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Nicotine withdrawal modulates frontal brain function during an affective Stroop task

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Abstract

Background—Among nicotine-dependent smokers, smoking abstinence disrupts multiple cognitive and affective processes including conflict resolution and emotional information processing (EIP). However, the neurobiological basis of abstinence effects on resolving emotional interference on cognition remains largely uncharacterized. In this study, functional magnetic resonance imaging (fMRI) was used to investigate smoking abstinence effects on emotion–cognition interactions.

Methods—Smokers ($n=17$) underwent fMRI while performing an affective Stroop task (aST) over two sessions: once following 24-h abstinence and once following smoking as usual. The aST includes trials that serially present incongruent or congruent numerical grids bracketed by neutral

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or negative emotional distractors and view-only emotional image trials. Statistical analyses were conducted using a statistical threshold of $p < 0.05$ cluster corrected.

Results—Smoking abstinence increased Stroop blood-oxygenation-level-dependent response in the right middle frontal and rostral anterior cingulate gyri. Moreover, withdrawal-induced negative affect was associated with less activation in frontoparietal regions during negative emotional information processing; whereas, during Stroop trials, negative affect predicted greater activation in frontal regions during negative, but not neutral emotional distractor trials.

Conclusion—Hyperactivation in the frontal executive control network during smoking abstinence may represent a need to recruit additional executive resources to meet task demands. Moreover, abstinence-induced negative affect may disrupt cognitive control neural circuitry during EIP and place additional demands on frontal executive neural resources during cognitive demands when presented with emotionally distracting stimuli.

Keywords

Smoking; Withdrawal; Emotion; Affect; Cognition; fMRI; Nicotine; Stroop; Cingulate; PFC

Introduction

The ability to exercise cognitive control over impulses is a key process in self-regulating healthy behavior. A hallmark feature of drug addiction is compromised control over behaviors related to drug taking. For example, in spite of 80% of dependent cigarette smokers expressing a desire to quit (AHA et al. 2010), between 85% and 95% who attempt to quit relapse within the first year (Krall et al. 2002). Two of the most commonly reported reasons smokers report for lapsing/relapsing are the beliefs that smoking reduces withdrawal-related cognitive deficits (Gilbert et al. 2000; Spielberger 1986) and negative affective or stressful responses (Shiffman et al. 1986; Shiffman and Waters 2004; Spielberger 1986) including anxiety (Piper et al. 2011) and depression (Japuntich et al. 2007). Therefore, deficits in cognitive control and affective function associated with nicotine withdrawal likely subserve the ongoing maintenance of nicotine dependence.

Consistent with smokers self-reported motivations for smoking to improve cognition, prior research demonstrates robust withdrawal-related decline in a broad range of cognitive functions (Heishman et al. 1994) including attention (Gilbert et al. 2004a; Knott et al. 1999), conflict resolution (Drobes et al. 2006), decision making (Field et al. 2006), inhibitory control (McClernon et al. 2008; Pettiford et al. 2007), novelty detection (Froeliger et al. 2009), and working memory (Mendrek et al. 2006). Furthermore, functional magnetic resonance imaging (fMRI) studies have consistently implicated dysregulated function in executive control circuitry (e.g., ACC, PFC) following abstinence across a wide range of tasks including working memory (Loughead et al. 2009; Xu et al. 2005), sustained attention (Hong et al. 2009b; Kozink et al. 2010b), inhibitory control (Kozink et al. 2010a), novelty detection (Froeliger et al., in revision), and conflict-related attentional control (Azizian et al. 2010).

In addition to cognitive disturbances, smoking and negative affect are tightly intertwined (APA 2000; Baker et al. 2004). Smokers report smoking in the face of negative affect or stress-inducing situations (Shiffman and Waters 2004) and often report that smoking reduces negative affect (Shiffman and Waters 2004; Spielberger 1986). Moreover, smoking cessation significantly increases negative affect (Parrott et al. 1996). According to an attentional bias model (Gilbert 1995), nicotine/smoking reduces negative affect by shifting attention away from negative affect-provoking stimuli. In this model nicotine increases frontal, ‘top-down’ regulation of emotional reactions. Consistent with this model, brain

responses (i.e., evoked response potentials) to negative stimuli are potentiated by nicotine withdrawal (Gilbert et al. 2004b). Furthermore, nicotine abstinence disrupts target detection and P300 response at parietal sites when targets followed negative, but not neutral, emotional distractors (Gilbert et al. 2007). While prior research demonstrates that smoking abstinence biases attention to negative emotional information and interferes with ongoing cognition, the neural mechanisms underlying smoking withdrawal-related effects on emotion–cognition interactions remain largely uncharacterized.

Outside of the context of nicotine dependence, a dominant neurobiological model posits that emotion–cognition interactions are coordinated via an interaction between a dorsofrontal executive network and a ventral affective circuit (Drevets and Raichle 1998; Mayberg 1997). Task-relevant targets activate the dorsolateral prefrontal cortex (dlPFC), whereas emotional distractors activate the amygdala (Yamasaki et al. 2002). Exerting cognitive control over emotional processes leads to increased activation in the dlPFC, with corresponding reciprocal deactivation in the amygdala (Ochsner et al. 2002; Ochsner and Gross 2008).

Evidence also suggests the neural circuitry subserving emotion and cognition is disrupted in chronic drug users (Koob and Volkow 2009). Task-related hypoactivation in frontal executive function occurs among chronic users of cocaine (Garavan et al. 2008) and methamphetamine (Salo et al. 2009). In contrast, event-related hyperactivation is found among abstinent smokers and may reflect greater effort in performing tasks (Kozink et al. 2010b; Xu et al. 2006). Hyperactivation of ventral affective circuitry (e.g., amygdala) in response to emotional stimuli has been documented among chronic users of cocaine (Asensio et al. 2010) and methamphetamines (London et al. 2004). While there is evidence that nicotine modulates non-task-related ventral affective circuitry (e.g., cerebral blood flow); Rose et al. 2003; Stein et al. 1998), the neuro-cognitive basis of the effects of smoking abstinence on emotion–cognition interactions is unknown.

The Stroop task (Stroop 1935) and its numerous variants [affective Stroop (Blair et al. 2007), emotional Stroop (Mathews and MacLeod 1985), and number Stroop (Pansky and Algom 2002)] have proven effective probes for examining emotion–cognition interactions. Neuroimaging studies demonstrate that the dorsal anterior cingulate cortex (dACC) plays a role in cognitive and emotional conflict monitoring (Bush et al. 2000; Egner et al. 2008; Kerns et al. 2004), the rostral ACC (rACC) in emotional conflict resolution (Egner et al. 2008), whereas the dorsolateral prefrontal cortex (dlPFC) subserves attentional control (Botvinick et al. 2001; Botvinick et al. 2004; Kerns et al. 2004; Kim et al. 2011) and cognitive conflict resolution (Egner et al. 2008).

