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Greater Risk-Sensitivity of Dorsolateral Prefrontal Cortex in Young Smokers than in Nonsmokers

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Abstract

Rationale—Despite a national reduction in the prevalence of cigarette smoking, ~19% of the adult U.S. population persists in this behavior, with the highest prevalence among 18–25-year-olds. Given that the choice to smoke imposes a known health risk, clarification of brain function related to decision-making, particularly involving risk-taking, in smokers may inform prevention and smoking cessation strategies.

Objectives—This study aimed to compare brain function related to decision-making in young smokers and nonsmokers.

Methods—The Balloon Analogue Risk Task (BART) is a computerized risky decision-making task in which participants pump virtual balloons, each pump associated with an incremental increase in potential payoff on a given trial but also with greater risk of balloon explosion and loss of payoff. We used this task to compare brain activation associated with risky decision-making in smokers (n=18) and nonsmokers (n=25) while they performed the BART during functional magnetic resonance imaging (fMRI). The participants were young men and women, 17–21 years of age.

Results—Risk level (number of pumps) modulated brain activation in the right dorsolateral and ventrolateral prefrontal cortices more in smokers than in nonsmokers; and smoking severity (Heaviness of Smoking Index) was positively related to this modulation in an adjacent frontal region.

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Conclusions—Given evidence for involvement of the right dorsolateral and ventrolateral prefrontal cortices in inhibitory control, these findings suggest that young smokers have a different contribution of prefrontal cortical substrates to risky decision-making than nonsmokers. Future studies are warranted to determine whether the observed neurobiological differences precede or result from smoking.

Keywords

nicotine; functional MRI; prefrontal cortex; decision-making

Introduction

Cigarette smoking is the most preventable cause of disease and death in the United States (Center for Disease Control and Prevention 2008). Despite a generally successful public education campaign, in which the untoward effects of smoking have been well-publicized through the media, approximately 19 percent of the US population persists in smoking (Center for Disease Control and Prevention 2011). Studies of adult smokers suggest a deficit in choice behavior and decision-making and aberrant patterns of associated neural activation in brain regions including bilateral striatum, dorsal anterior cingulate cortex, frontoparietal cortex and insula (Chiu et al. 2008; Addicott et al. 2012). At 34% of smokers, 18–25-year-olds represent the age group with the highest smoking prevalence in the U.S., and virtually all cigarette smoking begins before adulthood (USDHHS 2012). Our goal, therefore, was to examine behavioral and neural correlates of risky decision-making in a sample of young smokers.

The Balloon Analogue Risk Task (BART) is a sequential, decision-making task that is widely used as a measure of risky choice (Lejeuz et al. 2002). It provides the participant with the opportunity to pump virtual balloons to increase potential monetary reward, but each pump simultaneously increases the risk that the balloon will explode and that the accumulated reward for that trial/balloon will be forfeited (Lejuez et al. 2002). Risk-taking on behavioral versions of the task is generally measured by the “average adjusted pumps”, a term that denotes the mean number of pumps across trials for balloons that did not explode. The BART has been modified for use with fMRI to identify neural correlates of risky decision-making. In a previous fMRI study of healthy adult participants performing the BART (Rao et al. 2008), brain activation in the striatum, the insula, the anterior cingulate cortex (ACC) (see also Bogg et al. 2012) and the dorsolateral prefrontal cortex (DLPFC) was modulated by the level of risk (probability of explosion and magnitude of loss) as well as potential gain. When another version of the BART was used, parametric modulation of the BOLD response by level of risk, as measured by pump number, was similarly observed in bilateral insula, ACC and DLPFC (Schonberg et al. 2012). In addition, a sample of participants with alcohol use disorder exhibited greater activation in ACC, insula and striatum when participants made risky versus non-risky decisions (Claus and Hutchison 2012).

Performance on the BART has also been correlated with neurobehavioral phenotypes hypothesized to influence the onset and maintenance of cigarette smoking, specifically impulsivity (Coggins et al. 2009; Fields et al. 2009) and propensity for risk-taking (Reyna and Farley 2006). For instance, the mean number of adjusted pumps in the BART has been positively correlated, in a predominantly college-age sample, with self-reports of impulsivity, risky sexual behavior, number of cigarettes smoked per day, and drug abuse other than cigarette smoking (Lejuez et al. 2002). In two other studies, one of college undergraduates (Lejuez et al. 2003a) and another of high-school students (Lejuez et al. 2005), smokers took more pumps than nonsmokers (Lejuez et al. 2005). However, when we

recently compared 18–20-year-old smokers and nonsmokers in a sample of 64 participants, of which 38 were included in the present investigation, the smokers did not exhibit greater risk-taking, as measured by mean adjusted pumps, on a behavioral version of the BART (Dean et al. 2011). As the present study aimed to identify differences in neural function linked to a particular behavior, it was preferable for the groups to be matched on behavioral performance (Price and Friston 1999), obviating the possibility that behavioral differences underlie neural differences between the groups during risk-taking in the task.

The goal of the study presented here was to determine whether young smokers differ from nonsmokers in brain activation and sensitivity of activation to levels of risk as measured by the BART. A second goal was to examine how activation in these regions differed as a function of smoking severity.

Methods

Participants

Internet advertisements were used to recruit healthy, daily smokers and nonsmokers, 14–21 years old (although only one participant between the ages of 14 and16 years enrolled). As required by the UCLA Institutional Review Board, participants received an explanation of the study. Those who were ≥ 18 years old gave written informed consent; younger participants gave assent, their parents giving consent. Twenty-five English-speaking, right-handed nonsmokers (mean age: 19.08 ± 1.15, 17–21, 11 female) and 18 daily smokers (mean age: 19.47 ± 1.33, 17–21, 9 female) were included in the final analysis. The groups did not differ significantly in age, education, ethnicity, or number of marijuana joints smoked per week; but they differed significantly on number of alcoholic drinks per week (Table 1) [Also see Table 1 for data related to smoking history and clinical features of smoking behavior.]. There wase also no group difference in the total score on the Barratt Impulsiveness Scale (BIS-11) but a nearly significant effect in the motor subscale (p=0.06) (Table 1), similar to findings of a previous behavioral study with a partly overlapping cohort (Dean et al. 2011). There were no correlations between BIS scores and any of the behavioral risk-taking measures of the task.

