during the non-abstinent session. We further examined whether severity of craving and withdrawal during abstinence, controlling for non-abstinent levels, were predictive of lapse outcomes. Contrary to expectations, higher craving at 24 hrs abstinence was associated with significantly lower likelihood of lapse ($OR = .957$, $p < 0.05$, *CI*: .918 – .997); withdrawal was unrelated to lapse. Results were unchanged when the participant with missing data was dropped from analyses.

Neuroimaging predictors of lapse outcomes

Extracted values for money and puff anticipation during abstinent and satiated conditions from right and left caudate were entered into logistic regression models to evaluate their association with lapse outcome, with separate models created for each hemisphere. For each model, activation to smoking and monetary rewards during non-abstinence were entered during a first step to examine baseline differences between lapsers and abstainers in a satiated state. Activation to each reward type during abstinence was added in the next step to examine abstinence-induced changes in activation as predictors of lapse outcomes. When the addition of a new step significantly improved the overall model, specific predictors (i.e., monetary or smoking reward) were then examined to determine their relative contributions. Significance was set to $p < 0.025$ to control for multiple comparisons across two models (right and left striatum).

For all measures, activation during the non-abstinent condition was not significantly associated with lapse. In the right caudate, activation during abstinence significantly predicted lapse outcomes ($\chi^2 = 1.02$, $p < 0.025$). Specifically, blunted anticipatory activation to monetary reward during abstinence relative to non-abstinence predicted higher likelihood of lapse ($OR = .038$, $p < 0.025$, *CI*: .003 – .534) (Fig 3). This association remained significant even when controlling for behavioral predictors (i.e., abstinence-induced craving

and cigarettes per day). Indeed, when behavioral and neuroimaging measures were included in the model, both craving and monetary reward anticipation during abstinence were significant predictors of lapse (both p 's < 0.05). Follow-up pairwise comparisons indicated that individuals who lapsed during CM exhibited a significant decrease in anticipatory activation to monetary reward during abstinence relative to non-abstinence in the right VS ($t = 4.6$, $p < 0.001$), while no change was observed for non-lapsers ($t = .4$, ns). Abstinence-induced changes in anticipatory activation for monetary reward in the left caudate or for puff reward in the right or left caudate were not significantly predictive of lapse (all p 's > 0.10). Results were unchanged when the subject with missing data was dropped from analyses.

Discussion

The present study examined associations between abstinence-induced changes in striatal reward processing and the ability to maintain abstinence during a quit attempt supported by contingency management. We hypothesized that individuals who exhibited greater blunting of striatal response to monetary reward and heightened response to smoking reward during abstinence relative to satiation would be most likely to lapse despite monetary incentives for abstinence. Our hypothesis was partially supported: we found that an attenuated response to monetary reward anticipation in the right caudate during abstinence predicted greater likelihood of lapse during CM, while response to smoking reward was not predictive of lapse outcomes.

Striatal processing of non-drug rewards has been increasingly implicated in nicotine dependence, with several human neuroimaging studies showing decreased activation among smokers relative to nonsmokers or occasional smokers (Buhler et al. 2010; Lessov-Schlaggar et al. 2013; Luo et al. 2011; Martin-Soelch et al. 2003; Peters et al. 2011; Rose et al. 2012), or altered functioning during abstinence relative to satiation (Addicott et al. 2012; Rose et al. 2013; Sweitzer et al. 2013b) but see also (Buhler et al. 2010). The present results extend our previous findings for this dataset and suggest that individual differences in abstinence-induced changes in striatal function have important implications for real-world smoking behavior and cessation outcomes. Given the central role of the ventral striatum in salience attribution and subjective valuation of rewards (Kahnt et al. 2010; Knutson et al. 2001; O'Doherty et al. 2004), smokers attempting to quit may find themselves increasingly motivated to smoke against a backdrop of declining motivation for other rewards. Interestingly, although our previous work demonstrated a main effect of smoking abstinence on striatal activation to monetary reward anticipation, our current findings indicate that this effect was not observed among the subset of smokers (33%) who were able to maintain continuous abstinence during CM. This suggests that intact reward processing during withdrawal may be a protective factor for smoking cessation, particularly in the context of reinforcement for abstinence, and highlights the importance of individual differences in mechanisms maintaining smoking behavior that may impact treatment response.

The present findings are consistent with a small number of recent studies that have examined associations between reactivity to affective or rewarding stimuli and ability to abstain from smoking. Wilson and colleagues similarly observed attenuated striatal response to monetary reward among abstinent smokers who subsequently smoked during a delay of smoking

reinforcement task compared with those who abstained throughout the entire task (Wilson et al. 2014). Another recent study examined neural response to images of emotional and cigarette cues as a predictor of quit outcome among smokers interested in quitting (Versace et al. 2014). Smokers classified as low in reward sensitivity (based on lower reactivity to pleasant versus cigarette-related stimuli across several cortical regions) were significantly less likely to be abstinent from smoking at 6 months post-quit. Although initial classification of reward sensitivity was based on findings of attenuated activation to pleasant stimuli relative to cigarette cues in regions of the extended visual system, the authors also observed a similar pattern of lower reactivity to positive versus smoking stimuli within the dorsal striatum among low reward sensitivity smokers. The current results provide further support for the importance of blunted reward sensitivity as a risk factor for relapse and highlight the moderating effect of abstinence state. Importantly, associations between striatal functioning and lapse outcomes were not evident during satiation, suggesting that early abstinence may be a particular period of vulnerability. Additional work is needed to determine whether deficits in reward functioning emerging early in a quit attempt may improve with extended abstinence.