Smokers exhibit alteration in Stroop blood-oxygenation-level-dependent (BOLD) response in frontal executive brain regions (i.e., ACC and PFC). For example, smokers while abstinent, as compared to when satiated exhibit hyperactivation in ACC and hypoactivation in dlPFC while performing a color-word Stroop task (Azizian et al. 2010). Moreover, the magnitude of ACC activation to smoking cues inside the scanner has been reported to predict the magnitude of attentional bias to smoking words outside of the scanner (Janes et al. 2010). Though these recent findings suggest that nicotine dependence and smoking withdrawal are associated with dysregulated frontal executive brain function—neural circuitry known to play an important role in attention and cognitive control over emotional processes—no known studies have reported on the neural substrates of the effects of smoking abstinence on emotion–cognition interactions.

In the present study, we sought to investigate the neural substrates underlying the effects of smoking abstinence on emotion–cognition interactions. Dependent smokers were scanned

twice: once while smoking satiated and once following 24-h smoking abstinence. During scanning, they performed an event-related affective Stroop task ((aST); Blair et al. 2007; Hasler et al. 2009; Mueller-Pfeiffer et al. 2010; Vythilingam et al. 2007), a modified version of the number Stroop task (Pansky and Algom 2002). The aST was designed to evaluate emotional information processes and its effects on cognitive conflict resolution. We hypothesized that smoking abstinence, relative to satiety, would result in worse task performance, greater task-related brain activation in the executive control system (e.g., dlPFC, ACC), and increased emotional distraction in response to negative stimuli.

Methods and materials

Participants Smoker participants ($n=18$) from the community were enrolled in the study. Data from one participant was excluded from analyses due to problems during image reconstruction, resulting in a final $N=17$. To be enrolled, smokers had to report smoking 10 cigarettes per day for at least 2 years and have an afternoon expired air carbon monoxide (CO) level >10 ppm (in order to establish smoking status). In addition, participants had to be right handed, free of serious health problems (e.g., hypertension), free of any current/lifetime psychiatric condition, free of medications altering CNS functioning, have a negative urine drug test, not have any conditions making MRI research unsafe, and among females having a negative serum pregnancy test.

Procedures After screening, eligible participants completed one training session during which they practiced the experimental task and were placed in a mock scanner in order to habituate to the scanning environment. Following training, smokers completed two fMRI sessions separated by 3–14 days: once while smoking satiated during which participants smoked immediately prior to entering the scanning suite and once following 24-h into a 48-h abstinence period. Requiring participants to remain abstinent for a full 24-h prior to scanning has been previously shown to results in significant withdrawal at test time, and remaining abstinent 24-h post scanning reduces participants anticipating smoking as soon as the scanning is complete (Kozink et al. 2010a, b; McClernon et al. 2009). The order of condition was randomly assigned and counterbalanced. A quit check visit was conducted 24-h following the abstinent condition scan to biochemically confirm abstinence. Expired air CO concentrations were measured using a handheld CO monitor (Vitalograph Inc., Lenexa, KS) and were calculated by subtracting the background (ambient) CO from the peak CO reading. Criterion CO in the abstinence condition was 6 ppm.

Assessment of mood, smoking dependence, and withdrawal Baseline mood and nicotine dependence were assessed with the Center for Epidemiological Studies-Depression (CES-D) scale (Radloff 1977) and Fagerström Test of Nicotine Dependence (FTND; Heatherton et al. 1991), respectively. State-dependent negative affect and craving were measured at the beginning of each session using the Shiffman–Jarvik scale (Shiffman and Jarvik 1976).

Affective Stroop task The aST used in the present study was similar to that used in other studies evaluating emotion– cognition interactions (Blair et al. 2007; Hasler et al. 2009; Mueller-Pfeiffer et al. 2010; Vythilingam et al. 2007). During each imaging session, participants performed two runs of the aST (Fig. 1). Stimuli consisted of number grids and distractor images. The number grids consisted of numerals (1s through 6s) randomly presented within a nine-point grid field. Distractor stimuli were negative and neutral valence images selected from the International Affective Picture Series (Lang et al. 1997) on the basis of a nine-point arousal (1, lowest; 9, highest) and valence (1, negative; 5, neutral; and 9, positive) scales. Valence and arousal ratings for chosen images did not overlap across categories (Negative: valence <3 , arousal >6 ; Neutral: valence 4 to 6, arousal <3) and were matched on mean luminance, chromatic features, and scene complexity. Within the aST, two

primary types of trials are randomly presented: numerical trials that contain distractor images and view-only image trials (Fig. 1). The numerical trials began with a fixation cross, followed by a number grid, a negative or neutral distractor image, a unique number grid, and concluded with the re-presentation of the distractor image each for 800 ms. Participants were instructed to report by pressing the button which number grid presented (first or second) contained greater numerosity (the quantity of numbers presented) as quickly and accurately as possible. Numerical trials were further broken down into two subcategories: congruent and incongruent trials. During congruent trials, the number grids presented numerals with a face value congruent with the numerosity (e.g., two 2s; five 5s). During the incongruent trials, the face value of the numerals did not match the numerosity (e.g., four 3s; three 4s). Response accuracy and reaction times (RTs) were recorded for each trial. In view-only trials, numerical displays were replaced with a fixation cross and no behavioral response was required. During each 8 1/2-min run, 6 event types (negative congruent, negative incongruent, neutral congruent, neutral incongruent, negative view, and neutral view) were each randomly presented equally (15 events), resulting in a total of 30 events per type during each scanning session.

Analysis of behavioral data

Analyses of the effects of smoking condition on overall task response RT and accuracy during the Stroop trials was conducted using a 2 (smoking condition: abstinent, satiated) $\times$ 2 (task condition: congruent, incongruent) $\times$ 2 (distractor valence: negative, neutral) ANOVA. Behavioral analysis of the effects of smoking condition and emotional distractor valence on Stroop [incongruent–congruent] accuracy and RT were evaluated in a 2 (smoking condition: abstinent, satiated) $\times$ 2 (valence: negative, neutral) ANOVA.

fMRI methods A 3T General Electric Signa EXCITE HD scanner (Milwaukee, WI, USA) equipped with 40 mT/m gradients was used for image acquisition. At the start of each fMRI session, a high-resolution 3D fast spoiled gradient-recalled echo anatomical sequence was collected (field of view (FOV)=25.6 cm, matrix=256², flip angle= 12°, 166 slices, slice thickness=1 mm). BOLD functional images were collected for 34 contiguous slices parallel to the horizontal plane connecting the anterior and posterior commissures. A gradient-recalled inward spiral pulse imaging sequence was used (34 slices, repetition time (TR)=1,500 ms, echo time (TE)=30 ms, FOV=25.6 cm, matrix=64 $\times$ 64, flip angle=60°, slice thickness=3.8 mm, resulting in 4 $\times$ 4 $\times$ 3.8 mm voxels).