Participants reported no medical or neurological disorders, and were classified as nonsmokers (< 5 cigarettes ever) or daily smokers (≥ 6 months). Additional requirements for nonsmokers were carbon monoxide (CO) < 5 ppm in breath at all sessions (Smokerlyzer®, Bedfont Scientific, Kent, UK) and urinary cotinine below the determination threshold (NicAlert$_{TM}$ test strips, Nymox Pharmaceutical Corp., Hasbrouck Heights, NJ). Thirty percent of the nonsmokers reported ever having smoked (mean = 40 months since last cigarette). A criterion of CO concentration ≥ 6 ppm in breath and/or urinary cotinine ≥ 200 ng/ml was required for inclusion in the smoker group. The Structured Clinical Interview for DSM-IV was used to exclude participants with Axis I psychiatric disorders unrelated to drug abuse, and/or current dependence or abuse of any drug other than nicotine. Urine testing confirmed abstinence from abused drugs (except nicotine) on each test day. Participants whose self-reports placed them 2.5 standard deviations above the group mean for number of drinks/week were excluded (two smokers), and one 15-year-old nonsmoker was excluded from the analysis because his age was 2.5 standard deviations below the mean for the combined sample of both groups. Thus, the final sample size included in the analyses reported here was 43 (n=25 smokers and n=18 nonsmokers). Severity of smoking was assessed using the Heaviness of Smoking Index (HSI) (Borland *et al.*, 2010), which was calculated as the sum of cigarettes/day score (“0” for 0–10, “1” for 11–20, “2 for 21–30, and “3” for ≥31) and time to the first cigarette of the day (“3” for 0–5 min., “2” for 6–30 min., “1” for 31–60 min., and “0” for ≥ 61 min). There was no significant association between age and HSI (r=0.05).

Since nicotine withdrawal can influence cognitive performance (Azizian et al. 2009; Heishman 1998; 1999; Mendrek et al. 2006; Xu et al. 2005; Xu et al. 2007), we did not require abstinence nor did we instruct participants to change their smoking pattern before scanning. Smoking abstinence ranged from 0.5–16 h. Long abstinence was usual for the light smokers, as indicated by a negative trend between abstinence duration and cigarettes/day ($r = -0.4$, $p = 0.07$). Cigarette craving before scanning was assessed using the Urge to Smoke Scale (UTS) (Jarvik et al. 2000), and nicotine withdrawal over the week before scanning was evaluated with the Minnesota Nicotine Withdrawal Questionnaire (MNWQ) (Hughes and Hatsukami 1986).

Immediately before scanning, smokers reported an average cigarette craving score of 2.9 (range: 1.2–5.1) on a scale of 1–7 on the UTS scale. Four smokers had smoked within 2 h of scanning, 11 smokers had not smoked for at least 2 h and data were unavailable for 3 smokers. The mean score of nicotine withdrawal over the 7 days before testing was 17.7 (maximum score on the MNWS = 60), with values ranging from 3–29, indicating that the smokers tested here generally did not suffer high levels of withdrawal.

The Balloon Analogue Risk Task (BART)

Participants pressed one of two buttons either to inflate (pump) a computer-simulated balloon image or to “cash out” (Figure 1). Each trial began with the presentation of a balloon and ended when the balloon exploded or the participant cashed out. Each pump increased the potential payoff on a given trial, and the payoff accumulated in a temporary bank. Participants could cash out and keep the amount accumulated at any point during a trial. If a balloon exploded, the trial provided no payoff, but earnings from previous trials were unaffected. Earnings were paid with real money after the experiment.

Balloons were red, blue or white. The colored balloons were associated with monetary payoff, each with the same amount (25¢/pump), but different explosion probabilities were associated with the two colors. The explosion point of each balloon was randomly selected by a computer program at the beginning of the experiment from a uniform distribution, ranging from 1 to 8 and 1 to 12 pumps for red and blue balloons, respectively. This meant that as pumping progressed during the trial, the conditional probability of an explosion (given that one had not yet occurred; i.e. the hazard rate) increased non-linearly. White balloons were not associated with reward or possible explosions, and provided control for the visual and motor aspects of the enlarging balloons and sequential pumping, respectively. Participants were instructed to pump every white balloon until it disappeared from the screen. After each pump, the balloon image disappeared (1–3 sec, variable duration) until the outcome was displayed: either a larger balloon or an exploded one (no exposions displayed on control trials). At the end of each trial, the screen was blank for a varying duration (1–12 sec, average 4 sec).

Participants received brief training on the BART before scanning. They were informed that they would receive their winnings after scanning and that the balloons associated with payoff were of two different colors, but information was not provided about the explosion probabilities of the colored balloons. Other information provided was that white balloons did not explode and were not associated with payoff. The participants were also told that each run was limited either by a time limit of 10 min (thereby limiting the number of balloons they could “play”) or by a maximal number of trials. The task was self-paced, and was performed in two separate, 10-min runs, with a maximum of 48 trials each (maximum of 20 trials each for red and blue balloons and 8 for the control balloon).

Analysis of Behavioral Data

The total number of pumps, cash-outs and explosions were recorded. “Adjusted pumps” (Lejuez et al. 2002), referring to the total number of pumps on trials in which the participant chose to cash out, was also calculated as a behavioral indicator of risk-taking. The number of adjusted pumps across trials was averaged to compensate for the variation in number of trials across participants. Behavioral data were analyzed using the GLM repeated measures analysis in the Statistical Package for the Social Sciences (SPSS). There were no significant correlations between average number of pumps per participant and age either across groups ($p>.5$) or within each group (NS: $p>.7$; S: $p>.5$).