Contrary to expectations, heightened striatal activation to smoking reward during abstinence did not predict lapse outcome. This was surprising given the robust increases in activation observed at the group level (Sweitzer et al. 2013b) and the putative role of striatal activation as an index of motivational salience of smoking reward, and in light of previous studies demonstrating an association between reactivity to smoking or alcohol-related cues and quit outcomes (Grusser et al. 2004; Janes et al. 2010). However, methodological differences in task design and timing of fMRI assessment may have contributed to discrepant findings, as these prior studies utilized passive viewing block-design tasks and did not examine a withdrawal state. The lack of a significant effect in the present study was not simply due to a ceiling effect restricting the range of meaningful individual differences, as variability in striatal activation to smoking reward during abstinence was positively correlated with several subjective measures, including self-reported craving, withdrawal, negative affect, and diminished positive affect. Thus, while heightened striatal activation to smoking reward did correspond to a subjective experience of increased desire to smoke, this did not translate to increased smoking behavior during CM. Interestingly, higher craving during the abstinence session was actually associated with *lower* likelihood of lapse during CM. This is in contrast with several studies that have demonstrated associations between increased craving and poorer abstinence outcomes in laboratory-based studies and smoking cessation trials (Bold et al. 2013; Sweitzer et al. 2013a; Van Zundert et al. 2012) but see also (Wray et al. 2013). Thus, it is possible that the availability of monetary incentives for abstinence may have enhanced extrinsic motivation to quit and thereby disrupted the association between subjective craving for cigarettes (and potentially increased striatal anticipation for smoking reward) and actual smoking behavior.

Given the recruitment of non-treatment seeking smokers and the use of CM in the present study, future work will be needed to determine the generalizability of these findings for smoking cessation. The availability of monetary incentives was a primary motivator for abstinence among this sample. Thus, it is possible that striatal activation to monetary reward served as an index of motivation for money, which in turn directly influenced motivation to

abstain from smoking during CM. It is noteworthy that the predictive relationship between striatal activation and lapse outcome was based on *abstinence-induced attenuation* in monetary reward anticipation, suggesting that these findings are not merely a reflection of baseline differences in desire for money. However, individual differences in valuation of money, whether due to socioeconomic status or other factors, will be an important consideration for future studies. Consideration of other non-drug rewards, such as personally relevant rewards, also deserves attention. Furthermore, it is unclear whether reward sensitivity may be modulated by intrinsic motivation to quit, or if deficits in reward functioning can be alleviated by nicotine replacement therapy or other pharmacotherapy. Prospective studies are needed to determine whether deficits in reward function precede and contribute to the onset of nicotine dependence or develop as a result of chronic exposure, and whether reward function improves with extended abstinence. Additional limitations include the relatively small number of abstainers during CM, recruitment of only Caucasian smokers, and short duration of follow-up. Future research will be needed to replicate these findings in a larger and more representative sample. Despite these limitations, the present findings illustrate the importance of abstinence-induced changes in pre-quit striatal response to reward, with implications for smoking behavior over the first several weeks of a quit attempt. Further work is needed to determine whether altered reward processing is associated with long term cessation outcomes.

The present findings may have important implications for understanding vulnerability to relapse and for smoking cessation interventions. Blunted sensitivity to reward may be an important mechanism contributing to the high prevalence of smoking and higher rates of relapse among individuals with psychiatric comorbidities that are themselves associated with deficits in reward function, including depression and ADHD (Breslau et al. 1998; Kollins et al. 2005). Although the present findings demonstrate the importance of individual variability in striatal reward processing among smokers without comorbid psychopathology, future research should examine whether abstinence-induced deficits are exacerbated among individuals with other disorders. The present findings also suggest that pharmacological or behavioral treatments targeting appetitive processing, such as behavioral activation, may be beneficial as a smoking cessation strategy for vulnerable individuals. Preliminary evidence suggests that behavioral activation contributes to greater abstinence among smokers with depression compared with supportive counseling (MacPherson et al. 2010), suggesting that targeting reward deficits as a mechanism for improving cessation outcomes may be a promising area of future research.

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Fig 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 (higher or lower than 5) 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 (Sweitzer et al. 2013b)

Fig 2. Functional regions of interest within the right (169 voxels) and left (121 voxels) striatum exhibiting a significant reward type by abstinence condition interaction. Panel shown at $x = 8$

Fig 3.

Eigenvariate for anticipatory activation to monetary (a and b) and puff (c and d) reward extracted from clusters in left and right ventral striatum, plotted by lapse status and condition. Error bars reflect standard error of the mean

Demographic predictors of lapse likelihood during contingency management in logistic regression model

Table 1

Variable	Lapsers Mean (and SD) (<i>n</i> = 23)	Abstainers Mean (and SD) (<i>n</i> = 13)	Odds Ratio	95% Confidence Interval	<i>p</i> -value
Age	35.3 (12.7)	31.9 (12.0)	1.024	(.965 – 1.085)	.434
Sex (% Female)	57%	46%	1.517	(.387 – 5.951)	.550
FTND	3.8 (2.6)	3.0 (2.0)	1.157	(.864 – 1.548)	.327
Cigarettes smoked per day	15.1 (6.5)	11.0 (4.8)	1.138	(.993 – 1.305)	.063

FTND: Fagerström Test of Nicotine Dependence