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Functional Neuroimaging Study in Identical Twin Pairs Discordant for Regular Cigarette Smoking

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Abstract

Despite the tremendous public health and financial burden of cigarette smoking, relatively little is understood about brain mechanisms that subserve smoking behavior. This study investigated the effect of lifetime regular smoking on brain processing in a reward guessing task using functional magnetic resonance imaging (fMRI) and a cotwin-control study design in monozygotic (MZ) twin pairs that maximally controls for genetic and family background factors. Young adult (24–34 years) MZ female twin pairs (n=15 pairs), discordant for regular smoking defined using Centers for Disease Control (CDC) criteria as having smoked ≥100 cigarettes lifetime were recruited from an ongoing genetic epidemiological longitudinal study of substance use and psychopathology. We applied hypothesis-driven region of interest and whole brain analyses to investigate the effect of regular smoking on reward processing. Reduced response to reward and punishment in regular compared to never-regular smokers was seen in hypothesis-driven region of interest analysis of bilateral ventral striatum. Whole brain analysis identified bilateral reward-processing regions that showed activation differences in response to winning or losing money but no effect of regular smoking; and frontal/parietal regions, predominantly in the right hemisphere, that showed robust effect of regular smoking but no effect of winning or losing money. Altogether, using a study design that maximally controls for group differences, we found that regular smoking had modest effects on striatal reward processing regions but robust effects on cognitive control/attentional systems.

Keywords

cigarette smoking; cotwin-control; fMRI

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Author Contributions

CNLS, PAFM, and ACH were responsible for the study concept and design. PAFM and ACH developed the smoking assessments in the parent twin study. ACH is the principal investigator of the parent twin study. RLL, BLS, and SEP contributed to the acquisition of neuroimaging data. CNLS and RLL performed all analyses. SDK, BLS, KAB, SEP, and DMB assisted with data analysis and interpretation of findings. CNLS wrote the manuscript. RLL, SDK, BLS, KAB, SEP, PAFM, ACH, and DMB provided critical revision of the manuscript for important intellectual content. All authors approved the final version for publication.

Introduction

Reward processing is a common mechanism of action for all drugs of abuse (Goodman, 2008; Koob and Le Moal, 2008). Investigation of monetary brain reward processing in relation to cigarette smoking behavior has consistently shown decreased response in the striatum in smokers compared to controls. Early positron emission tomography studies showed no activation in the striatum in smokers but robust activation in non-smokers (Martin-Soelch et al., 2003; Martin-Solch et al., 2001). However, these conclusions were qualitative as smokers and non-smokers were not statistically compared. More recently, functional magnetic resonance imaging (fMRI) studies have shown decreased activity in the striatum in smokers compared to non-smokers in response to the anticipation of monetary reward (Luo et al., 2011; van Hell et al., 2010). Decreased anticipatory reward-related activity in the striatum and frontal and cingulate cortex has also been shown in dependent compared to non-dependent smokers (Buhler et al., 2010), implicating blunted activation to monetary reward anticipation as a mechanism of nicotine dependence. However, in a large sample of 14-year olds who had varying but overall low levels of smoking exposure, with the majority not meeting criteria for nicotine dependence, lower activation to anticipation of monetary reward was also seen in the ventral striatum in smokers relative to never smoking controls (Peters et al., 2011). The authors surmised that the blunted ventral striatum activation “may reflect a risk factor for the development of early substance use.”(Peters et al., 2011, p. 547).

A cotwin-control study design is ideally suited to deal with the potential confound of predisposing factors on group differences by its ability to provide tight control of predisposing factors thus decoupling, as much as possible, the influence of predisposing factors from cigarette exposure itself. We investigated reward processing in monozygotic (MZ) twin pairs discordant for lifetime smoking behavior (but concordant for ever having tried smoking cigarettes). MZ twins are essentially genetically identical, share early family environmental factors, and commonly try smoking their first cigarettes on the same occasion (Pergadia et al., 2006). Thus, in a MZ cotwin-control study, within-pair differences in brain reward processing could be more readily attributed to within-pair differences in smoking exposure than to differences in genetic or environmental risk for smoking.

Methods

Sample

MZ twin pairs were recruited from a prospective, general population-representative study of a birth cohort of female like-sex twin pairs born in Missouri 1975–1985 (Heath et al., 2002). Twins were first targeted for assessment in adolescence, at mean age 15 years (baseline), with up to 5 follow-up psychiatric interview assessments and an ongoing 6th round of assessments (2011–2014). Polydiagnostic interview assessments were adapted from the Semi-Structured Assessment for the Genetics of Alcoholism (Bucholz et al., 1994; Hesselbrock et al., 1982) and focused on DSM-IV substance abuse and dependence and major axis one disorders. The smoking section was modified from the Composite International Diagnostic Interview (Cottler, Robins and Helzer, 1989; Robins et al., 1988).

Smoking behavior reported as part of the diagnostic interviews at waves 4 (2001–2005) and 5 (2005–2008) was used to identify a sample of MZ twin pairs who were matched for exposure to cigarettes (i.e., both twins of each pair had tried smoking cigarettes, at least “a puff”) to control for exposure effects, but differed in their cumulative lifetime exposure to cigarettes; one twin had smoked ≥100 cigarettes (regular smoker, RS), while the cotwin had smoked <100 cigarettes (never-regular smoker, NRS). Having smoked ≥100 cigarettes in one’s life defines a smoker according to the Centers for Disease Control and Prevention

(CDC, 2002) and is used to define smokers in large national surveys. There is also a nearly 1 to 1 correspondence (r=0.96) in individuals self-identifying as smokers and having smoked ≥100 cigarettes lifetime (Andrew Heath, personal communication). Furthermore, this measure reflects a substantially increased risk for continued smoking, other drug use, and psychopathology (Table S1, Supplemental Results). Altogether, the 100 cigarette phenotype reflects an important transitional stage in smoking behavior, yet it is a measure that captures smokers of varying smoking histories allowing investigation of brain mechanisms associated with transitions to more severe smoking stages.