MRI Data Acquisition

Data were acquired using a 3-T Siemens Trio MRI scanner, each run producing 302 functional T2*-weighted echoplanar images (EPI) [slice thickness, 4 mm; 34 slices; TR, 2 sec; TE, 30 msec; flip angle, 90°; matrix, 64 × 64; FOV, 200 mm; voxel size, 3 × 3 × 4 mm^3]. Two volumes, collected at the beginning of each run to allow for T1 equilibrium effects, were discarded. A T2-weighted, matched-bandwidth (MBW), high-resolution, anatomical scan and magnetization-prepared rapid-acquisition gradient echo (MPRAGE) scan were acquired for registration purposes (TR: 2.3; TE: 2.1; FOV: 256; matrix: 192 × 192; sagittal plane; slice thickness: 1 mm; 160 slices). The orientation for MBW and EPI scans was oblique axial to maximize brain coverage. Matlab and Psychtoolbox (www.psychtoolbox.org) were used on an Apple Powerbook (Apple Computers, Cupertino, CA) for task presentation and timing.

Image Preprocessing

Analyses were performed using FSL 4.1.6 (www.fmrib.ox.ac.uk/fsl). The images were realigned to compensate for small head movements (Jenkinson et al. 2002); Participants with data exhibiting > 2 mm in timepoint-to-timepoint translational movement were excluded (3 participants). Data were smoothed using a 5-mm FWHM Gaussian kernel, and filtered in the temporal domain using a nonlinear high-pass filter (100-second cutoff). EPI images were registered to the MBW image, then to the MPRAGE image, and finally into standard MNI space (MNI152, T1 2 mm) using linear registration with FSL FLIRT.

Analysis of Functional Imaging Data

One general linear model (GLM) was defined, and it included multiple regressors for the three event types: pumps, cash-outs and explosions. For pumps, which represented risk-taking on the task, three regressors were defined: 1) $Pumps_{Avg}$ (Average risk-taking) was the “main effects” regressor, and it did not take into account the increasing risk associated with each successive pump. It modeled all of the pump events, with the duration of events fixed at 0.78 sec, which was the average latency (reaction time, RT) to pump across all participants. 2) $Pumps_{parametric}$ was the parametric regressor (pump number). It tested for a linear relationship between brain activation and risk level, which increased in tandem with each pump and which is correlated with explosion probability as well as with increasing potential loss and potential gain. For this regressor, the demeaned pump number (i.e. pump number for each trial minus mean number of pumps across all trials) was used as a parametric modulator; each pump in a trial was assigned a weight that increased linearly across pumps within that trial. The duration of events was fixed at 0.78 sec. 3) $Pumps_{RT}$, the “reaction-time” regressor, used the same onset time as the aforementioned regressors, but the actual rather than the average RT served as the duration of the event. This regressor was orthogonalized with respect to $Pumps_{Avg}$ so that $Pumps_{Avg}$ would retain the unique variance related to average activity during pumping. We included this regressor to ensure that every effect found on $Pumps_{AVG}$ and $Pumps_{Parametric}$ was not merely a reflection of longer

reaction times on riskier decisions. Three similar regressors were also included for pumps of the control balloon ($Control_{Avg}$, $Control_{Parametric}$ and $Control_{RT}$), and they served to control for motor effects of repeated pumping and the enlarging of the balloons as the trials progressed.

For cash-out events, three regressors similar to the pump regressors were defined: 1) $Cashout_{Avg}$ (main effect of cash-outs across all risk levels); 2) $Cashout_{Parametric}$ (parametric modulation of cash-outs by pump number) which modeled the decision to cash-out in different levels of risk; and 3) $Cashout_{RT}$ (actual RT of cash-outs) to isolate effects of RT from the foregoing regressors.

For explosion events, two regressors were defined: 1) $Explosions_{Avg}$ (main effect of explosions across all risk-levels); 2) $Explosion_{Parametric}$, (parametric modulation by the pump number when the explosion occurred). This regressor modeled explosions with varying risk-levels. The event duration was 0.78 sec, beginning with the onset of the explosion.

Temporal derivatives were included as covariates-of-no-interest for all regressors. Null events, consisting of the jittered inter-trial intervals, were not explicitly modeled and therefore constituted an implicit baseline. Motion parameters plus temporal derivatives were included as regressors of no interest.

Analysis scheme

The FSL FEAT package was used for statistical analysis. Regressors of interest (defined as described above) were convolved with a canonical (double-gamma) HRF. At the next level, the two runs (treated as a fixed effect) from each participant were combined, and a one-sample t-test was performed at each voxel for each contrast. A group-level analysis was performed using the FMRIB Local Analysis of Mixed Effects module in FSL (Beckmann et al. 2003). Task-related variables were compared between groups using two-sample *t* tests. To test for common activations across groups, data from both groups were collapsed. Thresholded Z statistic images were prepared to show clusters determined by a cluster-forming threshold of $Z > 2.3$ and a corrected extent threshold of $p < .05$, familywise error-corrected using the Theory of Gaussian Random Fields (Poline et al. 1997). Outliers were de-weighted in the multi-subject statistics using mixture modeling (Woolrich 2008). To account for the group difference in recent alcohol intake, the number of drinks per week was included as a covariate in all analyses. For visualization, statistical maps of all analyses were projected onto a study-specific average brain of the participants. All fMRI data shown were cluster-corrected at $Z=2.3$, $p<0.05$ and controlled for multiple comparisons in FSL.

Correlation analysis with HSI: To examine correlations between risk-taking behavior on the BART and smoking severity in our primary comparisons of interest, HSI scores were used as explanatory variables in both the main and parametric effects of the risk-taking contrasts as well as the cash-out and explosion events.

Results

Behavioral Performance

There were no significant between-group differences in behavioral performance or in amount earned in payouts, nor were there within-group differences in number of pumps on the red and blue balloons (Table 2); therefore, data from the red and blue balloons were combined for the fMRI analyses. There were no significant between-group differences in average latency to pump (average RT: Nonsmokers = 0.76 sec; Smokers = 0.79 sec).

fMRI Results

Risk-taking—Results from each of the 3 regressors used to examine activation during pumping (risk-taking) ($Pumps_{Avg}$, $Pumps_{Parametric}$ and $Pumps_{RT}$) are presented, with visual and motor effects removed through subtraction of activation in the corresponding control condition.

