

Smoking withdrawal is associated with increases in brain activation during decision making and reward anticipation: a preliminary study

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Abstract

Rationale Acute nicotine abstinence is associated with disruption of executive function and reward processes; however, the neurobiological basis of these effects has not been fully elucidated.

Methods The effects of nicotine abstinence on brain function during reward-based probabilistic decision making were preliminarily investigated by scanning adult smokers ($n=13$) following 24 h of smoking abstinence and in a smoking-satiated condition. During fMRI scanning, participants completed the wheel of fortune task (Ernst et al. in *Neuropsychologia* 42:1585–1597, 2004), a decision-making task with probabilistic monetary outcomes. Brain activation was modeled during selection of options, anticipation of outcomes, and outcome feedback.

Results During choice selection, reaction times were slower, and there was greater neural activation in the postcentral gyrus, insula, and frontal and parietal cortices in the abstinent condition compared to the satiated condition. During reward anticipation, greater activation was observed in the frontal pole, insula, and paracingulate cortex in the abstinent condition compared to the satiated condition. Greater activation was also shown in the precentral gyrus and putamen in the satiated condition compared to the abstinent condition. During the outcome phase, rewards (compared to no rewards) resulted in significant activation in the paracingulate cortex in the satiated condition compared to the abstinent condition.

Conclusions The results of this preliminary study suggest that smoking withdrawal results in greater recruitment of insular, frontal, and parietal cortical areas during probabilistic decision making.

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Introduction

Nicotine addiction and withdrawal have been linked to disruptions in decision making and reward processing. Smokers have been reported to behave more impulsively than nonsmokers on tasks measuring a preference for smaller, sooner over larger, later monetary rewards (i.e., delayed discounting) (Baker et al. 2003; Bickel et al. 2008) and smokers have also been shown to discount cigarettes more rapidly than money (Bickel et al. 1999). In a probabilistic reversal learning task, smokers earned less money than nonsmokers, but had more activation in the

right insula during monetary gain and less activation in the ventrolateral prefrontal cortex during monetary loss than controls (de Ruiter et al. 2009).

Smoking cessation results in the disruption of multiple forms of cognition including sustained attention (Gilbert et al. 2004; Hendricks et al. 2006; Myers et al. 2008) and working memory (Snyder et al. 1989; Mendrek et al. 2006; Myers et al. 2008). These abstinence-induced deficits begin soon after the last cigarette is smoked (Hendricks et al. 2006), can persist for weeks (Gilbert et al. 1999, 2004), and are predictive of cessation outcomes (Patterson et al. 2010). In rodents, nicotine withdrawal increased intracranial self-stimulation reward threshold, representing decreased function in brain reward systems (Epping-Jordan et al. 1998). Similarly, overnight abstinent smokers had reduced cue reactivity, pleasure expectancies, and responsiveness to financial incentives, whereas satiated smokers performed similarly to nonsmokers (Powell et al. 2002).

Numerous fMRI studies have shown that smoking and nicotine abstinence modulate brain activation during cognitive performance and results in modulation of regions known to specifically subservise these processes, such as the parietal cortex and caudate during a sustained attention task (Lawrence et al. 2002), the dorsolateral prefrontal cortex and anterior cingulate during *n*-back tasks (Xu et al. 2005; Loughhead et al. 2010), and the ventrolateral prefrontal cortex, inferior parietal cortex, temporal poles, and medial frontal gyrus during verbal working memory tasks (Jacobsen et al. 2007; Sweet et al. 2010). In an fMRI study on the motivation to obtain cigarettes versus money, responding was not affected by nicotine withdrawal, but a cluster of increased anticipatory brain activity was shown in the prefrontal cortex (Buhler et al. 2010). Additionally, in a recent study, we observed that smoking abstinence decreased right frontal activation during periods of sustained attention, yet transiently increased activation in regions such as the precuneus and right superior frontal gyrus in responses to targets (Kozink et al. 2010).

Fewer studies have examined the effects of smoking abstinence on cognitive processes related to decision making. However, evidence is accumulating that, within a group of smokers, smoking abstinence results in increased preference for smaller, sooner over larger, later rewards (Mitchell 2004; Field et al. 2006) and impaired ability to inhibit prepotent responses (Powell et al. 2002; Pettiford et al. 2007; McClemon et al. 2008; Kozink et al. 2010). As such, the existing literature suggests that smoking abstinence biases the smoker toward more impulsive responding; however, the neurobiological basis of such a shift is unknown.

In an effort to preliminarily examine the effects of smoking abstinence on neural correlates of probabilistic decision making, we scanned smokers under satiated and abstinent conditions while they completed the wheel of