Subject recruitment and eligibility

The study protocol was approved by the Institutional Review Board of Washington University and was carried out using ethical principles for medical research involving human subjects in accordance with the Declaration of Helsinki. The study included a screening interview over the telephone to determine study eligibility and a neuroimaging appointment. Exclusion criteria were: (1) only one twin from a pair agreed/was eligible to participate; (2) current or past 12-month heavy alcohol (>4 drinks/day) or illicit drug use (>1 use/week for cannabis; >1 use/month for other drugs); (3) pregnancy; (4) history of significant neurological diagnosis; (5) claustrophobia; or (6) presence of any metal in the body. Individuals with lifetime history of psychopathology or substance dependence as well as current diagnosis of tobacco dependence were *not* excluded. Current or past 12-month use of psychotropic medication was an exclusion criterion at the start of the study. However, this criterion significantly limited our ability to recruit twins because antidepressant medication use was common. Consequently, this initial exclusion criterion was dropped. As a result, 3 of the never-regular smokers were using antidepressants (selective serotonin reuptake inhibitors), 2 regular smokers were taking topiramate for migraines and one of them was also using cyclobenzaprine for muscle spasms on as-needed basis, and one never-regular smoker was using cetirizine for seasonal allergies.

Behavioral assessment

At the neuroimaging appointment, subjects provided signed informed consent and completed a questionnaire assessing past 4-week (1) frequency and quantity of caffeine, tobacco, alcohol, and illicit drug use; (2) physical activity; (3) secondhand smoke exposure; (4) nicotine withdrawal using the Minnesota Nicotine Withdrawal Scale (Hughes and Hatsukami, 1986); (5) mood using the 20-item positive and negative affect schedule (PANAS (Watson, Clark and Tellegen, 1988)); (6) past two-week depressive symptoms using the 21-item Beck Depression Inventory (BDI; (Beck et al., 1961)); and (7) current anxiety using the 20-item State Trait Anxiety Inventory (STAI; (Spielberger et al., 1983)). Participants completed 2-subtests (vocabulary and matrix reasoning) of the Wechsler Abbreviated Scale of Intelligence to estimate IQ. Prior to MRI scanning, current regular smokers (n=9) were given opportunity to smoke a cigarette (n=8) to minimize the experience of nicotine withdrawal while in the scanner. Time between cigarette smoking and entrance into the scanner was about 15 minutes, which included measurement of breath carbon monoxide (CO) (~ 2 min), assessment of mood in the past hour (~ 2 min), reading directions for task performance (~ 3 min), and setup of the subject on the scanner table (~ 8 min).

Cognitive task

We adapted the card-guessing task (Delgado et al., 2003; Delgado et al., 2000) by eliminating the card cue, because of its potential association with gambling, and implementing a rapid event-related fMRI design. In our modified “number-guessing task” subjects saw a white question mark in the middle of a black screen (Figure S1). Subjects were told that there is a number behind the question mark that could range from 1 to 9.

Subjects had to guess whether the number behind the question mark was smaller or larger than 5 by pressing a left or right button on a button box. Button mapping was the same within twin pairs but counter-balanced across twin pairs. Subjects won $1 for correct guesses (reward condition) and lost $0.50 for incorrect guesses (punishment condition). No money was won or lost when the number 5 was behind the question mark (neutral condition).

Each run consisted of 20 reward trials, 20 punishment trials, 20 neutral trials, 60 fixation trials (for jittering), in addition to 3 fixation trials at the beginning and 9 fixation trials at the end. Each trial was 2 sec long. For calculation of event-related responses, reward, punishment, and neutral trials were pseudorandomly jittered at 0, 1 and 2 MR frames where 50% of the time two task trials could follow each other without fixation between them, 25% of the time, one fixation separated task trials, and 25% of the time two fixations separated task trials, to allow extraction of signal associated with each event-related response (Miezin et al., 2000). The trial type sequence was pre-determined; if the trial type was “reward”, subjects won money regardless of their guess (i.e., if they guessed above 5, the outcome was above 5). The sequence of trials was different for each task run, and the order of the 4 runs was randomized within and across twin pairs. The total possible number of different orders of the 4 runs was 24 (4 factorial).

The number-guessing task was controlled by scripts compiled using PsyScopeX (Cohen et al., 1993). Visual stimuli were projected (Boxlight CP730e, 832 × 624 pixels) to a magnet compatible rear-projection screen (CinePlex) viewable by the subjects through a mirror mounted on the head coil (usable visual field=24° wide × 14° high).

Image acquisition

All images were obtained with a Siemens MAGNETOM Trio 3 Tesla scanner (Erlangen, Germany) using FDA approved sequences and a 12-channel head matrix coil. A high-resolution T1-weighted sagittal MP-RAGE structural image was obtained (TE=3.08 ms, TR(partition)=2.4 sec, TI=1000 ms, flip angle=8 degrees, 128 slices with 1x1x1.25 mm voxels) (Mugler and Brookeman, 1990). A rapid low-resolution (4x2x2 mm) 3D anatomical MP-RAGE volumetric image(Mugler et al., 1990) was also acquired and warped to a target MP-RAGE data set that represents the Talairach atlas (Talairach and Tournoux, 1988). The alignment parameters were then used to adjust the scanner such that functional images were acquired parallel to the anterior-posterior commissure plane.