Across groups (data from smokers and nonsmokers combined): for **$Pumps_{Avg}$ > $Control_{Avg}$**, there was significant activation, associated with pumping, in the bilateral occipital cortex, bilateral parietal cortex, right DLPFC, right insula, bilateral nucleus accumbens, bilateral caudate nucleus, bilateral middle frontal gyrus (MFG) and superior frontal gyrus (SFG), cingulate cortex, cerebellum, and thalamus (Table 3). The opposite contrast (**$Control_{Avg}$ > $Pumps_{Avg}$**) revealed a decrease in activation with pumping in bilateral supramarginal gyrus, parietal cortex, and ventromedial prefrontal cortex (vmPFC) across groups (Table 3). The test of parametric modulation of activation with number of pumps (**$Pumps_{Parametric}$ > $Control_{Parametric}$**) revealed significant effects in the bilateral insula, right DLPFC, bilateral superior parietal, right inferior frontal, middle frontal and superior frontal gyri (IFG, MFG, SFG), cingulate cortex and cerebellum (Table 3). In the opposite contrast (**$Control_{Parametric}$ > $Pumps_{Parametric}$**), a significant effect was observed in the precentral gyrus, vmPFC, precuneus, superior temporal gyrus, parietal cortex and occipital cortex. The RT regressor **$Pumps_{RT}$ > $Control_{RT}$** showed task-related activation in the occipital cortex.

Group differences: A direct group comparison of **$Pumps_{Parametric}$ > $Control_{Parametric}$** revealed that sensitivity of the BOLD signal to increasing number of pumps was greater for smokers than for nonsmokers in the right DLPFC (specifically MFG (Figure 2a)), the right ventrolateral prefrontal cortex (VLPFC, specifically IFG (Figure 2b)) and right occipital cortex (Table 3); no region exhibited greater association of activation with the level of risk in nonsmokers than in smokers. When age was included as a covariate, group differences in sensitivity of BOLD signal to increasing number of pumps did not reach whole-brain cluster corrected statistical significance at $p<.05$, but this contrast showed effects in the same clusters at uncorrected thresholds: right MFG ($z=3.7$, $p=0.0001$) and right VLPFC ($z=3.1$, $p=0.0009$ voxelwise). No group differences were found for **$Pumps_{Avg}$** > **$Control_{Avg}$** or the **$Pumps_{RT}$ > $Control_{RT}$** contrasts.

Cash-out events

Across groups (data from smoker and nonsmoker groups combined)—There were significant main effects showing activation associated with cashing out (**$Cashout_{Avg}$ > baseline**) in bilateral insula, bilateral superior parietal cortex, bilateral nucleus accumbens, bilateral caudate and putamen, bilateral IFG, MFG and SFG, bilateral occipital cortex, bilateral temporal gyrus, bilateral thalamus, cingulate cortex and cerebellum (Table 4). In the opposite contrast (**baseline > $Cashout_{Avg}$**), there was a significant effect in cuneus, bilateral occipital cortex, and vmPFC (Table 4). Number of pumps at the time of cashing out (**$Cashout_{Parametric}$ > baseline**) was related to activation in bilateral insula, bilateral nucleus accumbens, bilateral IFG and MFG, occipital cortex, right middle temporal gyrus, bilateral thalamus, bilateral parietal lobe, right postcentral gyrus, cingulate cortex, right postcentral gyrus (Table 4). The opposite contrast (**baseline > $Cashout_{Parametric}$**) indicated negative modulation of activity in right parietal cortex associated with cashing out (Table 4).

Group differences—There were no significant differences in the direct comparison between groups in either cash-out analysis.

Explosions

Across groups—There were significant main effects of explosions (**$Explosion_{Avg}$ > baseline**) across groups in bilateral insula, IFG, bilateral occipital fusiform gyrus, cingulate cortex and cerebellum (Table 5). In the opposite contrast (**baseline > $Explosion_{Avg}$**), lower activation in the cingulate cortex, left occipital cortex and vmPFC was associated with explosions (Table 5). Across groups, activation in right insula, bilateral caudate, SFG, bilateral thalamus, right supramarginal gyrus, and left occipital cortex during explosion was sensitive to modulation by number of pumps (**$Explosion_{Parametric}$ > baseline**) (Table 5). The opposite contrast (**baseline > $Explosion_{Parametric}$**), showed less modulation of activation in left lateral occipital cortex, precuneus, and left occipital fusiform gyrus during explosions than in the baseline condition (Table 5).

Group differences—There were no significant differences in the direct comparison between groups in either explosion analyses.

Correlation between Smoking Behavior and Neural Activation during Risk-Taking (Smokers only)

Severity of smoking behavior, as measured using the HSI, was positively correlated with the modulation of activation by risk level (**$Pumps_{Parametric}$ > $Control_{Parametric}$**) in the MFG and SFG (x=30, y=26, z=58; Max Z=3.53) (Figure 3; Online Resource 1). There were no significant correlations between smoking severity and average pumping (**$Pumps_{Avg}$ > $Control_{Avg}$**). To determine if smoking behavior was selectively associated with risk-taking, we subsequently examined associations between other components of the task (e.g., explosions and cash-outs), but neither was significantly related to the HSI. When analyses included age as a covariate, correlation of HSI with modulation of activation by risk was still detected in the same clusters at an uncorrected threshold (z=3.2, p=0.0006 voxelwise).

Discussion

This study showed that while deciding to take risk, smokers exhibited a greater sensitivity of activation in right dorsolateral and inferior frontal gyrus to level of risk than nonsmokers. In addition, severity of smoking behavior was correlated with the sensitivity of BOLD signal to risk levels in an adjacent frontal area. To our knowledge, this is the first study to assess the neural substrates underlying the interaction of risk with decision-making in smokers, and the findings suggest that differences in prefrontal cortical function during risky decision-making may contribute to the health-compromising decision to initiate or maintain smoking behavior despite the widely known health risks. Consistent with previous imaging studies that have used the BART (Rao et al. 2008; Schonberg et al. 2012; Claus and Hutchison 2012), both smoker and nonsmoker groups exhibited increasing activation in frontal regions, insula and the caudate nucleus as a function of risk level. Cash-out and explosion events also recruited a wide network of regions previsouly implicated in risky decsion-making (Rao et al. 2008; Claus and Hutchison 2012)

