Published in final edited form as:

Psychiatry Res. 2014 August 30; 223(2): 140–147. doi:10.1016/j.psychres.2014.04.007.

Abstinent adult daily smokers show reduced anticipatory but elevated saccade-related brain responses during a rewarded antisaccade task

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Abstract

Chronic smoking may result in reduced sensitivity to non-drug rewards (e.g., money), a phenomenon particularly salient during abstinence. During a quit attempt, this effect may contribute to biased decision-making (smoking > alternative reinforcers) and relapse. Although relevant for quitting, characterization of reduced reward function in abstinent smokers remains limited. Moreover, how attenuated reward function affects other brain systems supporting decision-making has not been established. Here, we use a rewarded antisaccade (rAS) task to characterize non-drug reward processing and its influence on inhibitory control, key elements underlying decision-making, in abstinent smokers vs. non-smokers. Abstinent (12-hours) adult daily smokers ($N=23$) and non-smokers ($N=11$) underwent fMRI while performing the rAS. Behavioral performances improved on reward vs. neutral trials. Smokers showed attenuated activation in ventral striatum during the reward cue and in superior precentral sulcus and posterior parietal cortex during response preparation, but greater responses during the saccade response in posterior cingulate and parietal cortices. Smokers' attenuated anticipatory responses suggest reduced motivation from monetary reward, while heightened activation during the saccade response suggests that additional circuitry may be engaged later to enhance inhibitory task performance. Overall, this preliminary study highlights group differences in decision-making components and the utility of the rAS to characterize these effects.

Keywords

Smoking; Reward; Inhibitory control; fMRI; Abstinence

1. Introduction

Nicotine, similar to other drugs of abuse, acts on regions of the brain underlying reward processing (e.g., ventral striatum) (e.g., McClernon et al., 2008; Robinson and Berridge, 1993). Chronic stimulation of reward pathways has been suggested to result in a

compensatory reduction in non-drug (e.g., money) reward sensitivity, consistent with opponent process theory (Koob and Le Moal, 2001). Evidence suggests that chronic smokers in an abstinent state experience diminished capacity for reward relative to both satiated smokers and non-smokers, including less enjoyment from ordinarily pleasurable events and reduced response to financial reward during a card sorting task (Dawkins et al., 2006; Powell et al., 2002, 2004). In addition, a handful of neuroimaging studies using PET and fMRI to assess neural response to non-drug rewards has demonstrated blunted activation in reward-related regions among smokers relative to non-smokers (Martin-Soelch et al., 2001, 2003; Rose et al., 2012).

Altered reward effects could have important implications for understanding why most quit attempts fail in that a reduced response to non-drug rewards may result in a biased preference for smoking vs. alternative, non-drug reinforcers. However, characterization of smokers' reward system function provides only a partial picture of the factors underlying decisions to smoke. Reward processes function in concert with cognitive control processes, like inhibitory control, to enable goal-directed behavior (e.g., choosing not to smoke) (Geier and Luna, 2009). Several studies have demonstrated deficits in inhibitory control among smokers—effects that are made worse by deprivation (Hatsukami et al., 1989; Pettiford et al., 2007; Powell et al., 2002; Spinella, 2002; Zack et al., 2001). However, little is known about how attenuated reward function may impact the *interaction* between reward systems and cognitive control processes in smokers.

In this preliminary study, we use functional magnetic resonance imaging (fMRI) to assess reward system function and its effect on inhibitory control in adult daily smokers vs. non-smokers. Our approach is novel in that we focus on brain and behavioral responses to reward elicited in the context of an established rewarded antisaccade (rAS) paradigm (Geier et al., 2010; Padmanabhan et al., 2011; Geier and Luna, 2012). The antisaccade task is a robust and reliable measure of response inhibition, requiring participants to resist the strong, prepotent urge to generate a rapid eye movement (saccade) towards a suddenly appearing peripheral stimulus and instead generate a voluntary saccade to the exact opposite location in space. In the rAS, participants are first presented with a cue indicating whether or not correct performance will be monetarily rewarded. After a short delay, performance is assessed for that trial. Behavioral studies using this task in non-smokers have shown that reward contingency enhances task performance (reduces response times and overall error rates) (Geier et al., 2010; Geier and Luna, 2012; Hardin et al., 2007; Jazbec et al., 2006; Padmanabhan et al., 2011). Our prior imaging work using this task (with non-smokers) has shown that reward vs. neutral contingency evokes heightened activation in the ventral striatum, a key region involved in attributing incentive salience to stimuli, as well as in task-related oculomotor and control circuitry (Geier et al., 2010; Padmanabhan et al., 2011). We chose to assess altered reward sensitivity in smokers in this experimental context given that a central feature of maintaining smoking abstinence is resisting (inhibiting) the urge to smoke. We assessed smokers in an abstinent state given prior evidence (noted above) that both reward processing and inhibitory control may be attenuated during deprivation and given the relevance of early abstinence to engaging in a quit attempt. The rAS enables concurrent assessment of brain systems mediating two key brain processes underlying decision-making.

