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Smoking Abstinence and Depressive Symptoms Modulate the Executive Control System During Emotional Information Processing

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Abstract

Background—Smoking abstinence disrupts affective and cognitive processes. In this study, functional magnetic resonance imaging (fMRI) was used to investigate the effects of smoking abstinence on emotional information processing (EIP).

Methods—Smokers (n=17) and nonsmokers (n=18) underwent fMRI while performing an emotional distractor oddball task in which rare targets were presented following negative and neutral task-irrelevant distractors. Smokers completed two sessions: once following 24-hr abstinence and once while satiated. The abstinent versus satiated states were compared by evaluating responses to distractor images and to targets following each distractor valence within frontal executive and limbic brain regions. Regression analyses were done to investigate whether self-reported negative affect influences brain response to images and targets. Exploratory regression analyses examined relations between baseline depressive symptoms and smoking state on brain function.

Results—Smoking state affected response to target detection in the right inferior frontal gyrus (IFG). During satiety, activation was greater in response to targets following negative versus neutral distractors; following abstinence, the reverse was observed. Withdrawal-related negative affect was associated with right insula activation to negative images. Finally, depression symptoms were associated with abstinence-induced hypoactive response to negative emotional distractors and task-relevant targets following negative distractors in frontal brain regions.

Conclusions—Neural processes related to novelty detection/attention in the right IFG may be disrupted by smoking abstinence and negative stimuli. Reactivity to emotional stimuli and the interfering effects on cognition are moderated by the magnitude of smoking state-dependent negative affect and baseline depressive symptoms.

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Keywords

affect; cognition; depression; emotion; fMRI; smoking

Introduction

Smoking cessation is associated with significant increases in negative affective mood states such as anxiety, depression, and irritability (APA, 2000; Baker *et al*, 2004). Elevated negative affect can persist for more than one month following cessation (Gilbert *et al*, 1999; Gilbert *et al*, 2002) and is a significant risk factor for smoking relapse (Ferguson and Shiffman, 2010). While the precise relationship between negative affect and cigarette smoking remains unclear, negative affect states are generally known to bias attention to negatively valenced information (Beck *et al*, 1979; Broadbent and Broadbent, 1988; Dichter *et al*, 2009; MacLeod *et al*, 1986; Phillips *et al*, 2003) and disrupt various forms of cognition, such as maintaining attention to task-relevant targets (Dai and Feng, 2011).

It has been posited that smokers become dependent on nicotine in part because it biases attention away from negative stimuli and thus reduces negative affect (Gilbert, 1995, 1997; Gilbert *et al*, 2000). Consistent with this model, nicotine withdrawal potentiates the startle response (Cinciripini *et al*, 2006) and amplifies electrocortical responses (Gilbert *et al*, 2004) to negative emotional stimuli, and reduces the hedonic rating of positive stimuli (Dawkins *et al*, 2007). Moreover, data from a small number of studies suggest nicotine withdrawal results in greater interference from emotional stimuli during task-relevant processes (Drobes *et al*, 2006; Gilbert *et al*, 2008; Gilbert *et al*, 2007; Powell *et al*, 2002; Rzetelny *et al*, 2008). Despite these findings, the neural mechanisms underlying the interaction between smoking abstinence and emotion–cognition remain poorly characterized. Therefore, the goal of the present study was to examine the effects of nicotine withdrawal on two aspects of emotion—reactivity to emotional cues (i.e. distractors) and the effects of distractors on subsequent task-related cognition.

Neural Substrates of Emotional Information Processing (EIP)

A dominant neurobiological model posits that EIP is 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). Moreover, the interaction between neural systems for executive and emotional processes is altered in patients with major depressive disorder (MDD) (Mayberg, 1997; Wang *et al*, 2008c), schizophrenia (Park *et al*, 2008; Pauly *et al*, 2008), and post-traumatic stress disorder (Morey *et al*, 2008).

Evidence also suggests the neural circuitry subserving cognition and EIP 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*, 2010; 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 nicotine modulates non–task-related ventral affective circuitry (e.g. cerebral blood flow)

(Rose *et al*, 2003; Stein *et al*, 1998), the neurocognitive basis of the effects of smoking abstinence on processing emotional information is unknown.