Previous studies of working memory (Jacobsen et al. 2007a), attention (Jacobsen et al. 2007b) and response inhibition (Galván et al. 2011) in young smokers found associations between brain activation and smoking behavior. However, we found no published reports on the neural correlates of risky decision-making in smokers. We interpret our findings in the context of previous studies in humans and animals (Fecteau et al. 2007; Jentsch et al. 2010; Rao et al. 2008), which have implicated the DLPFC in risk-taking behavior. When an fMRI version of the BART slightly different than the one used here was employed, greater DLPFC activation, specifically in the MFG, was observed during active compared to passive risk-taking (Rao et al. 2008). Fecteau and colleagues (2007) found that enhancment of DLPFC

activation using anodal transcranial direct current stimulation (tDCS) led to decreased risk-taking during the BART (Fecteau et al. 2007). Furthermore, temporary inactivation of a region homologous to the human DLPFC resulted in suboptimal choices in a rodent version of the BART (Jentsch et al. 2010). The group differences revealed by the parametric analysis of the present study showed that as the cost-benefit relationship of risk-taking became more complicated (decreasing marginal value of each additional pump), smokers showed greater right frontal activation than nonsmokers. This difference suggests that young smokers may need to recruit greater cognitive resources to perform as well as nonsmokers as the difficulty of a risk-related decision increases.

The positive correlation between modulation of brain activation in the MFG and SFG during risk-taking and smoking severity supports this speculation. The same brain regions were implicated in a previous study of the same sample, in which we examined the relationship between brain activation during response inhibition and smoking severity (Galván et al. 2011). When the Stop-signal Task was paired with fMRI, no group differences between smokers and nonsmokers were found, but inhibition-related activation in the MFG and SFG (along with the IFG) was related to smoking severity as measured by the HSI; however, although unlike the present findings, the association was negative (Galván et al. 2011). It therefore appears that while activation in these frontal regions is modulated by smoking severity, the cognitive functions tested in the Stop-signal Task and the BART are not congruent. Results using TMS in adults also suggest that the SFG plays a role in modulating cue-induced cigarette craving (Rose et al. 2011). The authors of that study concluded that the ‘SFG plays a role in both excitatory and inhibitory influences on craving, consistent with prior research demonstrating the role of the prefrontal cortex in the elicitation as well as inhibition of drug-seeking behaviors’ (Rose et al. 2011).

The behavioral results of this study differ from previous findings of increased risk-taking on the BART in smokers than nonsmokers (Lejuez et al. 2005; Lejuez et al. 2003a; Lejuez et al. 2003b). However, we do not believe that this compromises our findings. First, in the original BART study (Lejuez et al. 2002), the authors did not find any risk-related differences in balloons with average explosion distributions closer to the ones used here, which were limited because of the time constraints imposed by the fMRI environment. Furthermore our findings of no behavioral difference in the mean “adjusted pumps” measure are consistent with findings obtained by another research team (Acheson and de Wit 2008) and our own group (Dean et al. 2011). It is possible that the discrepant findings may be attributed to study design, including whether or not the BART was administered in the scanning environment and the value of monetary rewards offered, which would likely influence the results (Bornovalova et al. 2009; Hommel et al. 2012). In addition, studies that found group differences on the BART (Lejuez et al. 2005; Lejuez et al. 2003a; Lejuez et al. 2002) had inclusion criteria less stringent than those used here, possibly allowing conditions, other than cigarette smoking, which may be linked to risk-taking behavior. As noted previously, the lack of behavioral difference between smokers and nonsmokers allowed us to examine differences in neural processing without the potential performance confound that is present when two groups that differs in task performance are compared (Price and Friston 1999). Another difference between the current study and some that came before (Lejuez et al. 2005; Lejuez et al. 2003a; Lejuez et al. 2003b) is that smokers in the present study had light-to-moderate smoking frequency (average 6.76 cigarettes/day).

Our study has strengths but also several limitations. We belive that this is the first examination of neural correlates of risky decision-making in a sample of young smokers compared to age-matched nonsmoker controls. While the sample size was adequate for the analyses performed here, it was too small for other subgroup comparisons (e.g., sex differences) which warrant examination. The BART task (not only the one used here)

inherently confounds potential gain with risk of loss, thereby precluding definitive interpretations of the factors that modulate activation. Nonetheless, the task used here was sensitive and specific in revealing a group difference in the sensitivity of activation to risk ($Pumps_{parametric}$). We also note that risk-taking behavior may have been truncated because participants knew that there was a time limit on the task and perhaps sought to optimize earnings by "cashing-out" on some trials in order to move on to subsequent trials. Although the average number of pumps might seem low (2.5–3), the full pump range for most participants reached up to 8 (up to 12 in some). Furthermore these behavioral findings are consistent with the average number of pumps previsouly found in other task configurations (Bogg et al 2012; Fukunaga, Brown & Bogg, 2012; Claus & Hutchinson, 2012), and the neural results replicate our previous findings with the same task configuration in independent samples (Schonberg et al 2012; Telzer, Fuligni, Lieberman & Galvan, 2012) Another potential caveat is the greater extent of alcohol use in the smoker group than the nonsmoker group, which would be difficult to prevent in light of the long-recognized link between alcohol consumption and smoking (Romberger and Grant 2004). However, we controled for this difference statistically and found no correlation between fMRI measures and number of drinks per week. Lastly, it is notable that chronic smoking decreases basal cerebral blood flow (Kubota et al. 1983), thereby increasing the BOLD contrast (Levin et al. 2001). However, the goups did not differ in activation when risk level was not considered as a parametric modulator, suggesting that the observed group difference indeed reflected the influence of risk level on activation.