We hypothesized that abstinent daily smokers would show a reduced response to monetary reward and a weaker influence of reward on AS task performance vs. non-smokers. Further, smokers were expected to exhibit attenuated responses in the ventral striatum, a key brain region involved in attributing incentive salience to environmental stimuli, and oculomotor/inhibitory control related brain regions such as the frontal eye field (FEF), indicative of reduced motivational effects of rewards during motor planning. We predicted these effects would be the most pronounced prior to the eye movement given the importance of preparatory activity for correct anti-saccade performance (Munoz and Everling, 2004).

2. Methods

2.1. Participants

Forty-five participants (15 non-smokers and 30 daily smokers) aged 18–65 years were initially recruited. Inclusion criteria for smokers were as follows: 1) smoking five or more cigarettes per day (CPD) over the past year, 2) expired breath carbon monoxide (CO) level > 10 ppm (Bedfont CO monitor), 3) cotinine > 100 ng/ml, and 4) no intention to quit in the next month. Inclusion criteria for non-smokers were as follows: 1) smoking < 20 lifetime cigarettes, 2) use of other tobacco products < 10 times, 3) no tobacco use of any kind in the past year. Exclusion criteria for all participants included: 1) self-reported psychiatric or significant medical illness in the past year, 2) current heavy drug use or alcohol use (10+ days in past 30 years), 3) current use of psychotropic medication or other tobacco products, 4) pregnancy/lactation, and 5) contraindications related to imaging, including head trauma with loss of consciousness in past year, claustrophobia, and any known risk from exposure to high-field magnetic fields (e.g., permanent metal piercings). Smokers were recruited to reflect a range of scores (approximating tertiles of 'low', 'medium', and 'high') on the Nicotine Dependence Syndrome Scale (NDSS). However, data from four non-smokers and seven smokers were excluded due to excessive motion in the magnet (criteria below) and/or eye tracking technical issues. Given reduced sample sizes, we narrowed our focus on smoker vs. nonsmoker comparisons. In total, data from 11 non-smokers (20–61 years; $M=35.3$; S.D. =14.79; six females) and 23 daily smokers (19–51 years; $M=35.0$; S. D. =11.2; 11 females) are reported below. Smokers reported using between six and 25 CPD ($M=15.26$, S.D.=5.96) for an average of 16.5 years (S.D.=10.14), and scored from 41 to 76 ($M=57.12$, S.D. =11.3) on the NDSS.

2.2. Procedures

Participants attended an initial screening session during which consent was obtained and eligibility was determined. Eligible participants then completed the rAS task during a single fMRI session on a separate day. Smokers agreed to refrain from smoking for 12 h prior to this session. Self-reported abstinence was verified using expired CO level of < 8 ppm or 50% reduction from baseline. A measure of withdrawal, the Minnesota Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986), was administered both during screening and prior to the fMRI scan. Experimental procedures complied were reviewed and approved by the Institutional Review Board at the University of Pittsburgh. Participants received payment for their participation in the study in addition to task earnings (see below).