Functional images were obtained using a blood oxygenation level-dependent (BOLD) contrast sensitive gradient echo echo-planar imaging (EPI) sequence (TE=27 ms, TR=2.0 sec, flip angle=90°, in-plane resolution 4x4 mm). Whole brain coverage was obtained with 32 contiguous interleaved 4 mm axial slices. Each of four runs of functional imaging consisted of 132 consecutive frames of whole brain imaging.

Data analysis

Image pre-processing and estimation of event-related response—Analysis methods used tools developed in-house for image pre-preprocessing and visualization, and for statistical analysis implemented in a software program called FIDL (Miezin et al., 2000; Ollinger, Corbetta and Shulman, 2001; Ollinger, Shulman and Corbetta, 2001). Image pre-processing involved frame alignment and debanding to correct for asynchronous and interleaved slice acquisition, image realignment to correct for movement, and intensity normalization that scaled each functional run to a mode value of 1000. EPI images were registered to each subject’s T2-weighted structural volumes, which were registered to each

subject's T1-weighted MP-RAGE volumes, which in turn were transformed to Talairach atlas space (Talairach et al., 1988).

After pre-processing, a fixed effects general linear model (GLM) estimated the effect magnitude of each trial type for each subject, using an unassumed hemodynamic response function to model the BOLD response shape, yielding individual-specific estimates of the intercept, BOLD signal related to each of the reward, punishment, and neutral conditions, as well as error trials where subjects failed to press the button during the allotted 1 sec, with estimates for each of 9 timepoints (to model the timecourse of the hemodynamic response function over 18 seconds). This approach has been successfully implemented by others (Jimura, Locke and Braver, 2010; Padmala and Pessoa, 2010).

A priori region of interest (ROI) analysis—Because of findings in the literature of blunted reward-related activation in smokers in the ventral striatum, we conducted hypothesis-driven *a priori* analysis of bilateral ventral striatum. We examined ventral striatum ROIs based on coordinates with peak activation from the main effect of time image (Talairach x, y, z: −21, 3, −6 and 19, 3, −6 for left and right ventral striatum, respectively). The BOLD time series in the 10 mm spheres around these coordinates were subjected to a random effects three-way analysis of variance (ANOVA) with Condition (reward, punishment, neutral), Group (regular smoker, never-regular smoker), and Timepoint (9 TR frames) modeled as within-subject factors. The effect of primary interest was the three-way Condition x Group x Timepoint interaction testing differences in the BOLD response (i.e., evolution of the hemodynamic response function over the 9 TR frames) to reward or punishment between regular and never-regular smokers. Significant effects were followed by post-hoc pairwise comparisons using paired t-tests.

Whole brain analysis—A random effects three-way ANOVA was conducted with Condition, Group, and Timepoint as within-subject effects. The effects of interest were differences in the timecourse of the BOLD response across conditions (Condition x Timepoint interaction), across smoking history (Group x Timepoint interaction), and across both condition and smoking history (Condition x Group x Timepoint interaction).

For each interaction effect image, ROIs with activation reaching brain-wide significance $p<0.05$ after multiple comparisons correction using Monte Carlo simulation, were extracted. ROIs were defined using a peak detection procedure followed by a region growing procedure (Church et al., 2008). Images were first smoothed with a 4 mm radius hard sphere kernel. A peak search algorithm was used to identify peaks with a z threshold $3.5< z<-3.5$ in the smoothed image and a cluster size of ≥ 24 voxels. Peaks separated by less than 10 mm were consolidated via coordinate averaging.

Results

Sample characteristics

A total of 80 individuals from 47 twin pairs were screened for study eligibility. Of these, both twins from 22 pairs were eligible for participation and 16 pairs underwent the neuroimaging protocol. Data from one twin from 1 of these pairs were not usable due to excessive movement, leaving data from 15 twin pairs (n=30 individuals) for analysis. Sample demographic and behavioral characteristics are shown in Table 1. Based on birth record information, 2 of the pairs were African American and all others were of European American descent. Based on self-report on the Edinburgh Handedness Inventory (Oldfield, 1971), 10 pairs were right-handed, in 4 pairs one twin was right-handed and the cotwin was ambidextrous, and in 1 pair, one twin was left-handed and the cotwin was ambidextrous. The sample average age was 28.7 years (SD=3.27; range 24–34 years). Cotwins differed in

BDI and pre-scan CO where regular smokers had significantly higher levels (paired t-tests, $p<0.05$). Mean CO levels of the 8 regular smokers who smoked a cigarette prior to neuroimaging was 21.3 parts per million (ppm) (SD=12.3; range 9–43). Movement was low in both groups but significantly higher in regular smokers ($p<0.05$). There were no significant group differences in median reaction times; a three-way ANOVA with Condition, Group, and Hand (left or right) as factors, showed no significant interactions. Missing BDI data for one never-regular smoker and missing CO data for another were substituted based on mean sample values (Supplemental Methods). Within-pair differences in BDI scores and CO levels remained significant when missing data were excluded from analysis.