In summary, we report differences in brain function, primarily in the right prefrontal cortex, between young smokers and their nonsmoking peers during risk-taking. Future studies are warranted to examine the neurodevelopmental trajectories in adolsecent smokers to determine whether these neurobiological differences precede or result from smoking.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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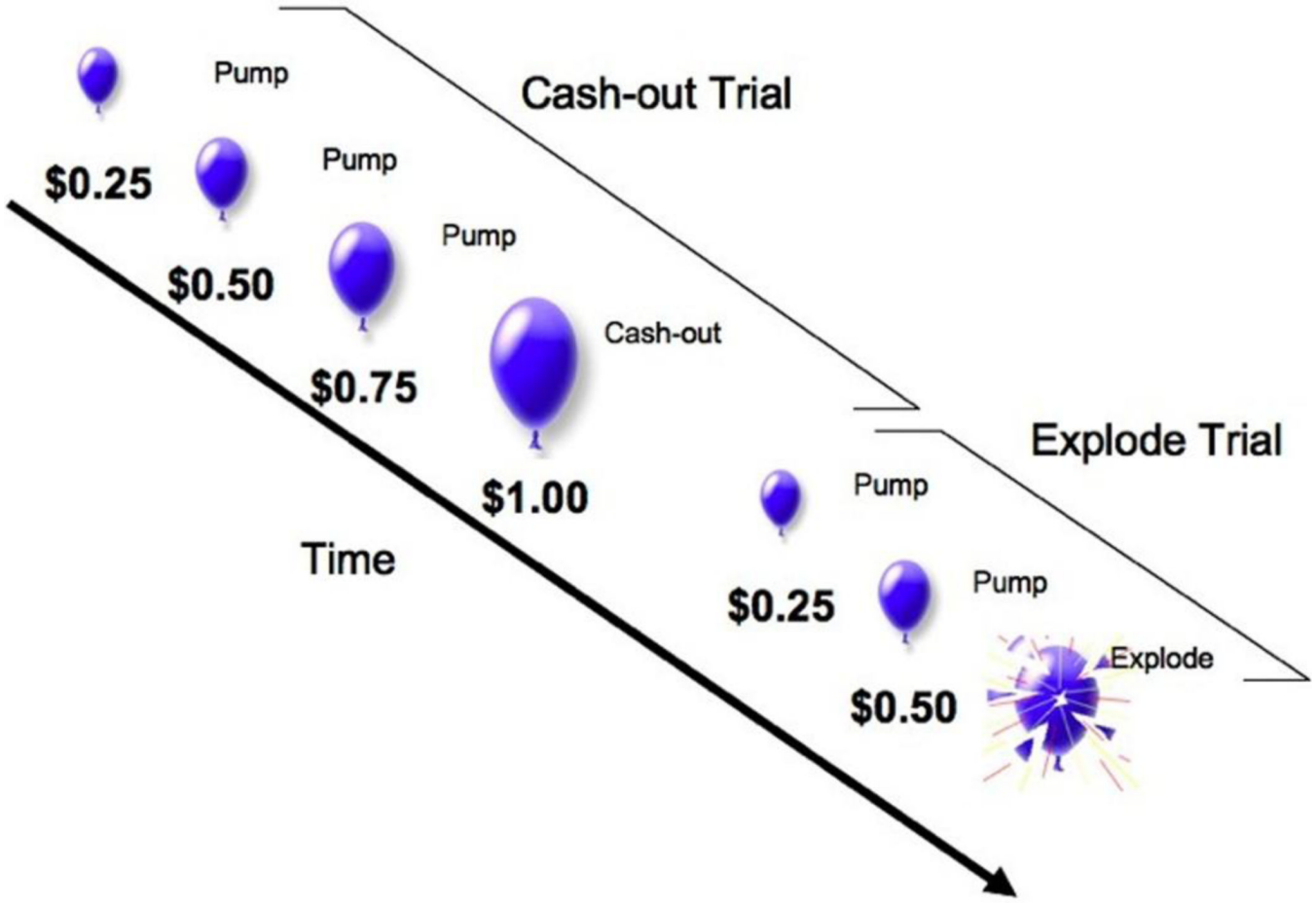

Fig. 1.
Balloon Analog Risk Task (BART) showing one representative cash-out trial and one representative explode trial

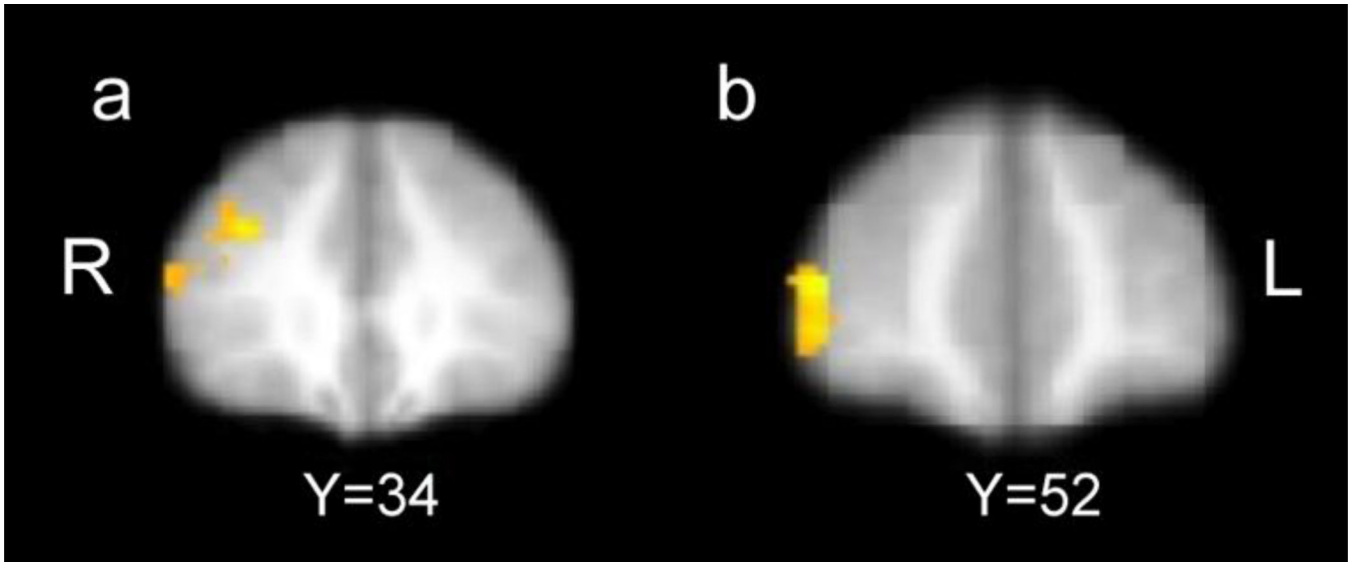

Fig. 2.