2.3. Rewarded antisaccade task

Each rAS trial began with one of two possible incentive ‘CUE’ images (1.5 s) (a ring of dollar signs or blue pound signs), indicating whether or not correct performance would be monetarily rewarded on that trial (see Fig. 1). Next, a central red fixation cross (1.5 s) indicated that the participant should prepare to inhibit a response (‘PREPARATION’). A peripheral stimulus (yellow circle) next appeared (1.5 s) at one of four unpredictable horizontal locations ($\pm 3, 61^\circ$ of visual angle) (‘RESPONSE’). Participants were instructed to resist looking at the stimulus and instead look toward the mirror location on the screen. As described in Geier et al. (2010), our task design included approximately 30% partial ‘catch’ trials and jittered (1.5–4.5 s; uniformly distributed) inter-trial fixations that enabled separate estimation of the BOLD response to the cue, preparation, and saccade response epochs (Ollinger et al., 2001a, 2001b). In each of four runs presented, 14 complete reward trials, six partial reward trials (three of each variant), 14 complete neutral trials, and six partial neutral trials (three of each variant) were presented in random order. Each run lasted 5 min 9 s. Participants were told they could earn up to US \$25 based on their performance.

2.4. Eye tracking

Eye movements were recorded using an Applied Science Laboratories (Bedford, MA, USA) long-range optics eye tracking system (Model 504LRO). Task stimuli were presented using the E-prime (Psychology Software Tools, Pittsburgh, PA), rear projected onto a flat screen behind the magnet. Participants viewed the screen via a mirror mounted on the head coil. Data were scored using ILAB software (Gitelman, 2002) and a suite of in-lab programs written in MATLAB (Mathworks, Inc., Natick, MA). Eye tracking variables of interest included latencies of correct antisaccades and error rates. A correct response occurred when the first eye movement during the saccade response epoch with velocity greater than $30^\circ/\text{s}$ (Gitelman, 2002) was made toward the opposite spatial location of the peripheral stimulus and extended beyond a 2.5° of visual-angle central fixation zone. Errors occurred when the first eye movement exceeding a $30^\circ/\text{s}$ velocity criterion and extending beyond the fixation zone during the response epoch was directed toward the stimulus. Overall error rate was calculated as the number of errors made on a particular trial type (e.g., reward or neutral) divided by the total number of opportunities. Overall latency was calculated as the mean latency across correct trials for a given trial type. Repeated measures ANOVA were used to assess group differences (between-subjects factor=group (smoker, non-smoker); within-subjects factors=incentive condition (reward, neutral)). Effect sizes are reported as partial eta squared (η_p^2).

2.5. Image acquisition

Imaging data were collected using a 3.0 T Siemens Trio magnet with gradient EPI sequence covering 29 sequential 4 mm axial slices with the following parameters: TR= 1.5 s; TE =29 ms; flip angle = 70° ; 64×64 acquisition matrix with FOV= $20 \times 20 \text{ cm}^2$. A 3D volume magnetization prepared rapid acquisition gradient-echo (MP-RAGE) pulse sequence with 192 slices (1-mm thickness) was used to acquire high-resolution structural images in the axial plane.

2.6. Preprocessing

Functional images were preprocessed in FSL/FMRIB software (Smith et al., 2004). Following image reconstruction, rotational and translational head motion estimates were calculated and images were corrected by aligning each volume in the time series to the volume obtained in the middle of acquisition. For each participant, translational and rotational movements were averaged across images and used to calculate total root mean square (RMS) movement measures. Participants moving more than 1-mm (translational) or 1° (rotational) were excluded from subsequent analyses. Slice timing correction was performed to adjust for sequential slice acquisition. Brain extraction was performed using the brain extraction tool (BET) (Smith, 2002). Structural and functional images were co-registered and normalized into Talairach space then resampled to a voxel size of 2 mm³. Functional images were spatially smoothed with a 5-mm FWHM kernel and subjected to high pass temporal filtering (sigma=37.5 s).

Deconvolution was conducted using AFNI (Cox, 1996). Our deconvolution model consisted of six orthogonal regressors of interest: stimulus onset times of reward and neutral cue, preparation, and saccade response epochs (for correct trials only). Separate regressors were included for reward and neutral error trials (not analyzed here), baseline, linear, and non-linear trends, and six motion parameters (*x*, *y*, *z* translational and roll, pitch, yaw rotational). An impulse response function (IRF) was uniquely estimated for each regressor of interest. An IRF reflects the estimated BOLD response to a particular type of stimulus after controlling for variations in the BOLD signal due to other regressors. The IRF was determined based on a weighted linear sum of five sine basis functions multiplied by five least squares-estimated beta weights. We specified the duration of the estimated response from stimulus onset (time=0) to 18 s post-stimulus (13 TR) but made no assumptions about the specific shapes of the time courses.