Data collected as part of the questionnaire survey at the time of the neuroimaging appointment showed that the regular smokers were overall "light" smokers (Table S2, Supplemental Results) though 46.7% met lifetime DSM-IV criteria for tobacco dependence (Table S3, Supplemental Results). Based on existing psychiatric interview data, within-pair comparison of other drug use and psychiatric history showed that significantly more of the regular smokers had used marijuana and met criteria for DSM-IV major depressive disorder (Table S3, Supplemental Results).

fMRI data

A priori ROI analysis—The Condition x Group x Timepoint interaction was significant for the left ventral striatum ($p=0.017$) and near significant for the right ventral striatum ($p=0.055$) (Figure 1). Table S4 shows p values of effect size estimations for all pairwise comparisons. Post-hoc paired t-tests at peak response (average of 4 and 6 seconds post-stimulus) in the left ventral striatum showed significantly greater activation to reward relative to punishment and neutral feedback in the never-regular smokers and no significant effects of condition in the regular smokers. There were no significant group differences in response to reward, punishment, or neutral feedback. In the right ventral striatum, the regular smokers showed significantly blunted response to reward and punishment compared to their MZ never-regular smoker cotwins. Further, the never-regular smokers had significantly greater activation to reward relative to punishment and neutral feedback, which did not differ from each other, and the regular smokers had significantly blunted response to punishment relative to both reward and neutral feedback, which did not differ from each other. As shown in Table S4, effects of medium to large size (Cohen's $d \sim .5–.8$) were statistically significant ($p<0.05$). Thus, never-regular smokers had similar effects in the left and right ventral striatum with relatively greater activation to reward than to both punishment and neutral feedback, while their MZ regular smoker cotwins showed attenuated response to punishment in the right ventral striatum.

Whole brain analysis—Differences in the timecourse of the BOLD response across conditions were found in subcortical, medial cortical, and occipital regions (significant Condition x Timepoint interaction) (Table 2, Figure 2). Some of these regions had positive timecourses (Figure 2 yellow spheres, Table 2). Most of the regions with negative timecourses (Figure 2 red spheres, Table 2) are recognized as part of the default mode network (posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC), medial precuneus, and left angular gyrus) (Raichle et al., 2001).

Timecourses for bilateral caudate regions are shown in Figure 3. The larger BOLD activation in response to winning money replicates previous findings (Delgado et al., 2003; Delgado et al., 2000). Timecourses for all other regions with positive BOLD activations are shown in Figure S2. Activation patterns for some regions were the same as that for the caudate with larger relative activation to winning money (medial frontal regions, inferior

parietal lobule, putamen/globus pallidus, thalamus, occipital cortex, and cerebellum). Other regions had a relatively greater activation to losing money (insula, superior frontal gyrus; more posterior medial frontal regions). All regions with negative timecourses had relatively smaller BOLD deactivation to monetary reward (Figure S3).

Within-pair differences in the timecourse of the BOLD response (significant Group x Timepoint interaction) was seen in regions located in the frontal, parietal, and insular cortex, mostly in the right hemisphere (Table 3, Figure 2 green spheres). There was significantly greater BOLD activation in the regular smokers compared to the never-regular smokers in all regions (Figure 4, Figure S4). We examined whether the larger activation in regular smokers was due to greater cognitive demands and found no significant group differences (Supplemental Results). In addition, post-hoc regression models showed that group differences remained significant after adjustment for BDI (square root transformed for normality), CO (log transformed), movement (log transformed), and lifetime marijuana use, suggesting that group differences in brain activation were not explained by group differences in depressive symptoms, movement, smoking recency, or lifetime marijuana use.

No regions were identified from the Condition x Group x Timepoint interaction, suggesting lack of a differential effect of processing of reward or punishment between regular and never-regular smokers.

Because of heterogeneity in smoking behavior among regular smokers, we examined whether within-pair activation differences in the Group x Timepoint regions were driven by current smokers or smokers with history of tobacco dependence. We compared average peak % BOLD change (4 and 6 sec after stimulus onset) between current (n=9) and former smokers (n=6) and between smokers with tobacco dependence history (n=7) and without such history (n=8) using one-way ANOVA (Table S5). Activation was overall very similar across subgroups of smokers, with the exception of significantly larger activation in the right angular gyrus of smokers with history of tobacco dependence compared to smokers without history of dependence.

Discussion

The aim of the present study was to investigate the effect of lifetime regular smoking on task-evoked brain activation using a reward and punishment guessing task and a study design that controls for genetic and family background factors on brain activation.

The modified number-guessing task evoked a pattern of reward-related brain activation consistent with results of previous studies (Delgado et al., 2003; Delgado et al., 2000; Knutson et al., 2001) lending validity to the implemented modifications. The timecourse of activation in the caudate, with a later peak and more sustained response to reward than to punishment, is almost identical to the previously reported activation in this region (Delgado et al., 2003; Delgado et al., 2000). Caudate activation in response to reward delivery is most frequently seen when subjects believe that their behavior affects reward delivery (Tricomi, Delgado and Fiez, 2004), suggesting that the caudate may be involved in the learning of stimulus-outcome associations and thus in guiding future reward-related behavior and habit.

Previous studies have consistently shown blunted reward-related activation in the ventral striatum in smokers compared to controls using *a priori* hypothesis-driven region of interest analysis or qualitative group comparisons (Buhler et al., 2010; Luo et al., 2011; Martin-Soelch et al., 2003; Martin-Solch et al., 2001; Peters et al., 2011; van Hell et al., 2010). Consistent with the literature, our region of interest analysis in ventral striatum showed attenuated response to reward and punishment in the regular smokers compared to the never-regular smokers and this effect was significant in the right hemisphere. Peak response to

reward in both left and right ventral striatum of regular smokers was the same as response to the neutral feedback, suggesting no effect of reward per se. However, while we do see an effect of regular smoking on reward processing in the ventral striatum consistent with the literature, it was only detected in the a priori region of interest analysis and not the whole brain analysis. Blunted activation to reward and punishment in the regular smokers is consistent with a direct effect of smoking on ventral striatum activation, rather than an effect of pre-existing genetic factors, which are controlled for in the MZ twin pair design used in the current study. It could be that the ventral striatum is a region that is particularly sensitive to cigarette exposure, which could help explain group differences in adolescent smokers with very low lifetime exposure to cigarettes (Peters et al., 2011). Further, it could be that the effect of cigarette exposure on ventral striatum activity varies as a function of predisposing risk for smoking we cannot make such a distinction with the available data.