Preprocessing was conducted using statistical parametric mapping software (SPM8; Wellcome Department of Imaging Neuroscience, London) to attenuate noise and artifacts. The first four volumes of each run were discarded to allow for T1 stabilization. All functional images underwent correction for acquisition timing and for head motion using rigid body rotation and translation (Friston et al. 1994). Each participant's data were then subsequently warped into a standard stereotaxic space (Montreal Neurological Institute) with an isotropic 2-mm voxel size and smoothed with an 8-mm FWHM Gaussian filter.

fMRI data analysis Participant's data from each session were entered into a first-level whole-brain analysis using the General Linear Model (Friston et al. 1994) to examine BOLD response to each of the six trial types: negative view, neutral view, negative congruent, neutral congruent, negative incongruent, and neutral incongruent. Each trial was modeled as a boxcar function equal to the duration of the trial and convolved with a canonical hemodynamic response function. Motion was removed through rigid body rotation and translation and included as covariates, and a high-pass filter (128 s; 0.008 Hz) was applied to remove slow signal drift. In order to reduce potential variability in the BOLD response due to differences in RT between the abstinent and satiated conditions, each individual's mean-centered RTs (calculated separately for each valence and each condition (abstinent,

satiated)) were entered as a nuisance regressor in the random effects ANOVA. Statistical images have a threshold with a mask containing regions of interest (ROI) that have been previously found to play a role in emotion–cognition interactions (Dolcos and McCarthy 2006; Drevets 2000; Ochsner et al. 2002, 2004; Wang et al. 2008; Yamasaki et al. 2002). These included bilateral posterior, dorsal, and paracingulate cortices; inferior, middle, and superior frontal gyri; inferior parietal lobule; and insula and amygdala. These ROIs were obtained from automated anatomical labeling (Tzourio-Mazoyer et al. 2002) in Marina (Walter et al. 2003). The goal of the analyses was to identify the effects of smoking condition (abstinent, satiated) on (1) Stroop-BOLD response (incongruent–congruent trials), (2) emotional distraction of Stroop-BOLD response, and (3) interactions in BOLD response between smoking condition (satiated, abstinent) and viewing emotional images (negative, neutral).

Analysis of smoking condition, emotional distraction, and Stroop effect To examine the effects of smoking condition and emotional distraction on the Stroop effect, a Stroop contrast image (incongruent–congruent) was created separately for (1) negative and (2) neutral emotional distractors trials at the first level, resulting in two contrast images: negative emotional and neutral emotional distractor Stroop contrast maps. Regressors for each event during each smoking condition were entered into a 2 (condition: satiated, abstinent) $\times$ 2 (valence: negative, neutral) random effects ANOVA. Main effects of condition and valence, and condition $\times$ valence interactions were evaluated.

Analyses of smoking condition and emotion reactivity To examine the effects of smoking condition on viewing negative emotional images, regressors for each event of interest (negative view, neutral view trials) during each smoking condition were entered into a 2 (condition: satiated, abstinent) $\times$ 2 (valence: negative view, neutral view) random effects ANOVA. The main effects of condition and valence, and condition $\times$ valence interactions were evaluated.

Analysis of withdrawal-related negative affect and BOLD response To examine the relationship between abstinence-induced negative affect and EIP, a contrast image ((abstinent: negative–neutral)–(satiated: negative–neutral)) was generated for the view-only trials. Relationships between the changes score from self-reported negative affect (abstinent–satiated) and BOLD response to the view contrast image for each participant were examined by random effects multiple regression analyses. To examine the relationship between abstinence-induced negative affect and emotion–cognition interactions, a contrast image of smoking condition (abstinent–satiated) was generated separately for negative distractor Stroop (incongruent–congruent) and neutral distractor Stroop contrast images. Relationships between the changes score from self-reported negative affect (abstinent–satiated) and BOLD response to each distractor valence Stroop contrast images for each participant were examined by random effects multiple regression analyses. Positive and negative correlations were explored.

In all analyses, voxels were considered significant if they passed a statistical threshold of $p < 0.005$, uncorrected, and were part of a 432- μ L cluster of contiguous significant voxels, resulting in a cluster corrected $p < 0.05$. Cluster size for the comparisons was determined through Monte Carlo simulations (Ward 2000).

Results

Sample characteristics Participants are smokers ($N=17$) wherein 55% are females. The mean [SD] age was 31.9 [8]; years of education, 14.5 [2.2]; race: 2 Asian, 4 Black, and 11

Caucasian; baseline CES-D, 13.4 [10.7]; FTND, 5.1 [2]; years smoking, 16.9 [4.9]; average daily cigarettes, 16.9 [4.9]; baseline CO level (ppm), 26 [13.4].

Biochemical confirmation of smoking status and abstinence Expired breath CO concentrations at baseline confirmed smoking status, the mean [SD] CO level (ppm) was 26 [13.4]. Expired breath CO concentrations indicated compliance with study requirements. In the satiated condition, the mean CO level (ppm) was 26.2 [13] whereas in the 24-h abstinent condition, the mean CO was 3.7 [2.9]. The mean CO 24-h after the abstinent fMRI session was 2.4 [1.2].

Self-Report data As expected, the mean [SD] self-reported negative affect was higher in the abstinent (3.9 [1.1]) as compared with the satiated condition (3.0 [1.0]), $t_{16}=2.6$, $p=0.008$. In addition, smokers reported significantly greater craving during abstinence (5.4 [1.3]) as compared to satiety (4.6 [1.5]), $t_{16}=2.2$, $p=0.02$.

Behavioral data

Reaction times Across all correctly detected trials (congruent and incongruent), smoking abstinence resulted in slower RTs ($F=4.7$; $df=1, 16$; $p=0.04$; satiated: $M=804$ ms, $SE=52.4$; abstinent: $M=844$, $SE=53.1$) (Fig. 2). As expected, a significant main effect of distractor valence on RT's was observed ($F=10.0$; $df=1, 16$; $p=0.006$; negative: $M=838$, $SE=52$; neutral: $M=810$, $SE=53$). With regard to Stroop effects (incongruent–congruent), no significant effects were found for the condition $\times$ valence interaction ($F=3.5$; $df=1, 16$; $p=0.07$) or the main effect of smoking condition ($F=3.8$; $df=1, 16$; $p=0.07$; abstinent>satiated; satiated: $M=-8.4$, $SE=10.3$; abstinent: $M=16.5$, $SE=8.7$). The main Stroop effect approached significance $F=3.8$, $p=0.059$ (congruent: $M=877$, $SE=32$; incongruent: $M=889$, $SE=31$).