2.7. Group analysis

A linear mixed effects model was run on participants' estimated IRFs, with incentive condition (reward, neutral), smoking status ('smoker', 'non-smoker'), and time (13 time points) as fixed factors and 'subjects' as random factor. Three 'main effect of time' images were generated, corresponding to each epoch of the task (one for 'CUE', one for 'PREPARATION', one for 'SACCADE') and showing voxels that were significantly modulated across time, collapsed across group and trial type. The 'main effect of time' maps served as base images for time course extraction, following prescribed methods (for details see Geier et al. (2010)). Briefly, for each main effect of time image, an algorithm was used to identify peak voxels that exceeded a threshold of $p < 0.001$ (uncorrected). These maps were then corrected for multiple comparisons using criteria from an AlphaSim (AFNI) simulation, which indicated that a cluster size of at least 31 contiguous voxels was required with an individual voxel p -value of $p < 0.001$ to achieve a FWE corrected image level significance level of $p < 0.05$. Next, a 9-mm sphere mask was centered on each maximum. Estimated time courses from all significantly active ($p < 0.05$, corrected) constituent voxels within these sphere masks were extracted from all participants and compared using repeated measures ANOVA (rmANOVA) in SPSS. First, an omnibus rmANOVA was run with group (smoker, non-smoker) as between subjects factor and time (13 time points, corresponding to

0–18 s in 1.5 s increments) and incentive (reward, neutral) as within-subjects factors. Given our hypotheses related to group differences in reward responses, we also examined group effects for each incentive trial type alone.

Our analyses focused on clusters of voxels located within the anatomical boundaries of known task-related regions (see Geier et al. (2010)) for detailed anatomical specification of these ROI). Areas of interest included the ventral striatum, ventral medial prefrontal cortex, areas along the inferior and superior precentral sulcus (putative human frontal eye field, FEF), anterior cingulate, posterior parietal cortex, and striatum.

3. Results

3.1. Behavior

Mean error rates and latencies across groups (smoker, non-smoker) and incentive trial type (reward, neutral) are shown in Table 1. Overall, error rates were lower on reward vs. neutral trials (main effect of incentive, $F(1,33) = 5.473$, $p < 0.05$, $\eta_p^2 = 0.142$) (Table 1). However, contrary to our predictions and a trend for abstinent smokers to make more errors, there was no significant main effect of group or group $\times$ incentive type interactions. Similarly, for latency, a main effect of incentive was also observed, $F(1,33) = 10.023$, $p < 0.005$, $\eta_p^2 = 0.233$, supporting the notion that participants perform faster (lower latencies) when there is a reward contingency (Table 1). There was no main effect of group or group by incentive interaction for latencies.

3.2. Imaging

Main effect of time images, indicating brain regions engaged during presentation of the incentive cue, preparatory period, and the saccade response, collapsed across incentive condition and group, is presented in Fig. 2. These images indicate that a largely similar distributed network of brain regions was engaged during the task by both smokers and non-smokers, including regions known to support antisaccade task performance (e.g., inferior precentral sulcus, superior precentral sulcus (putative human frontal eye field), and posterior parietal cortex) as well as key aspects of reward processing (e.g., ventral striatum, medial prefrontal cortex), consistent with our prior work. In the sections below, we report on regions showing differences in evoked responses between smokers and non-smokers.

3.2.1. Cue—We found that only the right ventral striatum (Talairach coordinates: 8, 13, 1) showed an overall group $\times$ time interaction, $F(12,384) = 2.129$, $p < 0.05$, $\eta_p^2 = 0.062$) and an overall incentive $\times$ time interaction, $F(12,384) = 2.374$, $p < 0.01$, $\eta_p^2 = 0.069$). Considering reward trials separately, a significant group $\times$ time interaction was observed for this region, $F(12,384) = 2.251$, $p < 0.01$, $\eta_p^2 = 0.066$) (Fig. 3) (Table 2). Consistent with our predictions, time courses showed a more robust reward response in non-smokers vs. smokers (Fig. 3), marked by an initial negative-going response in non-smokers followed by a later positive peak. No significant group effects were detected on neutral trials.