During risk-taking ($Pumps_{parametric}$ > Control), there was greater activation in smokers than nonsmokers in (a) right dorsolateral prefrontal cortex (DLPFC) (specifically middle frontal gyrus (x=36, y=34, z=30)), and (b) ventrolateral prefrontal cortex (VLPFC)) (specifically inferior frontal gyrus) (x=46, y=52, z=-2)) (cluster-corrected at z=2.3, $p<0.05$ and controlled for multiple comparison using Gaussian random-field theory in FSL).

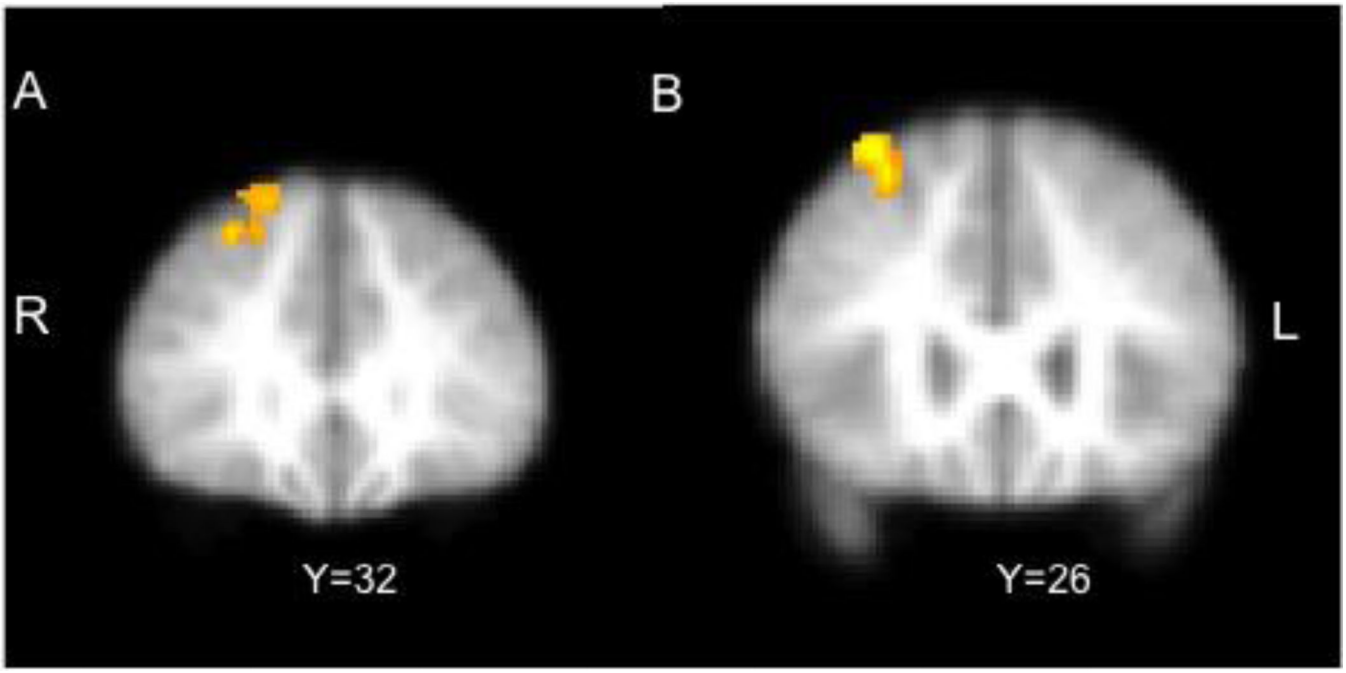

Fig. 3.

The Heaviness of Smoking Index was positively correlated with activation in the superior frontal gyrus (SFG) (x=20, y=32, z=56) and middle frontal gyrus (x=30, y=26, z=58) during risk-taking on the task (cluster-corrected at z=2.3, $p<0.05$ and controlled for multiple comparison using Gaussian random-field theory in FSL).

Table 1

Characteristics of Research Participants

Group	Nonsmokers (*n*=25)	Smokers (*n*=18)
Sex (M/F)	14/11	9/9
Age (years)	19.08 (1.15) (range: 17–21)	19.47 (1.33) (range: 17–21)
IQ	115.62 (11.76)	116.12 (8.41)
Ethnicity		
White Caucasian	16% (n=4)	27% (n=5)
African American	20% (n=5)	0.3% (n=1)
Hispanic	12% (n=3)	16% (n=3)
Asian	28% (n=7)	27% (n=5)
Native American	.04% (n=1)	0% (n=0)
Other	20% (n=5)	22% (n=4)
Education (years)	13.56 (1.26)	13.73 (1.30)
Age of Onset(years) (weekly smoking)	N/A	17.5 (1.45) (range: 14–20 yr.)
Smoking Duration (years)	N/A	2.5(1.25) (range: 5 mo.-4.9 yr.)
Cigarettes/day	N/A	6.76 (3.0) (range: 3–15)
Smoking Exposure		
(pack years)	N/A	1.13(0.68) (range: 0.12–2.45)
Time to first cigarette of the day (minutes after waking)	N/A	71 (58.18) (range: 2–180 min.)
Heaviness of Smoking Index	N/A	1.11 (1.05) (range: 0–3)
Marijuana (joints/week)	0.06 (0.2)	0.24 (0.37)
Alcohol (drinks/week)	2.02 (2.53)	6.20 (5.75)
BIS Total	60.44 (8.98)	63.29 (9.12)
BIS Motor	21.6 (4.09)	24.05 (4.09)

Data are presented as mean values (SD in parentheses).