Current Study

We examined EIP in dependent smokers who either smoked as usual or abstained for 24 hours. In addition, we examined the relationship between withdrawal-induced negative affect and brain responses. Furthermore, given previous data suggesting a relationship between high depression symptoms and greater withdrawal-induced negative affect (Gilbert *et al*, 1999) and worse cessation outcomes (Cook *et al*, 2010; Leventhal *et al*, 2009; Nieva *et al*, 2010), we performed an exploratory analysis of the effects of baseline depression symptoms on EIP. We hypothesized that smoking abstinence, as compared with satiety, would increase brain response to negative emotional distractor images in ventral-affective circuitry. Furthermore, we predicted that negative emotional distractor images would disrupt frontal executive function in response to subsequent target detection.

Materials and Methods

Participants

Thirty-six participants (18 smokers and 18 nonsmokers) from the community were enrolled in the study. To be enrolled, smokers had to report smoking ≥ 10 cigarettes per day for at least 2 years, have an afternoon expired-air carbon monoxide (CO) level > 10 ppm, be right-handed, be free of serious health problems (e.g., hypertension), have no history of psychiatric disorders, be free of medications altering CNS functioning, have a negative urinalysis for illicit drug use, not have any conditions making MRI research unsafe, and, if female, have a negative serum pregnancy test. The same inclusion/exclusion criteria were applied to nonsmokers except they had to report 1) having smoked < 50 cigarettes in their lifetime, 2) not having smoked at all in the last 6 months, and 3) have an afternoon expired CO concentration of ≤ 5 ppm. The nonsmoker group was age- and sex-matched to the smoker group.

Procedures

After screening, eligible participants completed one training session during which they practiced the experimental task and were placed in a mock scanner to habituate to the scanning environment. Following training, smokers completed two fMRI sessions: once while smoking satiated and once 24 hours into a 48-hour abstinence period. The abstinence period included 24 hours of abstinence following the session to minimize possible confounds from participants anticipating smoking immediately after the scanner session. Order of condition was randomly assigned and counterbalanced. The two sessions were separated by a minimum of 3 days and a maximum of 14 days. Session compliance was biochemically verified at the beginning of each scan and at a quit check visit that was conducted 24 hours following the abstinent condition scan. Nonsmoker participants completed one fMRI session under the same protocol excluding the smoking manipulation.

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 was assessed with the Center for Epidemiological Studies-Depression (CESD) scale (Radloff, 1977), and nicotine dependence was assessed with the Fagerström Test of Nicotine Dependence (FTND) (Heatherton *et al*, 1991). State-dependent mood and

craving were measured at the beginning of each session using the Shiffman Jarvik Scale (Shiffman and Jarvik, 1976).

fMRI Task

The emotional distractor oddball task (EDOT) used in the present study (Figure 1) is well-validated in fMRI studies of EIP in healthy controls (Wang *et al*, 2008a; Wang *et al*, 2006; Yamasaki *et al*, 2002) and depressed patients (Wang *et al*, 2008b; Wang *et al*, 2008c). Standard stimuli consisted of squares of varying sizes and colors (n=832). Infrequent target stimuli (n=64) consisted of circles of varying sizes and colors. Participants were instructed to respond with a button press upon detecting target stimuli. Distractor stimuli were either negative (n=48) or neutral (n=48) valence images selected from the International Affective Picture System (IAPS; University of Florida, Gainesville, FL) (Lang *et al*, 1997) [Supplementary Table 1] and from those acquired and validated within our laboratory. Negative image themes included human violence, mutilation, and disease, whereas neutral image themes represented ordinary activities. Distractor images across each valence were selected by the study team on the basis of mean luminance, chromatic features, and overall scene complexity. Distractors were selected on the basis of 9-point arousal and valence scales used in the IAPS. Valence and arousal ratings for chosen images did not overlap across stimulus categories. Participants performed the EDOT (run duration = 8.5 min) twice during the experimental session, with a 5-minute break between the first and second run to minimize task fatigue and allow the participant to communicate with the researcher.