3.2.2. Response preparation—A significant incentive $\times$ time interaction,

$F(12,384)=2.187, p < 0.05, \eta_p^2=0.064$, was found in the right superior precentral sulcus (putative human frontal eye field, FEF; Talairach coordinates: 26, -11, 49). This effect appears to be driven largely by non-smokers' heightened responses on reward trials (Fig. 4), in line with our hypothesis of reduced motivation effects in smokers. A cluster in the right superior parietal lobule (23, -62, 49) also showed an overall group $\times$ time interaction, $F(12,384) = 1.968, p < 0.05, \eta_p^2=0.058$, with non-smokers showing strikingly more robust responses than smokers for both rewarded and neutral trials (Fig. 4).

Notably, time courses from the right superior precentral gyrus and right superior parietal lobule, as well as a cluster in the right inferior precentral sulcus (43, -7, 36; data not shown in figure), showed similar response profiles in non-smokers vs. smokers. That is, non-smokers showed a robust, canonical BOLD response in these areas while smokers showed a comparatively lower peak and a temporally extended response.

3.2.3. Saccade response—A significant group $\times$ time interaction, $F(12,384)=2.510, p < 0.005, \eta_p^2=0.073$, was found in right inferior parietal lobule (38, -44, 46). Considering reward trials separately, a significant group $\times$ time interaction was also observed for this region, $F(12,384)=2.577, p < 0.005, \eta_p^2=0.075$. In contrast to prior epochs, time courses showed a greater initial peak in smokers vs. non-smokers (Fig. 5).

We also observed a significant incentive $\times$ time interaction, $F(12,384)=2.035, p < 0.05, \eta_p^2=0.60$, in right anterior cingulate (2, 31, 16) (Fig. 5). Time courses showed a more robust response during reward vs. neutral trials, with smokers again showing a particularly heightened response. Another cluster in right posterior cingulate (11, -26, 37) showed a significant group $\times$ time interaction, $F(12,384)=2.751, p < 0.05, \eta_p^2=0.079$, and incentive $\times$ group $\times$ time interaction, $F(12,384) = 2.431, p < 0.01, \eta_p^2=0.071$. Considering reward trials only, we observed a significant group $\times$ time interaction, $F(12,384)=4.344, p < 0.001, \eta_p^2=0.120$. Smokers strongly engaged this region during reward trials while non-smokers showed essentially a flat response. No significant group differences were detected on neutral trials in this cluster.

4. Discussion

We assessed behavioral and brain responses evoked in the context of a rAS task in abstinent smokers and non-smokers. Overall, while both groups were found to recruit a largely similar neural circuitry during the task, abstinent smokers showed a differential profile of responses in areas previously implicated in AS task performance and reward processing across incentive conditions and trial epochs, described further below.

4.1. Behavioral results

Collapsed across groups, we observed a main effect of incentive for latencies and error rates (both were lower on reward vs. neutral trials), in line with past studies indicating that

participants perform better (make fewer errors) and respond more quickly when a reward contingency is at stake (Geier and Luna, 2012; Geier et al., 2010; Hardin et al., 2007; Jazbec et al., 2006). In contrast to previous studies, we did not observe a significant difference between smokers and non-smokers on neutral trials, although the differences were in the predicted direction (nonsmoker error rate < smoker error rate). Future work with larger sample sizes should explore the nature of neutral trial differences across abstinent smokers and non-smokers and build on our preliminary analyses.

4.2. Imaging results

One major finding was that the right ventral striatum showed a significantly more robust response during the 'CUE' epoch in non-smokers vs. abstinent smokers. This effect was specific to reward cues, as smokers' and non-smokers' time courses did not significantly differ on neutral trials. Across numerous studies, the ventral striatum has been implicated in aspects of reward processing, including the processing of expected reward value and the attribution of incentive salience to environmental stimuli (Berridge and Robinson, 1998; Brody et al., 2004a and 2004b; David et al., 2005; O'Doherty et al., 2004; Wyvell and Berridge, 2000). The ventral striatum signal evoked in this paradigm is likely related to participants' initial detection of monetary reward. Abstinent smokers' attenuated brain responses during this epoch, in conjunction with higher error rates on reward trials more generally, support the assertion that they may have experienced reduced sensitivity to monetary (non-drug) reward cues. It should be noted that smokers' responses to reward were assessed in this study *only* during smoking abstinence. We acknowledge that this design limitation does not enable generalization about how individual smokers' reward sensitivity may *change* across satiety vs. abstinent states. Additional work from our laboratory has focused on addressing this issue (Sweitzer et al., 2013).