fortune (WoF) task—a two-choice task with probabilistic monetary outcomes (Ernst et al. 2004). There are two types of probable outcome trials, the first type has a 30% chance of a large reward and a 70% chance of a small reward (30/70) and the second type has a 10% chance of a large reward and a 90% chance of a small reward (10/90). The “safe” choice is the option with a large probability of a small reward and the “risky” choice is the option with a small probability of a large reward. Following the selection phase, participants rate their confidence in their selection, and lastly, are informed whether they won and rate their hedonic response to the outcome (if the participant loses, no points are gained or lost). Previous studies have reported that the percentage of high-reward and high-risk options chosen for the 30/70 trials has been 21% and 63% and for the 10/90 trials has been 27% and 53%, respectively (Ernst et al. 2004; Dichter et al. 2009). Smith et al. (2009) found that participants chose the low probability of the high-reward option 49% of the time. Previous neuroimaging studies observed activation in the prefrontal cortex, cingulate, and caudate nucleus during the selection phase, activation in the nucleus accumbens, parietal cortex, cingulate, insula, globus pallidus/putamen, and temporal lobe during the anticipation phase (Ernst et al. 2004; Engelmann and Tamir 2009), and activation in the prefrontal cortex, striatum, and cingulate during the outcome phase (Engelmann and Tamir 2009). Given previous research, we hypothesized (1) that smokers would exhibit a greater preference for risky choices when abstinent and (2) that abstinence would result in increased transient activation in the prefrontal cortex and striatum on probabilistic decision-making trials. An understanding of the neural mechanisms that underlie the effects of smoking abstinence on probabilistic decision making could potentially inform the development of novel treatments that specifically address impulsive responding and could also provide insight into the neural mechanisms that govern decision making more broadly.

Methods

Participants

Thirteen adult nicotine-dependent smokers (6 women) completed the study. Potential participants were recruited via fliers, newspaper and Internet advertisements, and by word of mouth. To be enrolled, participants had to report smoking ≥ 10 cigarettes per day for ≥ 2 years and have an afternoon expired air carbon monoxide (CO) level > 10 ppm (in order to establish smoking status). Other inclusion criteria were age between 18 and 50 years, right-handedness, no serious health problems (e.g., hypertension), not currently undergoing treatment for a psychiatric

illness, no current use of medications affecting the central nervous system, negative urinalysis for illicit drug use, no MRI contraindications, and a negative serum pregnancy test for women. Participants were compensated up to \$250 for their time (\$30 for the training session, \$105 for each MRI scan, and \$10 for the 20-min quit check). Data from five additional subjects were excluded from the analyses due to incidental findings ($n=1$), subjects reporting to have fallen asleep during the task ($n=3$), or excessive head motion (>2.0 mm, $n=1$) during the MRI scan. This study was approved by the Duke University Institutional Review Board.

Procedure

Participants first completed a 1.5-h screening session in which they heard a description of the study, read and signed a consent form, completed questionnaires regarding smoking history and suitability for fMRI research, and provided a breath sample for CO monitoring. A mock MRI scanner was used to habituate participants to the scanning environment. Participants who passed screening then completed a 1-h training session in which they were familiarized with the behavioral task.

Following training, participants completed two fMRI sessions: once following smoking as usual (satiated condition) and once following a 24-h period of smoking abstinence (abstinent condition). Session order was counter-balanced. Sessions were held no less than 2 days and no more than 19 days apart. Smoking abstinence compliance was verified using breath CO levels and confirmed with saliva nicotine levels collected at the beginning of the session. Participants were required to maintain smoking abstinence for an additional 24-h following the abstinent condition scanning session to prevent cigarette anticipation from influencing the data. Continued abstinence was also verified 24 h following the abstinent condition scanning session with breath and saliva samples. The Shiffman–Jarvik Smoking Withdrawal Questionnaire (Shiffman and Jarvik 1976) was administered upon arrival to the fMRI sessions.

fMRI task

Participants completed the WoF task during each scanning session. The WoF task is a two-choice decision-making task with probabilistic outcomes (see Fig. 1) (Ernst et al. 2004). Participants were instructed that they would earn a fixed amount for each scanning session or whatever they made during the WoF task, whichever was more. In each trial, participants chose between two options, each with an assigned probability of winning a certain amount of money. If the computer randomly selected the same option as the participant, the participant won the designated amount of

money; if the computer randomly selected the other option, the participant won nothing.

Participants completed 2 runs of 53 trials, which lasted approximately 12.5 min each. Each trial lasted 12–16 s and consisted of three phases: a selection phase (3 s), an anticipation phase (5–9 s), and a feedback phase (4 s). Intertrial intervals were 1–4 s. All stimuli were presented using E-Prime presentation software (PST Inc., Pittsburgh, PA, USA) and displayed to participants in the scanner through magnet-compatible goggles (Resonance Technology, Inc., Northridge, CA, USA).

Three trial conditions were used (see Fig. 1): selecting between (1) a 10% chance of winning \$7 and a 90% chance of winning \$1, (2) a 30% chance of winning \$2 and a 70% chance of winning \$1, and (3) two 50% chances of winning \$2. Each of the three monetary outcomes was displayed as a two-slice WoF, with each slice representing a distinct option. The area of a slice matched the likelihood of winning an explicit amount of money (e.g., 10% chance of winning \$7).

During the selection phase, participants viewed one of the three trial types and made a selection with a button press. During the anticipation phase, the wheel remained on the screen while a four-point rating scale appeared. Participants had to rate their level of confidence of winning (one for “unsure” to four for “sure”). During the feedback phase, the amount won for that trial was shown (or \$0 if a no-win trial) along with the cumulative earnings. Participants were also shown a four-point pictorial rating scale along which they rated how they felt (win trials: 1—neutral, 4—very happy; no-win trials: 1—very sad, 4—neutral). The control condition consisted of a wheel of a single color (i.e., no slices), and participants were told to press the button corresponding to the color of the wheel. All responses were recorded on a four-key button box placed under the right hand (Current Designs, Inc., Philadelphia, PA, USA).