Accuracy Across all trials (congruent and incongruent), there was a nonsignificant trend for smoking abstinence to worsen response accuracy (% correct detections) ($F=3.9$; $df=1, 16$; $p=0.065$; satiated: $M=83\%$, $SE=4$; abstinent: $M=75\%$, $SE=6$) (Fig. 2). All other main effects and interactions failed to approach significance (all F 's < 1, p 's > 0.4).

The effects of smoking condition and valence on Stroop (incongruent–congruent) accuracy revealed no significant main effects or interaction (all F 's < 1, p 's > 0.4; satiated: $M=0.005$, $SE=0.01$; abstinent: $M=0.007$, $SE=0.01$). No significant Stroop effect on accuracy was observed ($F=1.7$, $p=0.2$; congruent: $M=82$, $SE=2$, incongruent: $M=83$, $SE=2$).

Imaging results

Effects of emotional distractor valence on Stroop-BOLD response Across smoking conditions and distractor valence, Stroop-BOLD response (incongruent trials–congruent trials) was observed in right dACC and right middle frontal gyrus (MFG) (Table S1). In addition, across smoking conditions, Stroop-BOLD response was greater when distractors were negative, compared with neutral, in the right superior frontal gyrus (SFG), bilateral IFG, left dACC, and right inferior parietal lobule (see Table S1). No regions were found where activation was greater during neutral, as compared with negative distractor trials.

Effects of smoking abstinence on task-related BOLD response A main effect of smoking condition on Stroop-BOLD response was found revealing greater BOLD response following smoking abstinence, as compared to satiety, in the right MFG and rACC (Table 1, Fig. 3). No brain regions were significantly more activated during the satiated condition.

Smoking condition×*distractor valence interactions* No significant smoking condition×distractor valence interactions on Stroop-BOLD response or view-only trials were found.

Regression analyses of abstinence-induced negative affect During view-only trials (negative–neutral), negative affect was negatively correlated with BOLD response in bilateral middle frontal gyrus, right superior frontal, dorsal cingulate, and supramarginal gyri; no positive correlations were found. Analyses of Stroop-BOLD response revealed that during negative emotional distractor trials, negative affect was positively correlated with BOLD response in the right inferior frontal and left middle frontal gyri; no negative correlation were found. With regard to neutral emotional distractor Stroop trials, no positive or negative correlations were found (Table 2).

Discussion

The present study utilized fMRI to investigate the effects of smoking abstinence on frontal executive function and emotional information processing in dependent smokers while performing an affective Stroop task. Smoking abstinence resulted in slower RT across both congruent and incongruent trials, but only a nonsignificant trend for smoking condition differences in a behavioral Stroop effect (incongruent–congruent trials) was observed. The lack of abstinence-related Stroop effects may have resulted from the overall decrements in task performance following abstinence. Furthermore, the lack of behavioral Stroop effects may have resulted from the relatively small sample size in this study. For example, smoking following abstinence has been previously shown to improve Stroop task performance in larger ($n=43$) (Domier et al. 2007) but not in similar sample sizes ($n=20$); Azizian et al. 2010). However, it is also plausible that the lack of behavioral findings may be due to a relatively weak Stroop manipulation in the present study.

With regard to the neuroimaging data, smoking abstinence resulted in greater Stroop-BOLD response in the right dlPFC (i.e., MFG) and rACC. Across smoking conditions and emotional distractor valence, Stroop-BOLD response was observed in the right dlPFC and dACC. This finding is consistent with the larger body of research implicating the role of dlPFC in cognitive control and conflict resolution (Botvinick et al. 2001; Egner et al. 2008) and dACC in conflict monitoring (Bush et al. 2000). In addition, negative, as compared to neutral emotional distractors increased Stroop-BOLD response in the frontal executive and parietal attentional network. These patterns of results are consistent with two complementary models: one where parallel frontal and parietal attentional control networks become engaged during effortful cognitive control (Egner et al. 2007) and the second which posits resolving emotional distraction on cognition requires recruitment of frontal executive resources in order to meet task demands (Blair et al. 2007; Dolcos and McCarthy 2006; Ochsner et al. 2002, 2004). In addition, withdrawal-related increases in negative affect were negatively correlated with BOLD response in frontoparietal circuitry during negative emotional information processing and positively correlated with BOLD response in frontal executive regions during task trials that included negative emotional distracting stimuli.

The effects of smoking abstinence on Stroop-BOLD response

The main effect of smoking abstinence on Stroop-BOLD response was observed in the right rACC and dlPFC, both of which have been associated with Stroop conflict resolution to emotional versus non-emotional tasks, respectively (Egner et al. 2008). The rACC has direct connectivity to the amygdala, nucleus accumbens, hypothalamus, anterior insula, hippocampus, and orbitofrontal cortex (Devinsky et al. 1995) and constitutes the affective division of the anterior cingulate cortex (Bush et al. 2000). The rACC is known to play an important role in resolving emotional conflict (Etkin et al. 2006) and becomes more

activated during emotional variants of the Stroop task (Blair et al. 2007; Etkin et al. 2006; Hart et al. 2010; Whalen et al. 1998). Moreover, smokers exhibit greater rACC BOLD signal in response to salient drug-related cues (McClernon et al. 2005) and abstinence increases cue-related metabolism in the region (Brody et al. 2002). These findings that abstinence increases Stroop-BOLD response in rACC suggest that, following a quit attempt, smokers may recruit additional neural resources for resolving emotional conflict in order to perform primary task demands. In addition to abstinence modulating rACC function, there was disruption in the right dlPFC—a node of the executive system that subserves attention (Cabeza and Nyberg 2000), execution of cognitive control (Kerns et al. 2004), and goal-directed processing (Blair et al. 2007). This finding suggests that during smoking abstinence, greater neural resources are required to execute cognitive control over competing information in efforts to perform primary task goals. This is consistent with prior research that has reported that abstinence disrupts dlPFC function across a broad range of cognitive tasks (Froeliger et al., in revision; Hong et al. 2009b; Kozink et al. 2010a, b; Loughhead et al. 2009; Xu et al. 2005) including studies that specifically report greater event-related activation following abstinence (Addicott et al., under review; Froeliger et al., under review; Kozink et al. 2010a). However, one study reports smoking abstinence attenuates Stroop-BOLD response in the right dlPFC (Azizian et al. 2010). The different outcomes may be due to the methodological differences in the manner and duration that smoking/abstinence conditions were manipulated (24-h in the present study vs. overnight abstinence), potentially due to Stroop-variant (aST in the present study, color-word Stroop) or differences in the magnitude of Stroop effect between studies. In sum, these findings suggest that smoking abstinence results in less efficient cognitive control and conflict resolution.