fMRI Methods

A 3T General Electric Signa EXCITE HD scanner (Milwaukee, WI) equipped with 40 mT/m gradients was used for image acquisition. At the start of each fMRI session, a high-resolution, three-dimensional, fast-spoiled gradient-recalled echo (3D-FSPGR) anatomical sequence was collected (FOV = 25.6 cm, matrix = 256^2 , flip angle = 12° , 166 slices, slice thickness = 1 mm). Blood-oxygenation-level-dependent (BOLD) functional images were collected for 34 contiguous slices (4 mm thick) parallel to the horizontal plane connecting the anterior and posterior commissures. A gradient-recalled inward spiral pulse imaging sequence was used (34 slices, TR = 1500 ms, TE = 30 ms, FOV = 24 cm, matrix = 64×64 , flip angle = 60° , slice thickness = 4 mm, resulting in $3.75 \times 3.75 \times 4$ mm voxels). Preprocessing was conducted using statistical parametric mapping software (SPM8; Wellcome Department of Imaging Neuroscience, London) to remove noise and artifact. 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 by using rigid-body rotation and translation (Friston *et al*, 1994). Each participant's data was 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.

Statistical Analyses

The goals of the analyses were to 1) identify effects of smoking condition (abstinent or satiated) on brain activation in response to emotional distractors (negative or neutral); 2) identify effects of smoking condition and emotional distractors on neural activation during target detection; and 3) compare activation between smokers and nonsmokers. Smoker's data from each session was entered into a first-level, whole-brain analysis using the General Linear Model (Friston *et al*, 1994) to examine activation in response to negative distractors, neutral distractors, targets following negative distractors, and targets following neutral distractors. Subjects detected all targets, therefore all target events were modeled. For the first-level model, each event type was modeled as a delta regressor at the onset of the event and convolved with a canonical hemodynamic response function. Motion parameters generated during realignment were included as nuisance covariates, and a high-pass filter

(128 seconds) was applied to remove slow signal drift. Regressors for each task event during each condition for each participant were then entered into a 2 (Condition: satiated, abstinent) $\times$ 2 (Category: distractor, target) $\times$ 2 (Valence: negative, neutral) random effects ANOVA, where effects were separately evaluated for distractors and targets. Statistical images were first thresholded 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; Ochsner *et al*, 2004; Wang *et al*, 2008c; Yamasaki *et al*, 2002). These included bilateral posterior, dorsal and paracingulate cortices; inferior, middle and superior frontal gyri; inferior parietal lobule (IPL); insula and amygdala. These ROI's were obtained from automated anatomical labeling (AAL) (Tzourio-Mazoyer *et al*, 2002) in Marina (Walter *et al*, 2003).

To further evaluate interactions and effects among smokers, percent signal change values were extracted from significant clusters using MarsBar (Brett *et al*, 2002), and the resulting values analyzed in SPSS. Further, the same clusters were applied to nonsmoker data, which were used to inform whether abstinent versus satiated brain responses among smokers represented a departure from normal function.

To examine the relationship between abstinence-induced negative affect and EIP, a contrast image (negative > neutral) was created for each event category (i.e. distractor, target after distractor) at the first level. Relationships between negative affect and each event category were examined separately by random-effects multiple regression analyses using the self-reported values from the Shiffman-Jarvik negative affect scale. In order to control for differences in state-dependent negative affect due to individual differences in trait negative affect, baseline CESD score was included as a covariate. Positive and negative correlations were explored.

Furthermore, regression analyses were performed separately for distractors and targets to explore the possible moderating effects of depression symptoms on EIP. Images examining abstinence-induced differences for the Neg-Neut contrast ([Abst: Neg-Neut] - [Sat: Neg-Neut]) were created for each event category (distractor or target) for each participant and included in random-effects multiple regression analyses using baseline CESD score as a covariate. Positive and negative correlations were explored. In all analyses, voxels were considered significant if they passed a statistical threshold of $p < .005$, uncorrected, and were part of a 432- μ L cluster of contiguous significant voxels, resulting in a cluster-corrected $p < .05$. Cluster size for the comparisons was determined through Monte Carlo simulations (Ward, 2000).

Finally, we examined the effects of smoking abstinence on behavioral performance on the EDOT and self-report withdrawal using paired t-tests and ANOVAs. Differences between smokers and nonsmokers are noted when significant.

Results

Participant Characteristics

Data from one smoker was excluded from analyses because of scanner-related malfunction. Smokers ($n = 17$) and nonsmokers ($n = 18$) had similar demographic characteristics; however, smokers had higher CESD scores at baseline (Table 1).