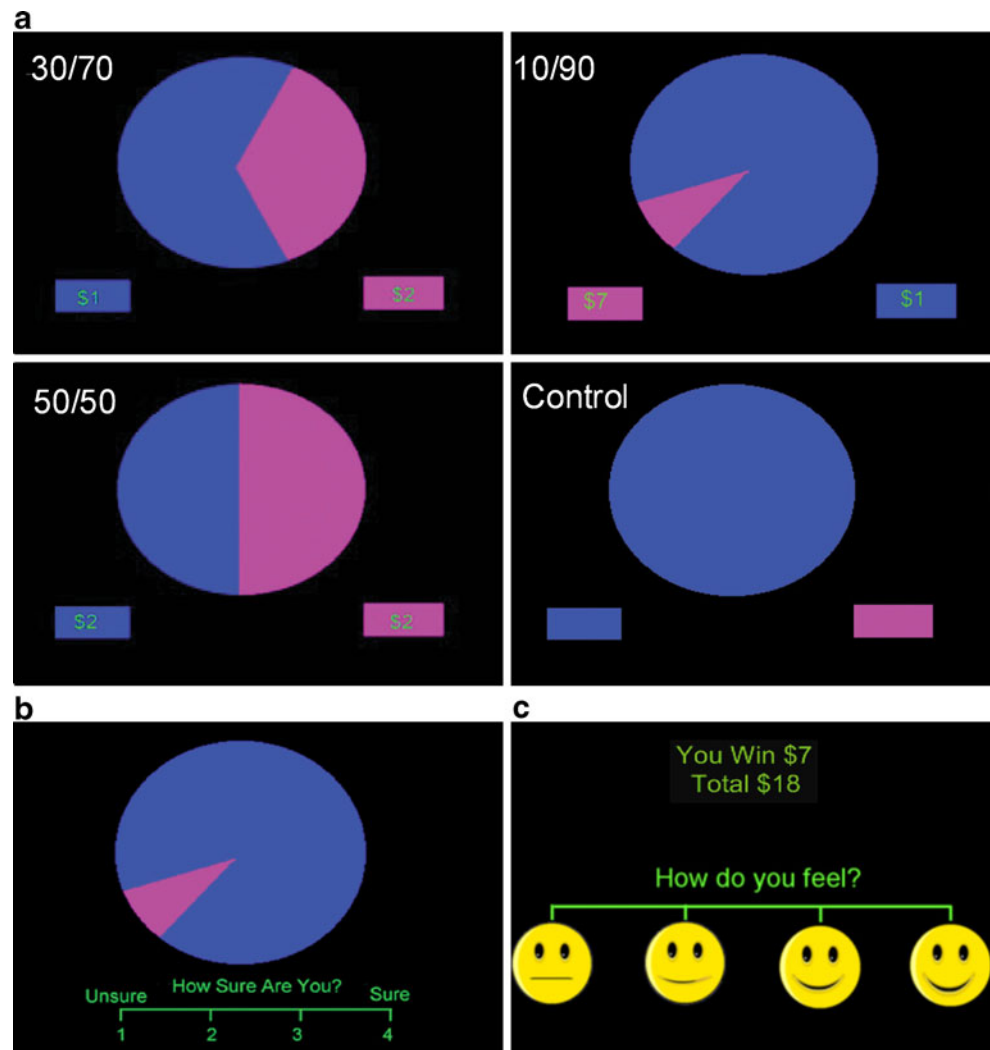
Data analysis

Behavioral data was analyzed with repeated-measures analysis of variance (ANOVA) to investigate the effects of condition (satiated or abstinent) and trial type (50/50, 30/70, and 10/90) on reaction time (RT) and responses. In the selection phase, RT and risky choice selection were analyzed with a 2 (condition) \times 3 (trial type) ANOVA. In the anticipation phase, confidence ratings were analyzed with a 2 (condition) \times 3 (trial type) \times 2 (risk preference) ANOVA. In the outcome phase, valence ratings were analyzed with a 2 (condition) \times 2 (outcome: win, no-win) ANOVA.

Imaging methods

Scanning was performed on a 4.0-T GE LX NVi scanner with 41 mT/m gradients (General Electric, Waukesha, WI,

Fig. 1 Screen displays for the three phases of the WoF task. **a** The selection phase consisted of three money trials in which participants chose to bet on either the *blue* or *magenta* slice, or a control trial. **b** In the anticipation phase, participants rated their confidence in winning the placed bet. **c** In the outcome phase, participants were informed whether or not they won and rated their emotional valence



USA). Blood oxygen level-dependent (BOLD) functional images were collected in 34 contiguous slices (4 mm thick) parallel to the horizontal plane connecting the anterior and posterior commissures. An inverse spiral pulse sequence sensitive to BOLD contrast was used, with TR=1.5 s, TE=6 ms, FOV=24 cm, matrix=64×64, flip angle=60°, and in-plane resolution=3.75 mm². After completion of the functional data collection, a T1-weighted 3D fast spoiled gradient-recalled structural image was collected for 68 slices (1.9 mm thick) with TR=12.3 s, TE=5.4 ms, FOV=24 cm, matrix=256×256, flip angle=20°, and in-plane resolution=0.9375 mm².