The influence of withdrawal-related negative affect on emotional information processing

We conducted an exploratory analysis evaluating the neural basis of the relations between withdrawal-induced negative affect and emotional information processing. We found that the severity of withdrawal-induced negative affect was negatively correlated with neural response to negative emotional images in regions involved in cognitive control ((dlPFC, SFG, MFG); Botvinick et al. 2001), conflict monitoring ((dACC); Bush et al. 2000), and attention ((supramarginal gyrus); Cabeza and Nyberg 2000; Corbetta and Shulman 2002). These results demonstrate that individuals with higher withdrawal-related negative affect recruit less frontal executive and attentional control brain regions during negative EIP. The pattern of results is consistent with the findings of substance abuse altering normal reactivity to naturally arousing negative emotional stimuli (see Verdejo-Garcia et al. 2006). Moreover, it extends the literature by suggesting that addiction-related deficits in executive brain function may underlie dysregulated affective processes. For example, prior research demonstrates that exerting cognitive control over emotional processes leads to increased activation in the dlPFC (Ochsner et al. 2002; Ochsner and Gross 2008). Furthermore, individuals with trait level affective disturbance (i.e., major depressive disorder) have less dlPFC activation in response to negative emotional stimuli (Hooley et al. 2005; Siegle et al. 2002, 2007). In addition, the dACC is thought to be a focus of cognitive symptoms related to smoking withdrawal (Cole et al. 2010) and a functional neuroanatomical circuit marker for nicotine addiction severity (Hong et al. 2009a).

The influence of withdrawal-related negative affect on emotion–cognition interactions

The severity of withdrawal-induced negative affective was found to be positively correlated with Stroop-BOLD response in rIFG and IMFG when negative, but not neutral, emotional distractors were presented. Activity in the IFG is associated with conflict resolution (Kemmons et al. 2005; Nee et al. 2007a, b) and thought to play an important role in mediating emotional interference during cognitive demands (Dolcos and McCarthy 2006; Mincic 2010). In addition, among healthy controls, IFG BOLD response during on the aST

has been shown to be associated with processing negative emotional information (Blair et al. 2007). The present study finding that smoking withdrawal-related negative affect predicts Stroop-BOLD response in IFG during negative distractor trials is consistent with the literature demonstrating that smoking abstinence results in greater emotional interference on cognition (Drobes et al. 2006; Gilbert et al. 2007; Rzetelny et al. 2008). Moreover, neural circuitry subserving emotion and cognition is disrupted in chronic drug users (Koob and Volkow 2009). Importantly, withdrawal-related stress response has been hypothesized to contribute to relapse (Koob and Le Moal 2008). The findings from the current study extend the extant literature by suggesting that the IFG may be a neural focus of stress-related dysregulated emotion–cognition interactions among dependent smokers following a quit attempt.

Conclusions and limitations

The present study included a robust withdrawal manipulation and an fMRI task that allows for modeling emotional information processing in isolation, and the investigation into the neurocognitive basis of smoking abstinence on emotion– cognition interactions—an area of research currently under-represented in the literature. However, limitations included a relatively small sample size and the use of a cognitive paradigm with sufficient task difficulty to subjects which may have attenuated the ability to detect behavioral Stroop effects. During the present study, we identified the neural correlates of smoking abstinence-induced effects on Stroop-BOLD response, and the effects of smoking withdrawal-induced negative affect on emotional information processing and emotion–cognition interactions. However, we failed to detect behavioral Stroop effects under any conditions. One possible explanation for a lack of findings may have been due to a relatively small sample size. In addition, a lack of not finding a behavioral Stroop effect may have been due to a relatively weak Stroop manipulation. Furthermore, the effects of emotional distractor valence on task demands may have been more salient than the cognitive demands from the Stroop trials. This rational is consistent with the behavioral data demonstrating a main effect of distractor valence on RT performance across all trials, but no difference in the Stroop effect. In addition, we failed to observe a smoking condition× distractor valence interaction in BOLD response. One possible explanation for a lack of findings may have been due to a relatively small sample size. We are addressing these issues in ongoing work in our laboratory by explicitly constraining cognitive control to emotional information processing in a larger sample of smokers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel-Smolter S, Wong ND, Wylie-Rosett J. American Heart Association Statistics Committee and Stroke

- Statistics Subcommittee. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation*. 2010; 121:e46–e215. [PubMed: 20019324]
- APA. Statistical Manual of Mental Disorders DSM-IV-TR. Washington: 2000.
- Asensio S, Romero MJ, Palau C, Sanchez A, Senabre I, Morales JL, Carcelen R, Romero FJ. Altered neural response of the appetitive emotional system in cocaine addiction: an fMRI study. *Addict Biol*. 2010; 15:504–516. [PubMed: 20579005]
- Azizian A, Nestor LJ, Payer D, Monterosso JR, Brody AL, London ED. Smoking reduces conflict-related anterior cingulate activity in abstinent cigarette smokers performing a stroop task. *Neuropsychopharmacology*. 2010; 35:775–782. [PubMed: 19907418]
- Baker TB, Piper ME, McCarthy DE, Majeskie MR, Fiore MC. Addiction motivation reformulated: an affective processing model of negative reinforcement. *Psychol Rev*. 2004; 111:33–51. [PubMed: 14756584]
- Blair KS, Smith BW, Mitchell DGV, Morton J, Vythilingam M, Pessoa L, Fridberg D, Zametkin A, Nelson EE, Drevets WC, Pine DS, Martin A, Blair RJR. Modulation of emotion by cognition and cognition by emotion. *NeuroImage*. 2007; 35:430–440. [PubMed: 17239620]
- Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD. Conflict monitoring and cognitive control. *Psychol Rev*. 2001; 108:624–652. [PubMed: 11488380]
- Botvinick MM, Cohen JD, Carter CS. Conflict monitoring and anterior cingulate cortex: an update. *Trends Cogn Sci*. 2004; 8:539–546. [PubMed: 15556023]
- Brody AL, Mandelkern MA, London ED, Childress AR, Lee GS, Bota RG, Ho ML, Saxena S, Baxter LR Jr, Madsen D, Jarvik ME. Brain metabolic changes during cigarette craving. *Arch Gen Psychiatry*. 2002; 59:1162–1172. [PubMed: 12470133]
- Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci*. 2000; 4:215–222. [PubMed: 10827444]
- Cabeza R, Nyberg L. Imaging cognition II: an empirical review of 275 PET and fMRI studies. *J Cogn Neurosci*. 2000; 12:1–47. [PubMed: 10769304]
- Cole DM, Beckmann CF, Long CJ, Matthews PM, Durcan MJ, Beaver JD. Nicotine replacement in abstinent smokers improves cognitive withdrawal symptoms with modulation of resting brain network dynamics. *NeuroImage*. 2010; 52:590–599. [PubMed: 20441798]
- Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci*. 2002; 3:201–215. [PubMed: 11994752]
- Devinsky O, Morrell M, Vogt B. Contributions of anterior cingulate cortex to behaviour. *Brain*. 1995; 118:279–306. [PubMed: 7895011]
- Dolcos F, McCarthy G. Brain systems mediating cognitive interference by emotional distraction. *J Neurosci*. 2006; 26:2072–2079. [PubMed: 16481440]
- Domier C, Monterosso J, Brody A, Simon S, Mendrek A, Olmstead R, Jarvik M, Cohen M, London E. Effects of cigarette smoking and abstinence on stroop task performance. *Psychopharmacology*. 2007; 195:1–9. [PubMed: 17634928]
- Drevets WC. Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. *Prog Brain Res*. 2000; 126:413–431. [PubMed: 11105660]
- Drevets WC, Raichle ME. Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: implications for interactions between emotion and cognition. *Cognit Emot*. 1998; 12:353–385.
- Drobes DJ, Elibero A, Evans DE. Attentional bias for smoking and affective stimuli: a Stroop task study. *Psychol Addict Behav*. 2006; 20:490–495. [PubMed: 17176185]
- Egner T, Delano M, Hirsch J. Separate conflict-specific cognitive control mechanisms in the human brain. *NeuroImage*. 2007; 35:940–948. [PubMed: 17276088]
- Egner T, Etkin A, Gale S, Hirsch J. Dissociable neural systems resolve conflict from emotional versus nonemotional distracters. *Cereb Cortex*. 2008; 18:1475–1484. [PubMed: 17940084]
- Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron*. 2006; 51:871–882. [PubMed: 16982430]