There were no significant differences between groups except on alcohol consumption (number of drinks per week) (*p<0.0025) and a trend towards differences on the BIS Motor (p=0.06) by Student's t test. M=male; F=female

Table 2

Behavioral Performance on the BART

Group	Nonsmokers	Smokers	*t* value
	M (SD)	*M (SD)*	
Total Pumps on Red Balloon	2.52 (0.79)	2.66 (0.82)	0.58, $p>0.05$
Total Pumps on Blue Balloon	2.99 (1.01)	3.06 (.83)	0.76, $p>0.05$
Adjusted Pumps on Red Balloon	2.60 (1.04)	2.75 (1.04)	0.65, $p>0.05$
Adjusted Pumps on Blue Balloon	3.01 (1.27)	3.29 (0.98)	0.38, $p>0.05$
Number of Cash-Out Trials Red	17 (5.08)	16.85 (6.06)	0.85, $p>0.05$
Number of Cash-Out Trials Blue	20.30 (5.87)	19.85 (5.58)	0.74, $p>0.05$
Number of Explosion Trials Red	11.96 (3.11)	8.92 (3.44)	0.53, $p>0.05$
Number of Explosion Trials Blue	11.2 (3.81)	8.45 (2.87)	0.74, $p>0.05$
Average Amount Earned	$17.25 (1.88)	$17.01(3.18)	0.76, $p>0.05$

Data are presented as mean values (SD in parentheses). There were no significant differences between-groups or within-groups).

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Table 3

Significant clusters of activation from a whole-brain analysis during Risk-Taking

Region	*X*	*Y*	*Z*	Max Z	Cluster Size
$Pumps_{Avg} > Control_{Avg}$					
R/L parietal cortex, R DLPFC, R insula, R/L middle frontal gyrus, R/L superior frontal gyrus, cingulate cortex, R/L occiptial cortex, R/L nucleus accumbens, R/L caudate, cerebellum, R/L thalamus	40	−44	42	7.34	48774
$Control_{Avg} > Pumps_{Avg}$					
R/L supramarginal gyrus	58	−20	26	7.41	36722
	−58	−24	24		
R parietal cortex	60	−20	20		
vmPFC	−2	58	−16	4.73	2155
Parametric Modulation of Activation by Risk Level $Pumps_{Parametric} > Control_{Parametric}$					
Cingulate cortex	4	20	38	4.58	1989
R parietal cortex	46	−44	44	5.79	1464
L parietal cortex	−40	−44	46	3.73	508
R insula, R inferior frontal gyrus	34	18	−4	5.3	1389
L insula	−40	16	−8	4.98	732
R middle frontal gyrus, R DLPFC	40	38	26	4.62	1295
Cerebellum	−40	−50	−44	4.37	1283
R superior frontal gyrus	28	6	68	4.52	593
$Control_{Parametric} > Pumps_{Parametric}$					
Precentral gyrus	36	−22	62	5.41	7082
vmPFC	0	36	−20	4.47	2447
Precuneous	−4	−56	42	4.38	2086
R superior temporal gyrus	62	6	−2	4.19	1074
L parietal cortex	−56	−24	20	4.2	938
L occipital cortex	−42	−76	36	3.55	518
Smokers > Nonsmokers $Pumps_{Parametric} > Control_{Parametric}$					
R middle frontal gyrus (RDLPFC)	36	34	30	3.84	740

Region	*X*	*Y*	*Z*	Max *Z*	Cluster Size
R VLPFC	46	52	−1	3.13	
R occipital cortex	40	−56	54	3.93	597

Notes: Cluster size refers to all voxels in the regions listed, as per FSL output. *X Y* and *Z* MNI coordinates indicate the location of peak voxel activation. R, right; L, left.

Table 4

Significant clusters of of activation from a whole-brain analysis during Cash-outs

Region	*X*	*Y*	*Z*	Max Z	Cluster Size
Cashouts$_{Avg}$ >Baseline					
R/L insula, R/L superior parietal lobe, R/L nucleus accumbens, R/L caudate, R/L putamen R/L superior frontal gyrus, R/L middle frontal gyrus, R/L inferior frontal gyrus, cingulate gyrus, cerebellum, R/L temporal gyrus, R/L occipital cortex, R/L thalamus	34	22	0	8.09	82289
Baseline >Cashouts$_{Avg}$					
Cuneous	4	−84	26	5.01	2331
R/L occipital cortex	−46	−74	38	5.42	1825
	58	−64	24	5.24	916
vmPFC	4	52	14	5.25	1179
Cashouts$_{Parametric}$ > Baseline					
R insula, cingulate gyrus, thalamus R/L nucleus accumbens, R inferior frontal gyrus R middle frontal gyrus	30	26	10	4.85	7965
Cerebellum, occiptial lobe	−14	−74	−40	4.2	2029
R middle temporal gyrus, R/L parietal lobe, R postcentral gyrus	52	−46	0	4.1	1735
Baseline >Cashouts$_{Parametric}$					
L parietal cortex	−42	−54	48	3.96	1007

Notes: Cluster size refers to all voxels in the regions listed, as per FSL output. *X Y* and *Z* MNI coordinates indicate the location of peak voxel activation. R, right; L, left.

Table 5

Significant clusters of of activation from a whole-brain analysis during Explosions

Region	*X*	*Y*	*Z*	Max *Z*	Cluster Size
$Explosions_{Avg}$ >Baseline					
R/L insula, R/L inferior frontal gyrus	32	24	−6	7.34	25785
R/L temporal occipital cortex	−30	−54	−12	6.27	10972
Cingulate gyrus	10	24	30	6.1	6017
Cerebellum	−8	−78	−36	4.2	725
Baseline >$Explosions_{Avg}$					
Cingulate gyrus	−2	−40	38	4.39	1268
L occipital cortex	−50	−72	34	4.18	697
vmPFC	0	60	0	3.8	583
$Explosions_{Parametric}$ > Baseline					
R/L caudate	6	12	0	4.56	2115
Superior frontal gyrus, cingulate, R/L thalamus	2	12	60	4.18	1748
R insula	36	20	−10	4.39	981
R supramarginal gyrus	62	−36	26	3.81	711
L occipital cortex	−20	−72	−6	4.09	507
Baseline >$Explosions_{Parametric}$					
L lateral occipital cortex	−50	−64	38	3.52	897
Precuneous	2	−60	38	4.79	833
L occipital fusiform gyrus	−36	−80	−16	3.86	749

Notes: Cluster size refers to all voxels in the regions listed, as per FSL output. *X Y* and *Z* MNI coordinates indicate the location of peak voxel activation. R, right; L, left.

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