Biochemical Confirmation of Smoking Status and Abstinence

Significant differences in expired-breath CO concentrations at baseline confirmed smoker versus nonsmoker status ($t = 17$, $p < .001$). Mean (SD) CO levels were 26 (13.4) ppm for smokers and 1.5 (1) ppm for nonsmokers. Among smokers, expired breath CO

concentrations indicated compliance with study requirements. Mean expired CO was 26.2 (13) ppm in the satiated condition and 3.7 (2.9) ppm in the abstinent condition. Mean expired CO 24 hours after the abstinent fMRI session was 2.4 (1.2) ppm.

Self-Report Data

As expected, mean (SD) Shiffman-Jarvik (SJ) withdrawal scale scores indicated that craving was greater during the abstinent (5.4 [1.3]) versus satiated condition (4.6 [1.5]) ($t[16] = 2.2$, $p = .04$). Mean negative affect was greater during the abstinent (3.8 [1.1]) versus satiated condition (3.0 [1.0]) ($t[16] = 2.7$, $p = .01$). Exploratory analyses were conducted to evaluate correlations between baseline CESD scores and self-reported craving and negative affect on each day. No significant correlations were found between CESD score and SJ craving or SJ negative affect scores on either day (p values $> .1$).

Behavioral Data

No significant differences in mean reaction time (RT) were observed between satiated smokers (464.9 [44.4] ms), abstinent smokers (474.0 [47.6] ms), or nonsmokers (476.4 [28.9] ms) (all F values < 2 , p values $> .2$). Performance did not vary as a function of distractor type ($F < 2$, $p > .2$). No significant differences in error rates were found between smoking condition within smokers, or between groups, all p 's $> .8$. Exploratory analyses were conducted to evaluate correlations between baseline CESD scores and task performance on each day. No significant correlations were found between CESD score and RT (p values $> .3$).

fMRI Results

Activation in response to distractors—For each smoking condition, activation was higher in response to negative versus neutral distractors in bilateral inferior frontal gyrus (IFG), amygdala and left precentral gyrus (Table S2). In contrast, activation to neutral distractors was greater bilaterally in right superior and left middle frontal gyri and right inferior parietal lobule. Activation was higher in response to distractors, regardless of valence, in the abstinent versus satiated condition in IFG, dorsal anterior cingulate cortex (ACC) and insula, all localized within the right hemisphere (Table S2). By contrast, no significant clusters were observed for satiety greater than abstinence. No interactions of condition and distractor valence were observed.

Activation in response to targets—For each smoking condition, activation was higher in response to targets following negative distractors versus neutral distractors in the left IFG (Brodmann area [BA] 45) (Table S3). By contrast, activation was greater to targets following neutral distractors in the right IFG (BA47) and bilateral anterior cingulate gyri (BA 24) (Table S3). Activation to targets, regardless of distractor valence, was higher during satiety versus abstinence in the right middle temporal gyrus (BA 38). Activation during abstinence was greater in the bilateral middle insula (BA 13) and right anterior insula (BA 47) (Table S3).

Significant smoking condition and distractor valence interaction was found in right IFG (BA 46) (Table 2). The pattern of activation was characterized by higher activation during satiety to targets following negative versus neutral distractors; following abstinence, higher activation occurred following neutral versus negative distractors (Figure 2). Furthermore, the pattern of brain response in satiated smokers was highly similar to that found in the nonsmoker control group.

Regression analyses of negative affect—During abstinence, activation to distractors was positively correlated with negative affect in right anterior insular and inferior frontal

gyrus (BA 47), no negative correlations were found (Table 3). During satiety, positive correlation was found in left IFG (BA 46), no negative correlations were found. For target stimuli, negative correlations were observed during satiety in left middle frontal gyrus (BA's 10), and right dorsal anterior cingulate cortex, no other correlations were found (Table 3).

Regression analyses of baseline depression symptoms—Activation to emotional distractors (relative to neutral) was negatively correlated with CESD in bilateral IFG and MFG (Table 4, Figure 3). No positive correlations between emotional distractors and CESD were found.

Activation to targets following emotional stimuli (relative to neutral) were negatively correlated with CESD in bilateral MFG and superior frontal gyrus (SFG). No positive correlations between emotional targets and CESD were found (Table 4, Figure 4).