- Field M, Santarcangelo M, Sumnall H, Goudie A, Cole J. Delay discounting and the behavioural economics of cigarette purchases in smokers: the effects of nicotine deprivation. *Psychopharmacology*. 2006; 186:255–263. [PubMed: 16609902]
- Friston KJ, Jezzard P, Turner R. Analysis of functional MRI time-series. *Hum Brain Mapp*. 1994; 1:153–171.
- Froeliger B, Gilbert DG, McClernon FJ. Effects of nicotine on novelty detection and memory recognition performance: double-blind, placebo-controlled studies of smokers and nonsmokers. *Psychopharmacology (Berl)*. 2009; 205(4):625–633. [PubMed: 19488741]
- Garavan H, Kaufman JN, Hester R. Acute effects of cocaine on the neurobiology of cognitive control. *Philos Trans R Soc Lond B Biol Sci*. 2008; 363:3267–3276. [PubMed: 18640911]
- Gilbert, DG. Smoking: individual difference, psychopathology, and emotion. Taylor & Francis; Washington: 1995.
- Gilbert DG, Sharp JP, Ramanaiah NV, Detwiler FRJ, Anderson AE. Development of a Situation×Trait Adaptive Response (STAR) model-based smoking motivation questionnaire. *Personal Individ Differ*. 2000; 29:65–84.
- Gilbert DG, McClernon J, Rabinovich N, Sugai C, Plath L, Asgaard G, Zuo Y, Huggenvik J, Botros N. Effects of quitting smoking on EEG activation and attention last for more than 31 days and are more severe with stress, dependence, DRD2 A1 allele, and depressive traits. *Nicotine Tob Res*. 2004a; 6:249–267. [PubMed: 15203798]
- Gilbert DG, Sugai C, Zuo Y, Claire NE, McClernon FJ, Rabinovich NE, Markus T, Asgaard G, Radtke R. Effects of nicotine on brain responses to emotional pictures. *Nicotine Tob Res*. 2004b; 6:985–996. [PubMed: 15801571]
- Gilbert DG, Sugai C, Zuo Y, Rabinovich NE, McClernon FJ, Froeliger B. Brain indices of nicotine's effects on attentional bias to smoking and emotional pictures and to task-relevant targets. *Nicotine Tob Res*. 2007; 9:351–363. [PubMed: 17365767]
- Hart SJ, Green SR, Casp M, Belger A. Emotional priming effects during Stroop task performance. *Neuroimage*. 2010; 49:2662–2670. [PubMed: 19883772]
- Hasler G, Mondillo K, Drevets WC, Blair JR. Impairments of probabilistic response reversal and passive avoidance following catecholamine depletion. *Neuropsychopharmacology*. 2009; 34:2691–2698. [PubMed: 19675538]
- Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict*. 1991; 86:1119–1127. [PubMed: 1932883]
- Heishman S, Taylor R, Henningfield J. Nicotine and smoking: a review of effects on human performance. *Exp Clin Psychopharmacol*. 1994; 2:345–395.
- Hong LE, Gu H, Yang Y, Ross TJ, Salmeron BJ, Buchholz B, Thaker GK, Stein EA. Association of nicotine addiction and nicotine's actions with separate cingulate cortex functional circuits. *Arch Gen Psychiatry*. 2009a; 66:431–441. [PubMed: 19349313]
- Hong LE, Schroeder M, Ross TJ, Buchholz B, Salmeron BJ, Wonodi I, Thaker GK, Stein EA. Nicotine enhances but does not normalize visual sustained attention and the associated brain network in schizophrenia. *Schizophr Bull*. 2009b; 37(2):416–425. [PubMed: 19713300]
- Hooley JM, Gruber SA, Scott LA, Hiller JB, Yurgelun-Todd DA. Activation in dorsolateral prefrontal cortex in response to maternal criticism and praise in recovered depressed and healthy control participants. *Biol Psychiatry*. 2005; 57:809–812. [PubMed: 15820239]
- Janes AC, Pizzagalli DA, Richardt S, Frederick BD, Chuzi S, Pachas G, Culhane MA, Holmes AJ, Fava M, Evins AE, Kaufman MJ. Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. *Biol Psychiatry*. 2010; 67:722–729. [PubMed: 20172508]
- Japuntich SJ, Smith SS, Jorenby DE, Piper ME, Fiore MC, Baker TB. Depression predicts smoking early but not late in a quit attempt. *Nicotine Tob Res*. 2007; 9:677–686. [PubMed: 17558825]
- Kemmotsu N, Villalobos ME, Gaffrey MS, Courchesne E, Müller RA. Activity and functional connectivity of inferior frontal cortex associated with response conflict. *Brain Res Cogn Brain Res*. 2005; 24:335–342. [PubMed: 15993771]