During the 'PREPARATION' epoch, two regions were differentially engaged in smokers and non-smokers—an area along the banks of the superior precentral sulcus (putative human FEF, (Curtis and Connolly, 2008)) and another in the superior parietal lobule (SPL). Both regions have previously been implicated in aspects of antisaccade task performance. Neurons in FEF contribute to inhibitory response preparation, crucial for the top-down 'silencing' of brainstem oculomotor neurons and the ability to inhibit saccade responses (Munoz and Everling, 2004), while SPL activity contributes to shifts of spatial attention (Corbetta et al., 1995). In the FEF, we found greater responses during reward trials in non-smokers, but no differences across groups during the neutral condition. Increased preparatory (pre-response) activity in FEF during reward trials has been hypothesized as one mechanism by which reward contingency enhances behavioral performance in this task (Geier et al., 2010). Abstinent smokers appear not to benefit in the same way from this reward-related enhancement. In SPL, non-smokers also showed significantly more robust responses than smokers across incentive conditions. These results are consistent with previous reports that smoking abstinence may be associated with diminished (sustained) attention (Foulds et al., 1996; Heishman, 1998; Lawrence et al., 2002). In this study, an overall reduction in attention to task demands could be one factor contributing to the slightly higher error rates in smokers vs. non-smokers.

During the ‘SACCADE’ epoch, smokers showed heightened activity compared to non-smokers in right anterior and posterior cingulate, as well as right inferior parietal lobule. This pattern was in contrast to the cue and response preparation periods in which non-smokers generally showed more robust response. These regions have all been implicated in various roles related to antisaccade task performance. The anterior cingulate cortex is frequently described as contributing to error detection and conflict monitoring (Barch et al., 2001; Botvinick et al., 1999; Polli et al., 2005; van Veen and Carter, 2002), but this region has also been associated with the implementation and enhancement of cognitive (inhibitory) control, particularly in antisaccade tasks (e.g., Phillips et al., 2010). The inferior parietal lobule may play a role in the calculation of antisaccade amplitude (Hoenig et al., 2001). Prior work has linked increased posterior cingulate activation with increased craving (Franklin et al., 2007), suggesting that this region is sensitive to disruption by nicotine. In fact, one case study suggested that a lesion to posterior cingulate disrupted nicotine addiction altogether (Jarraya et al., 2010). In oculomotor studies, posterior cingulate, similar to anterior cingulate, has been noted to contribute to active saccadic inhibition (Brown et al., 2006). Collectively, greater activation in these regions in smokers vs. non-smokers, particularly during reward trials, could indicate that smokers require additional, effortful processing to correctly inhibit their responses (i.e., smokers have to ‘work harder’ in some areas to produce a correct response). In addition, given that these regions are recruited closer in time when the peripheral stimulus appeared, smokers may be more reactive in their task behavior in contrast to the more planned behavior of non-smokers.

We note the following limitations in the current study. First, the modest sample size of non-smokers may have limited our ability to detect differences with smaller effect sizes between groups or conditions, both behaviorally and in the brain. Further, the bulk of attenuated, flattened response profiles were observed which were in the smoker group ($N=23$). Using time course response averaging approaches as employed in this study, one would expect more canonical hemodynamic response profiles as participant numbers and trial numbers increased. We argue that our results show that smokers showed attenuated responses is in line with our supposition that there are altered processes in these brain regions. Another limitation of this study is the lack of significant relationships between self-reported withdrawal (MNWS) and nicotine dependence with the behavioral and neuroimaging results. In our recent work using a within-subjects design, we have characterized significant relationships among these variables in abstinent vs. non-abstinent smokers (Sweitzer et al., 2013). The null findings in the present study might be related to our use of a between-subjects design, the modest sample size, or perhaps reflect that the relationship between these measures and antisaccade performance is not as straightforward as in other paradigms. Future work employing a within-subjects' design using the rAS task with a larger sample of nonsmokers and smokers could help clarify this issue. Finally, given our comparisons across groups who differ in their exposure to a drug (nicotine), a fair question is whether the observed neuroimaging effects could simply be explained by ‘low level’ cerebral vascular perfusion effects, above and beyond any neuronal firing differences. Within the scope of this study we cannot exclude this possibility; additional work in humans using techniques such as arterial spin labeling could inform this issue (e.g., Pfefferbaum et al., 2011; Sullivan et al., 2013).