Whole brain analysis did not identify regions with an effect of smoking exposure on reward processing. It could be that heavy levels of smoking are necessary to robustly disrupt reward processing in the brain and the regular smokers in our sample were overall light smokers, though 46.7% (n=7 of 15) had a history of DSM-IV tobacco dependence. Some studies that show an effect of smoking on reward processing have included heavy smokers (Luo et al., 2011; Martin-Soelch et al., 2003; Martin-Solch et al., 2001), but others have included a heterogeneous group of light to heavy smokers (van Hell et al., 2010). Thus, heavier levels of smoking do not seem necessary for blunted reward activation to be detected. However, these previous studies did not control for genetic influences on reward processing.

The group differences found in the frontal/parietal cortex were unexpected. Greater activation in these task control regions (Dosenbach et al., 2008; Dosenbach et al., 2007; Dosenbach et al., 2006) in the smokers could mean that smokers relied on greater cognitive effort than did non-smokers to perform the number guessing task. However, reaction time and button switching response data from the present study do not support any group difference in effort or demand. Others have also failed to demonstrate differences in cognitive effort in tasks designed to elucidate attentional bias to smoking cues (Luijten et al., 2011). Another interpretation is that group differences in frontal/parietal activation were driven by smokers with more extensive smoking history. Overall, current smokers or smokers with history of tobacco dependence had very similar peak BOLD response in these regions compared to former smokers or smokers with no history of tobacco dependence, respectively. Overall, these results support the epidemiological evidence that individuals who have smoked 100 or more cigarettes in their life, though with overall varying smoking histories, are different from those who have smoked less than 100 cigarettes. Nonetheless, these conclusions are tentative and made in the context of the small sample size in the subgroup analyses.

The findings of an effect of regular smoking in frontal/parietal regions are consistent with the interpretation that cigarette exposure is associated with greater reliance on frontal/parietal cortex to perform the task. The frontal/parietal regions are part of task control networks (Dosenbach et al., 2008; Dosenbach et al., 2007; Dosenbach et al., 2006) and a preponderance of regional activation in the right hemisphere has been associated with target detection at an attended location (Shulman et al., 2010). It could be that mechanisms of target detection reflect changes in attentional processing in smokers, which could be related to the general attention-enhancing properties of nicotine (Heishman, Kleykamp and Singleton, 2010). Results in the frontal/parietal control regions could provide insights into methods for smoking cessation treatment, such as cognitive behavioral therapy which can alter processing in frontal/parietal and insular cortex regions (Huyser et al., 2010). A clinical trial of nicotine replacement therapy showed that smokers who did not maintain abstinence, compared to those who did, had relatively greater activation to smoking cues in many

frontal/parietal regions prior to cessation (Janes et al., 2010), implicating control mechanisms in the maintenance of smoking behavior. Further, greater activation of anterior and middle right insula in regular compared to never-regular smokers supports previous findings of the importance of the right insula in craving and tobacco addiction (Gray and Critchley, 2007; Naqvi et al., 2007).

This study has several limitations. The regular smokers are a heterogeneous group of smokers comprising current and former smokers, as well as dependent and non-dependent smokers. It is possible that differences in exposure to cigarettes as a function of longer duration of smoking or as a function of heavier levels of smoking could have a different effect on brain reward processing than that shown in this paper. It is notable, though, that in frontal/parietal regions that showed group differences, peak BOLD activation was in large part similar between subgroups of smokers. There are individual differences in past 12-month use of prescription medication. On the one hand, prescription medication could be a confounder in the study, but on the other hand, it provides a better representation of the general population. Larger samples are necessary to evaluate the impact of differences in smoking history and medication use on brain function. Finally, the number-guessing task does not distinguish anticipatory versus receipt phases of monetary reward. Reward-processing regions activated by the number-guessing task overlap with regions that activate both in response to anticipation and receipt of monetary reward (Knutson et al., 2001). It is possible we may see more robust effects of smoking on reward processing using tasks that explicitily distinguish between the anticipation and receipt phases of reward processing. To the extent that there are dissociable mechanisms of anticipation versus receipt of monetary reward, both mechanisms are likely involved in the number-guessing task.