Functional data were preprocessed using FSL version 4.1.4 (Oxford FMRIB, Oxford, UK). Onset times of events were used to model a signal response containing a regressor for each response type, which was convolved with a double- γ function. Group-wise activation images were carried out using FMRI Expert Analysis Tool Version 5.98. Significant voxels passed a statistical threshold of $p < 0.01$ uncorrected and were required to be part of a 424- μ l (53-voxel) cluster of contiguous signif-

icant voxels resulting in a cluster-corrected $p < 0.05$. Cluster size for the comparisons was determined through Monte Carlo simulations (Ward 2000). Clusters were localized using the Montreal Neurological Institute (MNI) coordinates. Brain areas were identified using the Harvard–Oxford Atlas. The imaging contrasts were modeled after Dichter et al. (2009) and consisted of the comparison between the smoking conditions (satiated versus abstinent) during each phase of the WoF task. During the selection and anticipation phases, decision-making trials (50/50, 30/70, and 10/90) were contrasted against the control condition (monochrome wheel, no decision). During the outcome phase, win trials were contrasted against no-win trials.

A post hoc exploratory analysis was conducted to reduce potential variability in the BOLD response due to differences in RT between the abstained and satiated conditions. In the selection phase analysis, individuals' mean-centered RTs (calculated separately for abstained and satiated conditions) were entered as two nuisance regressors (abstinent RT, satiated RT) in the group-level paired t test.

Results

Participant characteristics

The final sample ($n=13$) was 46.2% female ($n=6$). Reported racial/ethnic group membership was 92.3% Caucasian ($n=12$) and 7.7% African American ($n=1$). On average, participants were 30.7 years of age ($SD=9.7$) and smoked 16.8 cigarettes per day ($SD=4.0$). They smoked for 13.5 years ($SD=8.1$) and had Fagerström Test for Nicotine Dependence (FTND) scores of 4.7 ($SD=1.7$). Their baseline afternoon CO was 25.8 ($SD=14.2$) and salivary nicotine level was 269.8 ng/ml ($SD=149.3$). During the abstinent condition, paired-samples t tests revealed greater Schiffman–Jarvik subscale scores for craving ($t=9.7$, $p<0.001$), negative affect ($t=3.9$, $p<0.005$), arousal ($t=2.7$, $p<0.05$), and habit withdrawal ($t=6.1$, $p<0.001$) than during the satiated condition.

Abstinence verification

Expired breath CO concentrations and salivary nicotine levels indicated compliance with study requirements. In the satiated condition, mean CO level was 30.5 ppm ($SD=21.6$), whereas in the 24-h abstinent condition, mean CO was 2.4 ppm ($SD=0.8$). Mean CO 24 h after the abstinent fMRI session was 2.3 ppm ($SD=2.1$).

Mean salivary nicotine was 411.1 ng/ml ($SD=308.7$) in the satiated condition and 14.7 ng/ml ($SD=9.0$) in the abstinent condition. Salivary nicotine 24 h after the abstinent fMRI session was 23.4 ng/ml ($SD=23.6$).

Behavioral results

During the selection phase, RTs were slower under the abstinent condition compared to the satiated condition (main effect of condition: $F(1,12)=14.3$, $p<0.005$); see Fig. 2a. Abstinence did not affect the number of risky choices selected overall, and the condition \times trial type interaction did not reach significance; for ratios of risky choices by trial type, see Fig. 2b and Table 1. There was no difference in the amount of money earned between the abstinent and satiated conditions. Post hoc correlations were performed between percentage of risky selections and FTND, cigarettes per day, and Schiffman–Jarvik scores in each condition. No significant associations were found.

Confidence ratings during the anticipation phase were greater for “safe” choices than for “risky” choices (main effect of risk preference: $F(1,12)=27.7$, $p<0.001$). Moreover, across the three trial types (50/50, 30/70, and 10/90) confidence scores for safe choices increased (mean=2.4, 2.8, 3.0, respectively), while scores for risky choices decreased (mean=2.4, 2.2, 1.7, respectively; interaction