In sum, we found that abstinent smokers showed heightened activations in ACC, PCC, and PPC during the saccade response epoch but relatively attenuated activations earlier during the cue and response preparation periods. This suggests that abstinence-related effects in smokers may vary depending on task demands (e.g., across phases of reward processing—stronger effects during reward anticipation vs. consummatory/outcome processing). While this preliminary study may have limited power to delineate perhaps more subtle behavioral effects (e.g., neutral trial error rates across groups), the use of sensitive fMRI techniques clearly demonstrates differences in predicted brain regions warranting further study. Future work will be needed to support these data, delineate person-specific response profiles, and perhaps inform more person-specific cessation strategies.

Acknowledgments

This research was supported by the Global Research Awards for Nicotine Dependence Program grant, an independent competitive grants program sponsored by Pfizer, to Eric C. Donny. Additional support was provided by NIH under Grant DA023459 to ECD. Ms. Sweitzer was supported by the Behavioral Brain Research Training under Grant (T32GM081760).

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Fig. 1.

Rewarded antisaccade task. Participants viewed either a ring of dollar bills or hash tags indicating whether correct performance on the forthcoming trial would be rewarded or not. The cue, response preparation, and saccade response periods all were 1.5 s in duration. The intertrial interval varied from 1.5 to 4.5 s. Randomly interspersed with full trials were partial or 'catch' trials (~30% of trials) that terminated unpredictably after either the preparation/anticipation phase (Partial 'Catch' Trial 1) or an incentive cue (Partial 'Catch' Trial 2). Partial trials were included to enable deconvolution of trial components (see Section 2). Note that white arrow is shown in this figure to indicate the reader where the participant should look; this arrow was not shown to participants during testing.

Fig. 2. Main effect of time images for incentive cue/assessment (left column of images), preparation/anticipation (center column), and saccade response (right column) epochs.

Fig. 3.

Cue epoch. Ventral striatum (indicated in red) time courses in smokers (solid lines) and non-smokers (dashed lines) in response to reward (left figure) and neutral (right figure) cues. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 4.

Response preparation/anticipation epoch—smokers (solid lines) vs. non-smokers (dashed lines). Right superior precentral sulcus (frontal eye field; 26, -11, 49), and right superior parietal lobule (23, -62, 49).

Fig. 5. Saccade response epoch—smokers (solid lines) vs. non-smokers (dashed lines). Right inferior parietal lobule (38, -44, 46), right anterior cingulate (2, 31, 16), and right posterior cingulate (11, -26, 37).

Table 1

Mean error rate (%) and latency (ms) for smoker ($n=23$) and non-smoker ($n=11$) groups. Values on parentheses indicate standard deviations.

Group	Error rate (%)		Latency (ms)	
	Reward	Neutral	Reward	Neutral
Smoker	25.1 (19.1)	32.8 (24.4)	380.4 (80.9)	402.4 (73.6)
Non-smoker	19.3 (22.2)	24.3 (25.9)	381.1 (70.6)	390.9 (64.8)

Table 2

Summary of primary imaging results for each trial epoch.

Region	Talairach	coordinates	Results	Direction of effect
<i>CUE</i>				
Right ventral striatum	8	13 1	Overall $G \times T$; $I \times T$; reward only: $G \times T$	NS > S
<i>PREPARATION</i>				
Right superior precentral sulcus (FEF)	26	-11 49	Overall $I \times T$	NS > S
Right superior parietal lobule	23	-62 49	Overall $I \times T$	
<i>SACCADÉ</i>				
Right inferior parietal lobule	38	-44 46	Overall $G \times T$	NS < S
Right anterior cingulate	2	31 16	Overall $I \times T$	
Right posterior cingulate	11	-26 37	Overall $G \times T$; $I \times G \times T$; reward only: $G \times T$	

Abbreviations: $G \times T$ =group by time; $I \times T$ =incentive by time; $I \times G \times T$ =incentive by group $\times$ time; FEF=frontal eye field; NS=non smokers; S =smokers.