- Kerns JG, Cohen JD, MacDonald AW, Cho RY, Stenger VA, Carter CS. Anterior cingulate conflict monitoring and adjustments in control. *Science*. 2004; 303:1023–1026. [PubMed: 14963333]
- Kim C, Kroger JK, Kim J. A functional dissociation of conflict processing within anterior cingulate cortex. *Hum Brain Mapp*. 2011; 32:304–312. [PubMed: 21229616]
- Knott V, Bosman M, Mahoney C, Ilivitsky V, Quirt K. Transdermal nicotine: single dose effects on mood, EEG, performance, and event-related potentials. *Pharmacol Biochem Behav*. 1999; 63:253–261. [PubMed: 10371654]
- Koob GF, Le Moal M. Neurobiological mechanisms for opponent motivational processes in addiction. *Philos Trans R Soc Lond B Biol Sci*. 2008; 363:3113–3123. [PubMed: 18653439]
- Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology*. 2009; 35:217–238. [PubMed: 19710631]
- Kozink RV, Kollins SH, McClernon FJ. Smoking withdrawal modulates right inferior frontal cortex but not presupplementary motor area activation during inhibitory control. *Neuropsychopharmacology*. 2010a; 35:2600–2606. [PubMed: 20861830]
- Kozink RV, Lutz AM, Rose JE, Froeliger B, McClernon FJ. Smoking withdrawal shifts the spatiotemporal dynamics of neurocognition. *Addict Biol*. 2010b; 15:480–490. [PubMed: 21040240]
- Krall EA, Garvey AJ, Garcia RI. Smoking relapse after 2 years of abstinence: findings from the VA Normative Aging Study. *Nicotine Tob Res*. 2002; 4:95–100. [PubMed: 11906685]
- Lang, PJ.; Bradley, MM.; Cuthbert, BN. International Affective Picture System (IAPS). NIMH Center for the Study of Emotion and Attention; Gainesville: 1997.
- London ED, Simon SL, Berman SM, Mandelkern MA, Lichtman AM, Bramen J, Shinn AK, Miotto K, Learn J, Dong Y, Matochik JA, Kurian V, Newton T, Woods R, Rawson R, Ling W. Mood disturbances and regional cerebral metabolic abnormalities in recently abstinent methamphetamine abusers. *Arch Gen Psychiatry*. 2004; 61:73–84. [PubMed: 14706946]
- Loughead J, Wileyto EP, Valdez JN, Sanborn P, Tang K, Strasser AA, Ruparel K, Ray R, Gur RC, Lerman C. Effect of abstinence challenge on brain function and cognition in smokers differs by COMT genotype. *Mol Psychiatry*. 2009; 14:820–826. [PubMed: 19065145]
- Mathews A, MacLeod C. Selective processing of threat cues in anxiety states. *Behav Res Ther*. 1985; 23:563–569. [PubMed: 4051929]
- Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. *J Neuropsychiatry Clin Neurosci*. 1997; 9:471–481. [PubMed: 9276848]
- McClernon FJ, Hiott FB, Huettel SA, Rose JE. Abstinence-induced changes in self-report craving correlate with event-related fMRI responses to smoking cues. *Neuropsychopharmacology*. 2005; 30:1940–1947. [PubMed: 15920499]
- McClernon F, Kollins S, Lutz A, Fitzgerald D, Murray D, Redman C, Rose J. Effects of smoking abstinence on adult smokers with and without attention deficit hyperactivity disorder: results of a preliminary study. *Psychopharmacology*. 2008; 197:95–105. [PubMed: 18038223]
- McClernon FJ, Kozink RV, Lutz AM, Rose JE. 24-h smoking abstinence potentiates fMRI-BOLD activation to smoking cues in cerebral cortex and dorsal striatum. *Psychopharmacology (Berl)*. 2009; 204:25–35. [PubMed: 19107465]
- Mendrek A, Monterosso J, Simon SL, Jarvik M, Brody A, Olmstead R, Domier CP, Cohen MS, Ernst M, London ED. Working memory in cigarette smokers: comparison to non-smokers and effects of abstinence. *Addict Behav*. 2006; 31:833–844. [PubMed: 16009504]
- Mincic AM. Neural substrate of the cognitive and emotional interference processing in healthy adolescents. *Acta Neurobiol Exp*. 2010; 70:406–422.
- Mueller-Pfeiffer C, Martin-Soelch C, Blair JR, Carnier A, Kaiser N, Rufer M, Schnyder U, Hasler G. Impact of emotion on cognition in trauma survivors: what is the role of posttraumatic stress disorder? *J Affect Disord*. 2010; 126:287–292. [PubMed: 20417971]
- Nee DE, Jonides J, Berman MG. Neural mechanisms of proactive interference-resolution. *NeuroImage*. 2007a; 38:740–751. [PubMed: 17904389]
- Nee DE, Wager TD, Jonides J. Interference resolution: insights from a meta-analysis of neuroimaging tasks. *Cogn Affect Behav Neurosci*. 2007b; 7:1–17. [PubMed: 17598730]

- Ochsner KN, Gross JJ. Cognitive emotion regulation: insights from social cognitive and affective neuroscience. *Curr Dir Psychol Sci*. 2008; 17:153–158.
- Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. Rethinking feelings: an FMRI study of the cognitive regulation of emotion. *J Cogn Neurosci*. 2002; 14:1215–1229. [PubMed: 12495527]
- Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JDE, Gross JJ. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *NeuroImage*. 2004; 23:483–499. [PubMed: 15488398]
- Pansky A, Algom D. Comparative judgment of numerosity and numerical magnitude: attention preempts automaticity. *J Exp Psychol Learn Mem Cogn*. 2002; 28:259–274. [PubMed: 11911383]
- Parrott AC, Garnham NJ, Wesnes K, Pincock C. Cigarette smoking and abstinence: comparative effects upon cognitive task performance and mood state over 24 hours. *Hum Psychopharmacol Clin Exp*. 1996; 11:391–400.
- Pettiford J, Kozink RV, Lutz AM, Kollins SH, Rose JE, McClernon FJ. Increases in impulsivity following smoking abstinence are related to baseline nicotine intake and boredom susceptibility. *Addict Behav*. 2007; 32:2351–2357. [PubMed: 17399907]
- Piper ME, Cook JW, Schlam TR, Jorenby DE, Baker TB. Anxiety diagnoses in smokers seeking cessation treatment: relations with tobacco dependence, withdrawal, outcome and response to treatment. *Addiction*. 2011; 106:418–427. [PubMed: 20973856]
- Radloff LS. The CES-D scale: a self report depression scale for research in the general population. *Appl Psychol Meas*. 1977; 1:385–401.
- Rose JE, Behm FM, Westman EC, Mathew RJ, London ED, Hawk TC, Turkington TG, Coleman RE. PET studies of the influences of nicotine on neural systems in cigarette smokers. *Am J Psychiatry*. 2003; 160:323–333. [PubMed: 12562580]
- Rzetelny A, Gilbert DG, Hammersley J, Radtke R, Rabinovich NE, Small SL. Nicotine decreases attentional bias to negative-affect-related Stroop words among smokers. *Nicotine Tob Res*. 2008; 10:1029–1036. [PubMed: 18584466]
- Salo R, Ursu S, Buonocore MH, Leamon MH, Carter C. Impaired prefrontal cortical function and disrupted adaptive cognitive control in methamphetamine abusers: a functional magnetic resonance imaging study. *Biol Psychiatry*. 2009; 65:706–709. [PubMed: 19136097]
- Shiffman SM, Jarvik ME. Smoking withdrawal symptoms in 2 weeks of abstinence. *Psychopharmacology*. 1976; 50:35–39. [PubMed: 827760]
- Shiffman S, Waters AJ. Negative affect and smoking lapses: a prospective analysis. *J Consult Clin Psychol*. 2004; 72:192–201. [PubMed: 15065954]
- Shiffman S, Shumaker SA, Abrams DB, Cohen S, Garvey A, Grunberg NE, Swan GE. Models of smoking relapse. *Health Psychol*. 1986; 5(Suppl):13–27. [PubMed: 3582321]
- Siegle GJ, Steinhauer SR, Thase ME, Stenger VA, Carter CS. Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biol Psychiatry*. 2002; 51:693–707. [PubMed: 11983183]
- Siegle GJ, Thompson W, Carter CS, Steinhauer SR, Thase ME. Increased amygdala and decreased dorsolateral prefrontal bold responses in unipolar depression: related and independent features. *Biol Psychiatry*. 2007; 61:198–209. [PubMed: 17027931]
- Spielberger, CD. Psychological determinants of smoking behavior. In: Tollinson, RD., editor. *Smoking and society: toward a more balanced assessment*. Heath; Lexington: 1986.
- Stein EA, Pankiewicz J, Harsch HH, Cho JK, Fuller SA, Hoffmann RG, Hawkins M, Rao SM, Bandettini PA, Bloom AS. Nicotine-induced limbic cortical activation in the human brain: a functional MRI study. *Am J Psychiatry*. 1998; 155:1009–1015. [PubMed: 9699686]
- Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935; 28:643–662.
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*. 2002; 15:273–289. [PubMed: 11771995]
- Verdejo-Garcia A, Perez-Garcia M, Bechara A. Emotion, decision-making and substance dependence: a somatic-marker model of addiction. *Curr Neuropharmacol*. 2006; 4:17–31. [PubMed: 18615136]