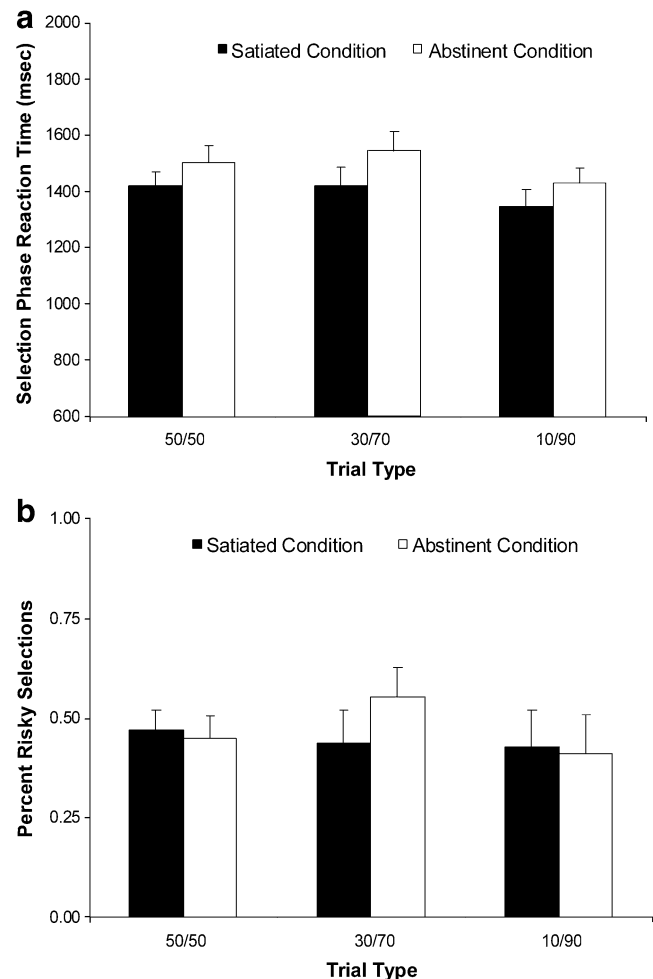


Fig. 2 **a** Average RT for both safe and risky choices. RT during the selection phase of the WoF task was slower during the abstinent condition than during the satiated condition across the three money trials ($p<0.005$). **b** Percentage of risky (magenta) selections across the three money trials. Risky selections were not affected by smoking condition (satiated versus abstinent)

effect of trial type \times risk preference: $F(2,11)=11.8$, $p<0.005$). No abstinence effects or interactions were observed.

Outcome phase valence ratings were analyzed as a function of whether the participant won money or not, irrespective of the trial type. Scores were higher after a win than after a loss (main effect of outcome: $F(1,12)=12.8$, $p<0.005$); average score after a win was 3.48 ($SD=0.38$) and average after a no-win was 2.55 ($SD=0.85$). There was no effect of abstinent condition on valence rating.

fMRI results

Selection phase When comparing conditions, greater activation was observed during the abstinent condition (money > control) in the bilateral postcentral gyrus, right insula, left lingual gyrus, bilateral rolandic operculum, left middle

Table 1 Ratio of red (risky) selections per subject in the satiated and abstinent conditions

Subject	Satiated		Abstinent	
	30/70	10/90	30/70	10/90
1	0.33	0.1	0.25	0.09
2	0.39	0.09	0.82	0.03
3	0.96	0.97	0.96	1
4	0.21	0.28	0.57	0.55
5	0.07	0.39	0.5	0.38
6	0.78	0.69	0.85	0.13
7	0.46	0.53	0.56	0.52
8	0.54	0.78	0.11	0.1
9	0.36	0.06	0.54	0.28
10	0.93	0.97	0.85	0.94
11	0.54	0.31	0.41	0.28
12	0	0.36	0.61	0.94
13	0.07	0.03	0.15	0.1

frontal gyrus, bilateral paracingulate cortex, right precentral gyrus, right supplementary motor area (SMA), left precuneus, the right inferior and orbitofrontal gyri, as well as in the left cerebellum and middle occipital gyrus, and the right supracalcarine cortex. There were no regions in which activation was greater in the satiated condition compared to the abstinent condition (see Table 2, Fig. 3).

Anticipation phase During outcome anticipation, greater activation was observed on the abstinent day (relative to the satiated day) for money > control trials in the right frontal pole, left insula, and right paracingulate gyrus. Activation was greater in the satiated condition than in the abstinent condition in the left precentral gyrus and the right putamen (see Fig. 4a, b).

Outcome phase During the outcome phase, brain activation was compared between trials in which the participant won (win) versus trials in which they did not win (no-win). When participants won money, greater activation was observed in the left paracingulate cortex in the satiated condition compared to the abstinent condition. No activation was greater during the abstinent condition relative to the satiated condition. In addition, no-win > win activation was not different between the two conditions (see Fig. 5).

In the post hoc covariate analysis, the BOLD activation contrast remained robust; however, regressing out RT resulted in a reduced number of regions activated during the selection phase (abstinent > satiated, money > control). Areas of activation that overlap between the analyses with and without the RT covariate are shown in Table 2.

Discussion

The purpose of this study was to investigate the effects of smoking abstinence on probabilistic decision-making behavior and brain activity among nicotine-dependent smokers. As we had hypothesized, the results showed that, during the selection phase of the task, there was greater activation in several brain regions including the insula, frontal, and parietal cortices during the abstinent condition. However, abstinence did not produce a greater activation in the striatum nor did it significantly affect risk preference. During the anticipation phase, confidence ratings changed according to the probability of the outcome and anticipation was associated with greater activity in the left insular cortex, right frontal pole, and right paracingulate cortex during the abstinent condition and with greater activity in the left precentral gyrus and right putamen during the satiated condition. Lastly, outcome valence was more positive on win trials than no-win trials and this phase of the task was associated with greater activity in the left paracingulate cortex during the satiated condition. Together, these preliminary findings suggest that smoking abstinence modulates brain function associated with probabilistic decision making and the anticipation and receipt of outcomes outside of any behavioral effects on risk preference, confidence, or hedonic ratings of outcomes.