Discussion

In this study, an event-related imaging paradigm was used to evaluate the neurocognitive effects of smoking abstinence on EIP during an emotional distractor oddball task. Smoking state (abstinence vs. satiated), pre-scan negative affect, and baseline depression symptoms influenced the emotional distraction effect on attentional targets in the executive control system. Smokers who abstained for 24 hours, as compared to when satiated, had increased activation to targets following neutral distractors in the right IFG, but decreased activation to targets following negative distractors in these same regions. Pre-scan negative affect was positively associated with brain response to negatively valenced images in brain regions associated with affect or drug craving (e.g. insula). In contrast, negative affect was negatively associated with brain response to targets following negative distractors in frontal executive systems (e.g. dACC). Activation by distractor images varied on the basis of severity of baseline depressive symptoms in bilateral dlPFC (i.e. IFG, MFG). In these regions, participants with low depressive symptoms had higher activation during smoking abstinence versus satiety, whereas participants with high depressive scores had higher activation during satiety versus abstinence. The pattern of brain activation among satiated smokers with low CESD scores resembled the pattern for nonsmoker control subjects in each contrast. These findings support the hypothesis that smoking abstinence modulates EIP by increasing susceptibility to distraction from emotional stimuli during executive functioning. Furthermore, these findings shed light on the relationship between depression symptomatology and risk for nicotine dependence and smoking relapse.

Smoking Withdrawal and EIP

In both satiated smokers and nonsmokers, negative emotional distractors increased BOLD responses in right IFG during subsequent target detection; in abstinent smokers, negative distractors decreased responses in this region. The finding that smoking abstinence disrupts neural processes related to executive function in the dlPFC is consistent with existing neurocognitive literature on attention processes.

The IFG is part of a network involved in social–emotional processes (Carr *et al*, 2003; Hooker *et al*, 2010), and the right IFG has a role in novelty detection (Strange *et al*, 2000). Neural response in this region increases as a function of attentional load (Hampshire *et al*, 2009). Furthermore, the magnitude of right IFG response has been associated with resolving emotional distraction during tasks such as target detection (Wang *et al*, 2008c), which explains the increased right IFG activation to targets following negative distractors in both satiated smokers and nonsmokers in this study.

The finding that abstinent smokers exhibit the opposite pattern, as compared to when satiated, whereby activation to targets is increased following neutral versus negative distractors is significant for two primary reasons. First, increased attention-related neural function in IFG may be an important neural marker of attention deficiency among smokers in withdrawal (Hahn *et al*, 2009; Kozink *et al*, 2010; Thiel and Fink, 2008; Froeliger *et al.*, in press). Second, decreased attention-related neural function in IFG following negative emotional distractors suggests abstinence disrupts the allocation of frontal attentional resources during EIP. In other words, abstinent smokers attention to task-relevant demands may be disrupted by negative emotional stimuli, and BOLD response in IFG may be an important neural marker of the interfering effects of emotion on cognition following quitting smoking. The attention modulating effects of negative emotional information in abstinent smokers is consistent with prior research demonstrating that smoking abstinence results in increased frontal processing negativity—an ERP measure of attention (Näätänen, 1982) to negative but not neutral or positive images (Gilbert *et al*, 2004). Furthermore, these findings may be indicative of a process in which abstinence potentiates the function of frontal control mechanisms (i.e. IFG) that are required to resolve conflict in the context of cognitive demands. This hypothesis is consistent with prior studies of smokers (Gilbert *et al*, 2007). In Gilbert *et al.* (Gilbert *et al*, 2008), abstinent smokers displayed attenuated P3 response to targets following negative but not neutral distractors and following receipt of a nicotine patch. However, given that smoking abstinence has been shown to result in an attentional bias to negative emotional information, an alternative explanation is that negative emotional stimuli may serve to prime attention in abstinent smokers. Future work evaluating the relationship between abstinence-induced modulation of frontal–executive function during EIP and task performance is needed to better understand the exact nature of these effects.

The Influence of State-Dependent Negative Affect and Emotional Reactivity

In this study, greater withdrawal-induced negative affect was associated with brain response to negative images in right anterior insula. The insula is known to be involved in interoception (Craig, 2002), is thought to play an important role in drug craving (Naqvi and Bechara, 2010; Naqvi *et al*, 2007), and among smokers, is associated with attentional bias to smoking cues (Luijten *et al*, In Press). Affective states guide attention to mood-congruent emotional stimuli (Koster *et al*, 2005; MacLeod *et al*, 1986), and our data suggest that the insula may play an important role in withdrawal-induced attention to negative emotional information.