- Vythilingam M, Blair KS, McCaffrey D, Scaramozza M, Jones M, Nakic M, Mondillo K, Hadd K, Bonne O, Mitchell DG, Pine DS, Charney DS, Blair RJ. Biased emotional attention in post-traumatic stress disorder: a help as well as a hindrance? *Psychol Med*. 2007; 37:1445–1455. [PubMed: 17559703]
- Walter, B.; Blecker, C.; Kirsch, P.; Sammer, G.; Schienle, A.; Stark, R.; Vaitl, D. MARINA: An easy to use tool for the creation of MAsks for Region of INterest Analyses [abstract]. 9th International Conference on Functional Mapping of the Human Brain; New York. 2003.
- Wang L, LaBar KS, Smoski M, Rosenthal MZ, Dolcos F, Lynch TR, Krishnan RR, McCarthy G. Prefrontal mechanisms for executive control over emotional distraction are altered in major depression. *Psychiatry Res*. 2008; 163:143–155. [PubMed: 18455373]
- Ward, B. Simultaneous inference for fMRI data. Biophysics Research Institute, Medical College of Wisconsin; Milwaukee: 2000.
- Whalen PJ, Bush G, McNally RJ, Wilhelm S, McNerney SC, Jenike MA, Rauch SL. The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biol Psychiatry*. 1998; 44:1219–1228. [PubMed: 9861465]
- Xu J, Mendrek A, Cohen MS, Monterosso J, Rodriguez P, Simon SL, Brody A, Jarvik M, Domier CP, Olmstead R, Ernst M, London ED. Brain activity in cigarette smokers performing a working memory task: effect of smoking abstinence. *Biol Psychiatry*. 2005; 58:143–150. [PubMed: 16038685]
- Xu J, Mendrek A, Cohen MS, Monterosso J, Simon S, Brody AL, Jarvik M, Rodriguez P, Ernst M, London ED. Effects of acute smoking on brain activity vary with abstinence in smokers performing the N-Back Task: a preliminary study. *Psychiatry Res*. 2006; 148:103–109. [PubMed: 17088048]
- Yamasaki H, LaBar KS, McCarthy G. Dissociable prefrontal brain systems for attention and emotion. *Proc Natl Acad Sci U S A*. 2002; 99:11447–11451. [PubMed: 12177452]

Fig. 1. Example trials on the aST. Each of the 6 trial types (Neutral and Negative View, Neutral Congruent and Incongruent, Negative Congruent and Incongruent) were randomly presented an equal number of times (30) over the scanning session. Each distractor image was presented only once during a scanning session

Fig. 2. Main effect of smoking condition on task performance

Fig. 3. fMRI contrast of the main effects of smoking condition on Stroop-related BOLD response. Activation was greater during smoking abstinence versus satiety in right middle frontal gyrus (*MFG*) ($x=36, y=30, z=26$) and rostral anterior cingulate cortex (*rACC*) ($x=4, y=36, z=-8$). No brain regions displayed greater activations during the satiated condition

Table 1
Main effect of smoking state on Stroop (incongruent–congruent)-related BOLD activation

Direction	Lobe	Side	Brain area	Brodmann area	Cluster size (mm ³)	MNI (x, y, z)	Z max
Abstinent>satiated	Frontal	R	Middle frontal gyrus	9	656	36, 30, 26	3.32
	Limbic	R	rostral ACC	32	720	4, 36, −8	3.34
Satiated>abstinent		none					

Table 2
Regression analyses of changes scores of negative affect on brain activation (abstinence-satiated)

Direction of relationship	Lobe	Side	Brain area	Brodmann area	Cluster size (mm ³)	MNI (x, y, z)	Z (max)
Regression analyses of SJ negative affect change scores (abstinence-satiated) on brain activation to negative-neutral view trials							
[+]			none				
[-]	Frontal	R	Superior frontal gyrus	10	1,712	20, 62, 4	4.17
	Frontal	R	Middle frontal gyrus	9	2,216	36, 30, 34	3.12
	Frontal	L	Middle frontal gyrus	10	864	-34, 44, 20	3.46
	Limbic	R	dorsal Anterior Cingulate	23	1,192	8, -24, 32	3.99
	Parietal	R	Supramarginal gyrus	2	1,248	54, -26, 36	3.98
Regression analyses of SJ negative affect change scores (abstinence-satiated) on Stroop-BOLD signal							
Negative emotional distractor trials							
[+]	Frontal	R	Inferior frontal gyrus	46	848	56, 30, 10	3.71
	Frontal	L	Middle frontal gyrus	9	800	-54, 14, 36	3.91
[-]			none				
Neutral emotional distractor Trials							
[+]			none				
[-]			none				