Individuals with substance use disorders have been shown to have impaired decision-making behavior (Barry and Petry 2008) similar to individuals with frontal lobe lesions (Bechara 2003), and neuroimaging studies support the idea of frontal lobe dysfunction in subjects with substance dependence (Bolla et al. 2003; Beck et al. 2009). While there is some evidence that nicotine-dependent smokers make riskier decisions (Lejuez et al. 2003; Businelle et al. 2009), many studies have not reported differences between smokers and nonsmokers on gambling task performance (Lejuez et al. 2003; Rotheram-Fuller et al. 2004; Harmsen et al. 2006), on pattern recognition with reward outcomes (Martin-Soelch et al. 2003), or on delay-discounting tasks (Ohmura et al. 2005). It is possible that smokers in a satiated condition perform similar to nonsmokers, although differences may be detected in neural activation patterns (Martin-Soelch et al. 2003). To date, no study has investigated neural or behavioral differences between smokers and nonsmokers on the WoF task, and the absence of a control group limits the interpretation of our results. Differences in reward processing and probabilistic decision-making strategies may be key mechanisms in the development of drug dependence and the inability to quit permanently.

During the selection phase, a previous neuroimaging study with healthy subjects revealed greater activation for money trials than control trials in the dorsal and middle frontal gyrus, cingulate gyrus, inferior parietal lobe,

Table 2 Areas showing significant activation during the WoF task

Brain area	Side	No. of voxels	Z_{\max}	MNI coordinates		
				x	y	z
Selection phase (abstinent > satiated, money > control)						
Postcentral gyrus	L	1,072	3.28	-26	-32	60
Insula	R	393	3.43	44	-8	-12
Lingual gyrus ^a	L	385	2.80	-16	-56	-4
Rolandic operculum ^a	R	362	3.61	52	-26	22
Postcentral gyrus	R	333	2.97	34	-30	54
Cerebellum	L	256	3.05	-2	-54	-16
Rolandic operculum ^a	L	241	3.07	-60	4	4
Insula	R	227	2.88	36	-8	-8
Middle frontal gyrus ^a	L	183	3.10	-34	52	8
Precentral gyrus	R	164	2.67	34	-8	46
Middle occipital gyrus ^a	L	163	3.04	-40	-70	6
SMA	R	159	3.05	14	-2	68
Supracalcarine cortex ^a	R	155	3.08	22	-66	16
Middle frontal gyrus	L	144	3.07	-30	22	58
Inferior frontal gyrus ^a	R	131	3.19	52	36	-14
Precuneus ^a	L	124	2.95	-2	-60	12
Paracingulate cortex	L	121	2.92	-12	16	36
Paracingulate cortex	R	65	2.56	12	-14	48
Orbital frontal gyrus ^a	R	55	2.89	4	54	-24
Anticipation phase (abstinent > satiated, money > control)						
Frontal pole	R	336	3.46	26	46	20
Insula	L	255	3.36	-38	6	-2
Paracingulate cortex	R	139	2.77	14	40	-6
Anticipation phase (satiated > abstinent, money > control)						
Precentral gyrus	L	394	2.8	-2	-28	56
Putamen	R	53	3.05	28	-14	-2
Outcome phase (satiated > abstinent, win > no win)						
Paracingulate cortex	L	122	3.04	-2	48	-6

Minimum cluster size=53 voxels

^a Area of overlapping activation in post hoc analysis with RT covariate

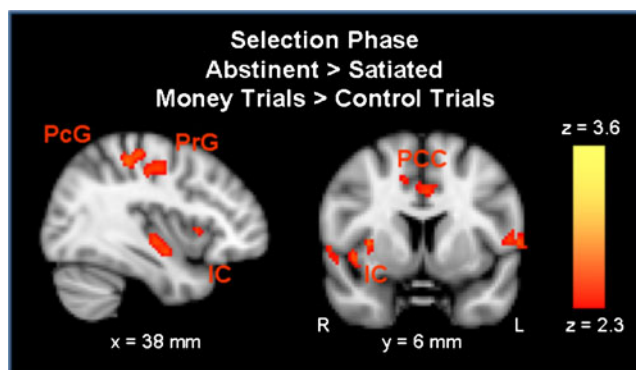


Fig. 3 During the selection phase, activation was greater in the abstinent condition than the satiated condition in the right insular cortex (IC), the right precentral gyrus (PrG), the right postcentral gyrus (PcG), and the bilateral paracingulate cortex (PCC) ($p < 0.01$ uncorrected, extent threshold=53 voxels; MNI brain template)

fusiform gyrus, and middle and inferior occipital lobe (Ernst et al. 2004). Similarly, we found increased activation in the abstinent condition in frontal, parietal, and occipital regions, as well as in the insula and paracingulate gyrus. In contrast, we did not find activation in the anterior cingulate, an area thought to be involved in conflict monitoring and shown to be activated during the WoF selection phase (Ernst et al. 2004; Engelmann and Tamir 2009). However, we did not report the activation caused by task performance in general, only the difference in activation between the abstinent and satiated conditions. Previous studies have also shown greater activation during risky selections than safe selections in the superior frontal gyrus, middle occipital gyrus, nucleus accumbens, caudate nucleus, and cingulate gyrus (Ernst et al. 2004; Engelmann and Tamir 2009; Smith et al. 2009). We were unable to compare risky versus safe selections because of an unequal number of trial types per