In conclusion, using a reward and punishment guessing task and a cotwin-control study of smoking behavior that maximally controls for between group differences on many potential confounding factors, we identified an effect of regular smoking on reward processing in *a priori* regions of interest in the ventral striatum. In addition, we identified a set of frontal and parietal regions that showed larger activation in the regular smokers and no effect of reward or punishment. Considering that regular smoking is significantly heritable (Agrawal et al., 2005), regular smokers from MZ twin pairs discordant for smoking represent an unusual group of smokers, since they are at overall low genetic risk for smoking by virtue of having a MZ cotwin who is not a regular smoker, yet they escalate in their smoking behavior to a point of dependence in some cases. The uniqueness of this group of smokers, and their apparent differential activation in attention and control regions of the cortex, could provide important insights into brain mechanisms involved in the development of tobacco addiction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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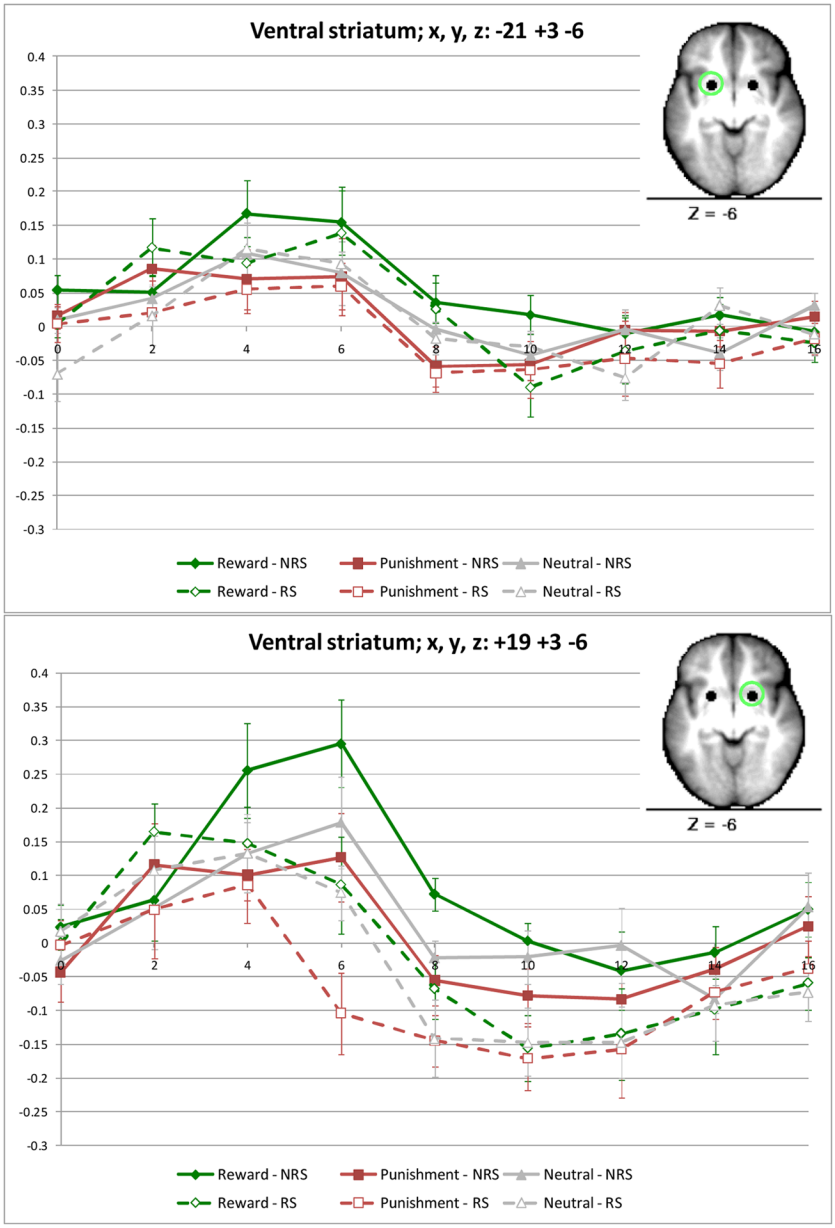

Figure 1.

Timecourses from a priori regions of interest (ROIs) in left (top) and right (bottom) ventral striatum. The x-axis shows16 seconds of BOLD signal after stimulus onset in 2-second intervals, and the y-axis represents percent BOLD change. Bars are standard error of the mean. RS=regular smoker, dashed lines; NRS=never-regular smoker, solid lines. Green=timecourse in response to winning money, Red=timecourse in response to losing money; Grey=timecourse in response to neutral feedback.

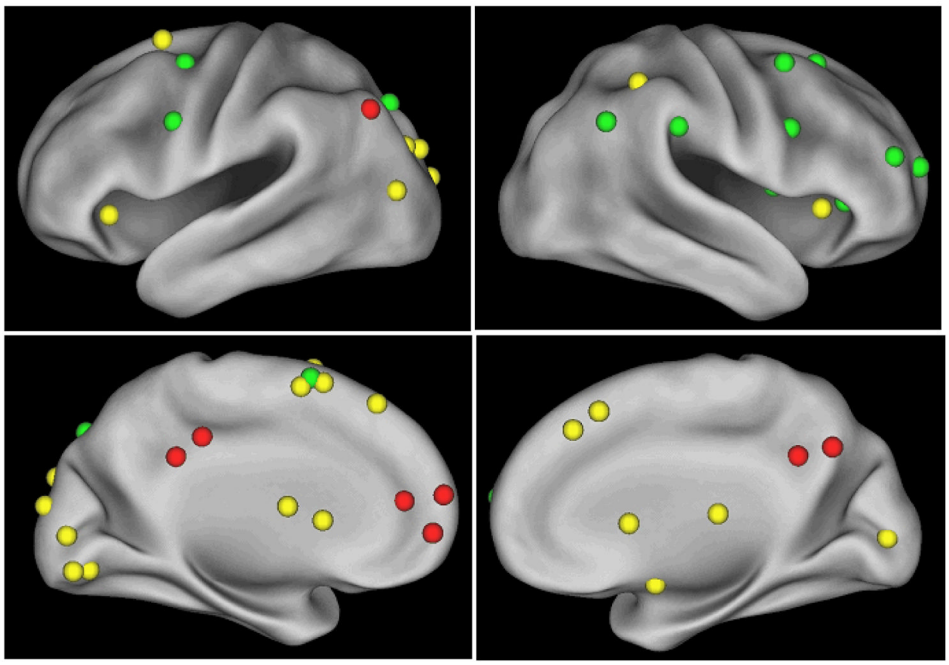

Figure 2.
Forty three ROIs extracted from the whole brain ANOVA corrected for multiple comparisons projected on the lateral (top) and medial (bottom) inflated surfaces of the left (on the left) and right (on the right) hemispheres. Green = ROIs from the Group x Timepoint interaction effect; yellow = ROIs from the Condition x Timepoint interaction effect that have positive timecourses; red = ROIs from the Condition x Timepoint interaction effect that have negative timecourses.