The severity of self-reported negative affect during satiety was negatively correlated with neural response to targets following negative distractors in executive brain regions, including the dlPFC and dACC. Negative EIP interferes with ongoing and subsequent cognitive processes (LeDoux, 1995, 2000), and individuals with mood disorders (e.g. MDD) experience both greater bias to negative stimuli (Erickson *et al*, 2005) and more interference on cognition (Erickson *et al*, 2005). The dACC is known to be critical in conflict resolution (Bush *et al*, 2000). Moreover, 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*, 2009). These findings suggest that the interfering effects of negative EIP on attention processes may persist among smokers who experience elevated state negative affect during smoking satiety.

Baseline Depression Interacts with Smoking State to Modulate EIP

In an exploratory analysis of relationships between baseline depressive symptoms and smoking condition, brain response to negative emotional images was varied on the basis of depressive symptoms at baseline and smoking condition. We found that the number of depressive symptoms reported at baseline corresponded with the magnitude of abstinence-

induced attenuation of brain activation to emotional stimuli in frontal regions (i.e. IFG, MFG). The finding that smokers with lower depression symptoms are more reactive to emotional stimuli following abstinence is consistent with a model of withdrawal increasing reactivity to negative emotional information (Gilbert, 1995; Gilbert *et al*, 2000). Moreover, the finding that individuals with higher baseline depression are less reactive to negative emotional stimuli during smoking abstinence is consistent with the broader depression literature reporting that individuals with MDD have less dlPFC activation in response to negative emotional stimuli (Hooley *et al*, 2005; Siegle *et al*, 2002; Siegle *et al*, 2007). Though speculative, these data suggest that for those with elevated depressive symptoms, smoking may normalize executive brain function during EIP.

During abstinence from smoking, baseline depression symptoms were associated with reduced neural activation to task-relevant targets following negative distractors in brain regions that play a role in inhibiting emotional distraction (i.e. IFG) (Dolcos *et al*, 2006) and in detecting novel stimuli (i.e. MFG) (Yamaguchi *et al*, 2004). In a prior study of MDD patients performing under the same task paradigm as in this study, activation among these regions in response to targets was reduced in MDD patients versus controls (Wang *et al*, 2008c). These findings suggest that baseline depression levels moderate abstinence-related disruption in EIP and the subsequent emotional distracting effects on cognition. These findings may help shed light on the relations between smoking-depression (Gilbert *et al*, 1998) and relapse vulnerability.

Limitations

Participants' behavioral performance on the experimental task was near ceiling, which means there is a possibility that important smoking-state or group-specific differences in motivation-dependent, task-related activations were not observed. Moreover, studies of the effects of smoking abstinence on cognition have revealed cognitive load-dependent effects, for example, conflict resolution (Domier *et al*, 2007). More difficult tasks could have elucidated different effects of emotional distractors on cognition.

In this study, nonsmokers were included as a reference point by which to compare brain function in smokers when drug state was manipulated. While the control group was closely matched on demographic variables, they were not matched on CESD scores. Therefore, the current study was unable to explore correlations between depression scores and smoking history (i.e. smoker nonsmoker differences). In addition, because nonsmokers were only scanned once, a full factorial analysis between subjects was not possible.

Finally, smoking state was necessarily unblinded, and we did not include nicotine-only or smoking (without nicotine) conditions. In addition, the effects of either nicotine (separate from smoking) (Perkins *et al*, 2010), or smoking on positive emotional stimuli were not explored.

Conclusions

To our knowledge this is the first study to identify the functional neuroanatomical correlates of smoking abstinence on EIP. We conclude that neural processes related to executive function in dlPFC are modulated by the interaction between smoking state and the emotional valence of distracting stimuli. Furthermore, baseline depressive symptoms moderate the effects of smoking abstinence during EIP in frontal executive brain regions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Each stimulus was presented for 1000 ms with a 200 ms inter-stimulus interval. The interval between distractor stimuli and target stimuli was randomly varied between 5 and 11 seconds in order to minimize distractors serving as predictors of an upcoming target stimulus. Furthermore, 33% of distractors occurred in the absence of a subsequent target. This method eliminated predictability of target onsets when used in conjunction with varying distractor/target SOA. Each run of the EDOT contained 24 negative distractors, 24 neutral distractors and 32 targets with an equal number following each distractor valence.