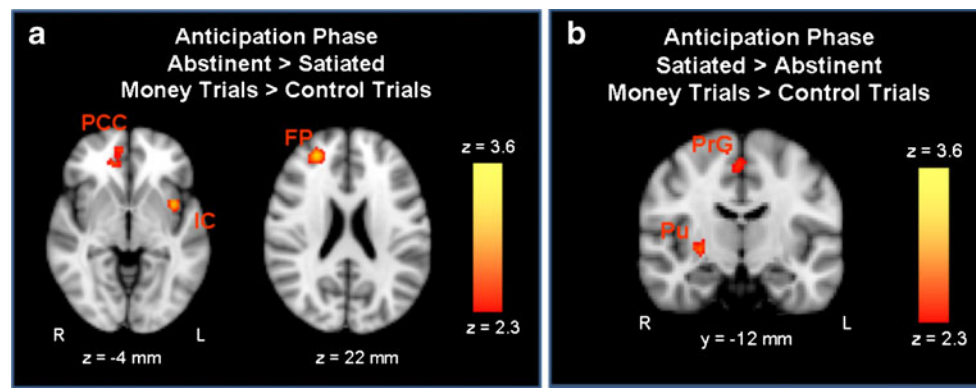


Fig. 4 a During the anticipation phase, activation was greater in the abstinent condition than the satiated condition in the left insular cortex (IC), right paracingulate cortex (PCC), and the right frontal pole (FP). **b**

Activation was greater in the satiated condition than the abstinent condition in the right putamen (Pu) and the right precentral gyrus (PrG) ($p < 0.01$ uncorrected, extent threshold=53 voxels; MNI brain template)

subject, but in the future, this may be possible with a larger sample size. This contrast analysis may be necessary to detect potential differences in striatal activation between the satiated and abstinent conditions.

In support of our hypothesis, there was greater activation in frontal regions during abstinence in the selection phase. This was accompanied by slower RTs (100 ms slower, on average). This may be indicative of an increased cognitive effort needed for probabilistic decision making during nicotine withdrawal, which can impair concentration and working memory (Xu et al. 2005; Mendrek et al. 2006; Myers et al. 2008; Kozink et al. 2010). The RT regressor was included to explore whether the differences in neural activity between the abstained and satiated conditions were dependent upon corresponding differences in RT. Regressing out RT reduced activation in frontal, motor, and somatosensory regions. These regions may play a role in general psychomotor performance, not specific to risky decision making. Several fMRI studies have used RT as a

correlate of cognitive performance. Yarkoni et al. (2009) correlated demeaned RT with the hemodynamic response from five data sets with different cognitive RT tasks. The authors reported BOLD activations in areas such as the insula, cerebellum, and precentral and postcentral gyrus (Yarkoni et al. 2009), which overlaps with areas reported in the present study. In another study, a RT regressor was used to identify brain areas modulated by task difficulty. During a word-naming task, areas that correlated with RT included the inferior and middle frontal gyrus, anterior insula, anterior cingulate gyrus, and SMA (Binder et al. 2005). In addition to representing sensorimotor function (precentral and postcentral gyrus, SMA, cerebellum), RT-related activation may also represent a “time-on-task” effect of general processes in frontal brain regions responsible for working memory, attention, decision, and response selection, instead of being task specific (Binder et al. 2005; Yarkoni et al. 2009). However, in our study, the difference in RT is between a nicotine-satiated state and a nicotine-abstinent state. Abstinence has been shown to produce slower RT during cognitive tasks (Shiffman et al. 1995; Parrott et al. 1996). Furthermore, there is evidence that abstinence decreases cognitive efficiency and other neural networks may be recruited to compensate for performance deficits (Kozink et al. 2010; Sweet et al. 2010). The brain regions that correlate with RT could be different between conditions, which make the reduced activation following the RT covariate more difficult to interpret.

Some regions of increased activation reported here (e.g., insula, paracingulate, orbitofrontal cortex [OFC]) have been identified as being involved in reward processing. Therefore, it is likely that the increased activation in frontoparietal regions is related to nicotine withdrawal modulation of probabilistic decision making. For instance, insula activity has been associated with cue-induced urges to take a drug (for review, see Naqvi and Bechara 2009) and specifically with cigarette cue-induced craving among smokers (Brody

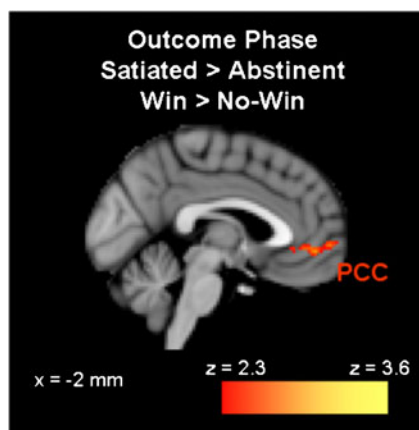


Fig. 5 During the outcome phase, activation was greater during the satiated condition than during the abstinent condition in the left paracingulate cortex (PCC) ($p < 0.01$ uncorrected, extent threshold=53 voxels; MNI brain template)

et al. 2002). Insula lesions have also been shown to interrupt smoking addiction; therefore, this area has been proposed to represent the interoceptive effects of drug use (Naqvi et al. 2007). Alternatively, in a gambling task, the insula may represent the excitement or internal arousal associated with anticipating a monetary win. Insula activity has also been associated with making and winning a gamble and with a measure of trait impulsivity (Xue et al. 2010); in addition, hyperactivation of the insula was shown during monetary gain in a probabilistic reversal learning task in smokers compared to controls (de Ruiter et al. 2009). The internal representation of a reward outcome is an important motivating influence during probabilistic decision making. The increased insular activity during the abstained condition of this study could indicate greater emotive reward valuation, independent of the cognitive (behavioral) expectation of winning the reward.