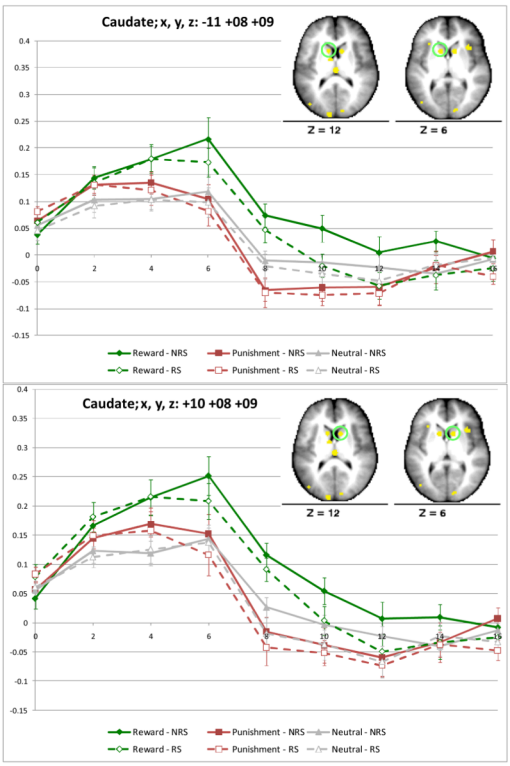

Figure 3.
Timecourses in left (top) and right (bottom) caudate regions. The yellow color of the regions overlaid on the brain surface denotes regions with positive timecourses in response to winning or losing money as shown in Figure 2. See Figure 1 legend for details.

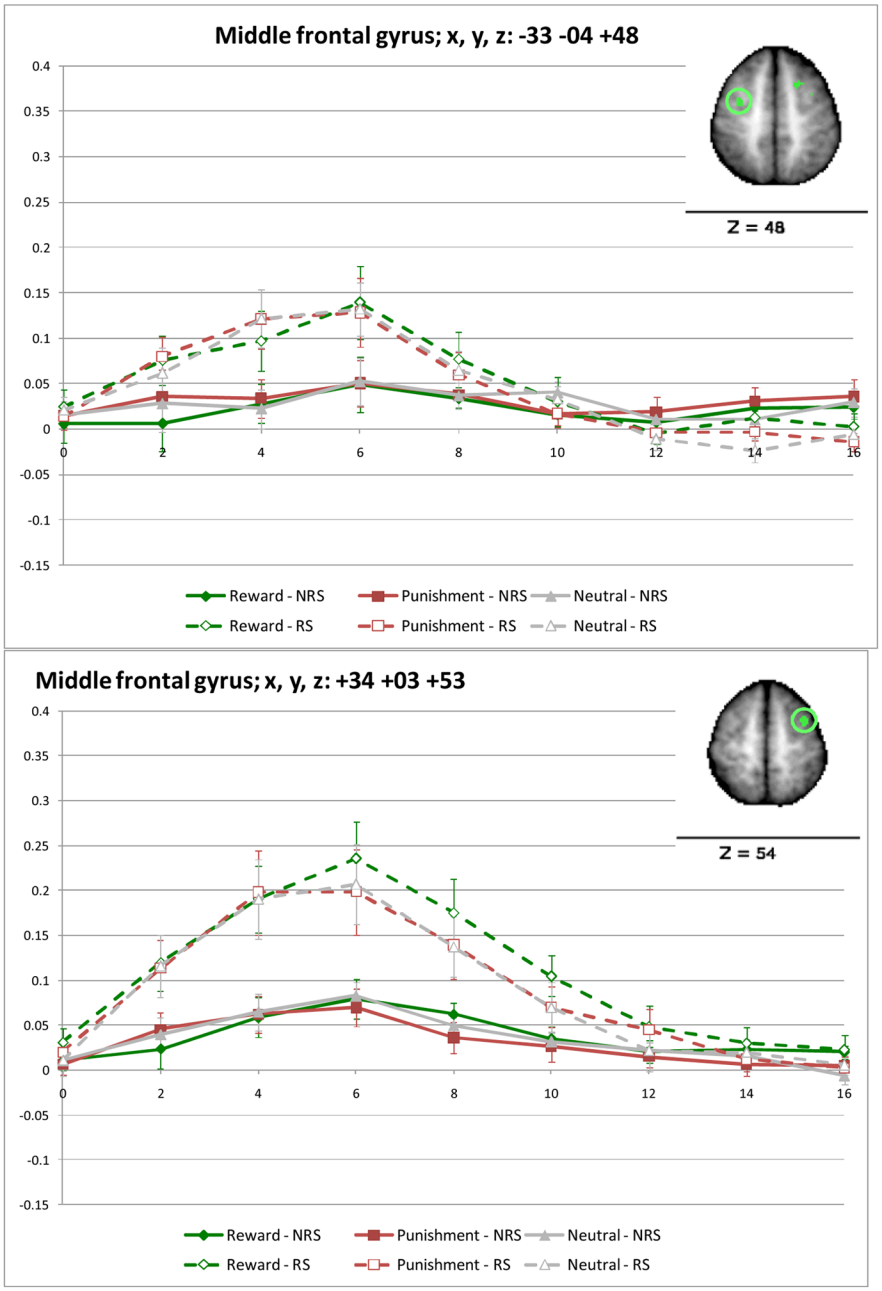

Figure 4.