Bold response as measured by % signal change to targets following either negative or neutral distractors.

Figure 2.

Smoking condition $\times$ emotional valence interaction for task targets

Bold response as measured by % signal change to targets following either negative or neutral distractors.

Right dlPFC (44, 42, 10)

Figure 3.
Regression analyses of baseline depression symptoms on brain activation to emotional distractors.

Figure 4.
Regression analyses of baseline depression symptoms on brain activation to targets

Table 1**Participant Baseline Demographics and Characteristics**

	Smokers n = 17	Nonsmokers n = 18	Statistic	<i>p</i> (2-tailed)
% Female	55%	50%	.03 ^a	NS
Age, mean (SD) yr	31.9 (8.0)	30.1 (8.1)	.50 ^b	NS
Education, mean (SD) yr	14.5 (2.2)	15.5 (2.6)	-1.30 ^b	NS
Race				
Asian	2	1		
Black	4	7		
Caucasian	11	10		
Baseline				
CESD score, mean (SD)	13.4 (10.7)	5.2 (6.2)	2.8 ^b	.009
FTND score, mean (SD)	5.1 (2)			
Years smoking, mean (SD)	14.0 (7.9)			
Daily no. cigarettes, mean (SD)	16.9 (4.9)			
Exhaled CO, mean (SD) ppm	26.0 (13.4)	1.5 (1)	17 ^b	<.000

CESD, Center for Epidemiological Studies-Depression; FTND, Fagerström Test of Nicotine Dependence; NS, not significant; SD, standard deviation

^a χ^2

^b _t

Table 2
Brain areas where a Smoking Condition × Emotional Valence interaction was observed^{ab}

State × Valence Interactions				
Contrast	Side	Brain Area	Brodmann Area	Cluster Size (mm ³) MNI x,y,z z
<i>Distractors: State × Valence</i>		<i>none</i>		
<i>Targets: State × Valence</i>	R	Inferior Frontal Gyrus	46	456 48 18 24 2.87

^a As measured by BOLD fMRI
^b Nicotine dependent participants
BA, Brodmann area; MNI, Montreal Neurological Institute coordinates.

Table 3

Brain areas for negative-neutral images as measured by BOLD-fMRI that are significantly correlated with self-report negative affect.^{ab}

State	Direction	Side	Brain Area	Brodmann Area	Cluster Size (mm ³)	MNI x,y,z	Z
<u>Abstinent</u>							
Distractors [Neg-Neut]	Positive	R	Anterior Insula	47	1432	38 16 -14	3.8
	Negative		None				
<u>Satiated</u>							
	Positive	L	IFG	46	456	-52 30 14	3.45
	Negative		None				

State	Direction	Side	Brain Area	Brodmann Area	Cluster Size (mm ³)	MNI x,y,z	Z
<u>Abstinent</u>							
Targets [Neg-Neut]	Positive		None				
	Negative		None				
<u>Satiated</u>							
	Positive		None				
	Negative	L	Middle Frontal Gyrus	10	448	-30 52 4	2.93
		R	Cingulate Gyrus	24	472	2 2 32	3.39

^a As measured by BOLD-fMRI

^b Nicotine dependent participants

BA, Brodmann area; IFG, inferior frontal gyrus; MNI, Montreal Neurological Institute coordinates, STG, superior temporal gyrus

Table 4
Regression analyses of baseline depression symptoms on brain activation to distractors and targets.^{abc}

	Direction	Lobe	Side	Brain Area	Brodmann Area	Cluster Size (mm ³)	MNI x,y,z	Z (max)	R ²
Distractors	Positive			None					
	Negative	Frontal	R	Middle Frontal Gyrus	46	1128	44 42 10	3.71	.61

	Direction	Lobe	Side	Brain Area	Brodmann Area	Cluster Size (mm ³)	MNI x,y,z	Z (max)	R ²
Targets	Positive			None					
	Negative	Frontal	L	Middle Frontal Gyrus	6	496	-34 6 62	3.34	.49

^a As measured by BOLD-fMRI
^b Nicotine dependent participants
^c Double subtraction: Abstinent > Satiated contrast for negative-neutral.
MNI, Montreal Neurological Institute coordinates