The paracingulate cortex was activated in all three phases of the WoF task (selection, anticipation, and outcome). In contrast to the selection and anticipation phases, in the outcome phase, there was greater activity in the satiated condition in the left paracingulate cortex. An adjacent region, the cingulate gyrus, has previously been reported to be activated during the selection (Ernst et al. 2004; Engelmann and Tamir 2009; Smith et al. 2009), anticipation, and outcome phases (Engelmann and Tamir 2009). The paracingulate was also a region that showed increased activation in subjects with major depression following behavioral therapy during the selection phase and decreased activation following therapy in the outcome phase of the WoF task (Dichter et al. 2009). Similarly, the paracingulate has been reported to be activated during the decision phase of a different task of probabilistic decision making (Rogers et al. 2004) and it appeared to be part of a larger network of brain regions (including the pregenual anterior cingulate cortex and dorsal medial prefrontal cortex) that represented the reward magnitude while subjects decided between two gambles. In the outcome phase, a similar study found greater activation in the frontal cortex, caudate, putamen, and insula during a win compared to a loss (Liu et al. 2007). Our results suggest that the difference in outcome monitoring between the satiated and abstained conditions was limited to the paracingulate cortex.

In the selection phase, the right OFC had greater activation during the abstinent condition. The OFC is involved in reward-based learning and is thought to maintain and update stimulus–reward associations (Schoenbaum et al. 2003b; Ghahremani et al. 2010); it has also been implicated in altering behavior when in response to a change in environmental reinforcement contingencies (for review, see Rolls 2000). For instance, in rodents, lesions to the OFC impaired reversal learning (Schoenbaum et al. 2003a). Evidence

suggests that the OFC is functionally altered in drug-addicted individuals (Schoenbaum et al. 2006). Therefore, the increased activation shown here in the abstinent condition may be indicative of an impairment in the ability to modify future decisions based on previous outcomes.

The relationship between the abstinent condition and increased activation in frontoparietal regions during a task of probabilistic monetary rewards is complicated because the motivation to obtain a drug reward is not equivalent to the motivation to obtain a nondrug reward. Hypothetically, in a substance-dependent individual, affective hedonic state is depressed during withdrawal (Koob and Le Moal 2008) and withdrawal may spur compulsive drug use, but primarily because it removes the negative affect (Koob 2009). In rodent studies, motivation to obtain nondrug rewards is typically diminished during withdrawal. In studies using delay-discounting tasks in humans, withdrawn smokers respond more impulsively for cigarettes than when satiated, but delay discounting of monetary rewards is not consistently affected by nicotine state (Mitchell 2004; Field et al. 2006). However, in real-world situations, money is needed to purchase the desired drug, and the strength of this conditioned association needs to be tested in future studies.

To our knowledge, this WoF task has not been administered in conjunction with other probabilistic decision-making tasks or other measures of risky/impulsive behavior for comparison. However, this study and another (Dichter et al. 2009) suggest that performance is stable within groups across repeated measures; therefore, risk preference may be a relatively stable trait. A study by Engelmann and Tamir (2009) found that the proportion of risky choices ranged between 0.14 and 0.59 across 10 subjects. Similarly, we found evidence of individual differences in risk preference. Some individuals in this sample almost exclusively selected risky or safe options across all trials (Table 1). Identifying personality traits or characteristics that predict performance and neural activation would strengthen the utility of the WoF task in future studies.

Though providing a preliminary assessment of the effects of smoking withdrawal on neural circuits underlying probabilistic decision making, this study is limited by several factors, many of which will be addressed in future research. First, the sample size is small and our statistical threshold, though providing some protection against type 1 error via cluster correction, is relatively liberal. As such, the findings should be considered preliminary and in need of replication with large samples. Second, only enough trials were presented to allow for an examination of brain responses during decision making (versus trials in which no decision was required). Since many subjects had an unequal number of risky/safe selections in each trial type (see Table 1), we were unable to assess neural circuitry specifically associated with the risk/reward balance of a

trial or with the selection of high-risk versus low-risk options. Subjects were not screened regarding a history of axis I psychiatric disorders, and a history of depression or anxiety could have affected reward/decision-making processing. Finally, the lack of a nonsmoking control group makes it unclear whether brain function during the abstinent condition versus the satiated condition more closely approximates normal functioning.

In conclusion, the WoF task elicited differences in neural activation between satiated and abstinent conditions among cigarette smokers. The increased activation in frontoparietal brain areas during abstinence suggests a modulation of probabilistic decision-making cognition during nicotine withdrawal. From a clinical perspective, these findings suggest that smoking abstinence changes probabilistic decision-making cognition, which might potentially have implications for understanding smoking lapse/relapse. Future studies could provide a more in-depth analysis of magnitude, probability, and risk in order to identify withdrawal-induced changes in behavioral decision making and individual differences that account for risk preference.

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