Representative timecourses from left (top) and right (bottom) middle frontal gyrus with an effect of smoking exposure. The green color of the regions overlaid on the brain surface denotes regions with an effect of smoking exposure as shown in Figure 2. See Figure 1 legend for further details. There was no significant effect of winning or losing money in these regions as evidenced by the overlap of the timecourses in response to reward, punishment and neutral conditions in both groups.

Table 1

Personal and behavioral characteristics of the 15 MZ twin pairs comprised of lifetime regular smokers (RS) and their never regular smoking (NRS) twin sisters

	RS (n=15)		NRS (n=15)	
Characteristics	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**
Weight (lb)	162.2 (43.4)	114–272	167.9 (50.9)	110–285
IQ (vocabulary + matrix reasoning)	102.2 (11.7)	77–120	104.3 (15.6)	71–127
Age first tried smoking cigarettes	13.20 (3.19)	8–17	14.27 (3.10)	8–18
BDI (total score)	5.67 (5.02)	0–13	2.87 (3.27) *	0–9
PANAS (positive affect total score)	28.47 (7.29)	12–42	32.93 (9.53)	10–47
PANAS (negative affect total score)	15.53 (3.72)	10–21	15.47 (4.75)	10–25
STAI (positive symptoms total score)	28.00 (5.69)	17–36	30.93 (3.61)	24–36
STAI (negative symptoms total score)	14.47 (4.34)	11–26	14.27 (4.79)	11–27
Carbon Monoxide (ppm)	12.67 (12.9)	2–43	2.13 (1.13) *	1–5
Movement (root mean square)	0.22 (0.11)	0.07–0.52	0.15 (0.07) *	0.08–0.32

* $p<0.05$

BDI=Beck Depression Inventory; PANAS=Positive Affect and Negative Affect Schedule; STAI=State Trait Anxiety Inventory; ppm=parts per million

Table 2

Regions identified from the Condition x Timepoint interaction

		Talairach Coordinates				
Condition x Timepoint Regions	**Hemisphere**	**x**	**y**	**z**	**Z Value**	**No Voxels**
Positive Timecourses						
Superior frontal gyrus	L	−22	3	62	3.74	26
Medial frontal gyrus	L	−4	8	58	3.66	34
Medial frontal gyrus	L	−7	−3	57	4.64	62
Medial frontal gyrus	L	−1	29	53	4.07	46
Medial frontal gyrus		0	19	49	4.46	62
Medial frontal gyrus		0	29	41	5.01	61
Caudate	L	−8	−5	15	4.82	56
Caudate	L	−11	8	9	8.15	66
Caudate	R	10	8	9	7.38	65
Putamen/globus pallidus	R	16	3	−3	3.94	33
Thalamus	R	1	−23	14	4.70	73
Anterior insula	R	33	14	6	4.33	44
Anterior insula	L	−31	19	2	4.07	43
Inferior parietal lobule	R	44	−48	49	3.69	29
Cuneus	L	−10	−95	12	5.63	57
Cuneus	R	11	−89	8	3.62	36
Lingual gyrus	L	−4	−88	−1	5.29	66
Lingual gyrus	L	−11	−80	−10	5.09	64
Middle occipital	L	−30	−79	19	4.53	64
Middle occipital	L	−41	−77	9	3.70	32
Middle occipital	L	−23	−88	22	5.00	69
Cerebellum	L	−1	−84	−21	3.77	38
Negative Timecourses						
Medial aPFC	L	−3	56	12	4.67	57
Medial aPFC	L	−1	47	3	4.97	65
ACC	L	−4	41	14	5.50	67
PCC	L	−2	−37	40	4.71	64

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Condition x Timepoint Regions	Hemisphere	Talairach Coordinates			Z Value	No Voxels
		x	y	z		
PCC	R	9	−51	31	3.98	50
Precuneus	L	−2	−47	33	4.80	64
Precuneus		0	−72	34	4.42	66
Angular gyrus	L	−41	−68	36	3.77	37

PFC=prefrontal cortex; ACC=anterior cingulate cortex; PCC=posterior cingulate cortex

Table 3

Regions identified from the Group x Timepoint interaction

		Talairach Coordinates				
Group x Timepoint Regions	**Hemisphere**	**x**	**y**	**z**	**Z Value**	**No Voxels**
Medial frontal gyrus	L	−3	1	60	4.24	42
Superior frontal gyrus	R	20	13	49	3.61	37
Middle frontal gyrus	R	34	3	53	4.09	47
Middle frontal gyrus	L	−33	−4	48	3.62	26
Inferior frontal gyrus	R	43	7	34	4.75	63
Inferior frontal gyrus	L	−51	0	32	4.13	34
aPFC	R	22	53	19	4.67	54
Middle PFC	R	36	42	19	3.6	31
Supramarginal gyrus	R	51	−32	33	3.87	36
Angular gyrus	R	51	−57	34	4.83	64
Precuneus	L	−21	−77	42	3.98	37
Insula	R	34	−3	15	3.57	24
Anterior Insula	R	27	22	11	3.78	32

aPFC=anterior prefrontal cortex; PFC=prefrontal cortex