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Smoking Reduces Conflict-Related Anterior Cingulate Activity in Abstinent Cigarette Smokers Performing a Stroop Task

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Prior research suggests that abrupt initiation of abstinence from cigarette smoking reduces neural cognitive efficiency. When cognitive efficiency is high, processing speed and accuracy are maximized with minimal allocation of cognitive resources. The study presented here tested the effects of resumption of smoking on cognitive response conflict after overnight abstinence from smoking, hypothesizing that smoking would enhance cognitive efficiency. Twenty paid research volunteers who were chronic cigarette smokers abstained from smoking overnight (>12 h) before undergoing fMRI while performing a color-word Stroop task during two separate test sessions: one that did not include smoking before testing and another one that did. Statistical analyses were performed by modeling the Stroop effect (incongruent >congruent) BOLD response within a collection of *a priori* regions of interest that have consistently been associated with cognitive control. Behavioral assessment alone did not reveal any significant differences in the Stroop effect between the two sessions. BOLD activations, however, indicated that in the right anterior cingulate cortex (ACC), smokers had significantly less task-related activity following smoking ($p<0.02$). In contrast, the right middle frontal gyrus exhibited significantly greater activity after smoking as compared to the no-smoking session ($p<0.003$). Exaggerated neural activity in the ACC during nicotine withdrawal may reflect a compensatory mechanism by which cognitive control networks expend excessive energy to support selective attention processes. Resumption of smoking may enhance cognitive control in smokers, involving a reduction in ACC response conflict activity together with improvement in conflict resolution involving the dorsolateral prefrontal cortex.

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INTRODUCTION

While most cigarette smokers endorse the desire to quit, it is estimated that only 14–49% will achieve full abstinence after 6 months (Holmes *et al*, 2004; Hughes *et al*, 1999; Hurt *et al*, 1997; Jorenby *et al*, 1999; Killen *et al*, 2000), with reported successful abstinence rates after 12 months of roughly 12% (Breitling *et al*, 2009). Relapse to smoking in part reflects withdrawal, which includes difficulty concentrating (Heishman, 1999; Newhouse *et al*, 2004) and other problems with cognitive functioning (Hatsukami *et al*, 1989; Parrott and Kaye, 1999; Powell *et al*, 2002; Pritchard *et al*, 1992; Rusted *et al*, 2000; Shiffman *et al*, 1995), all of which can be reversed by the re-initiation of smoking. Previous fMRI research, using a Stroop paradigm, has also demonstrated that even after only a brief period of abstinence (45–60 min), smokers show greater task-related neural activity than after cigarette smoking (Xu *et al*, 2007). We have also previously examined nicotine-dependent individuals while they performed the N-Back working memory task under both *ad libitum* smoking (<1.5 h abstinence) and overnight abstinence (⩾14 h abstinence) conditions (Xu *et al*, 2005), observing higher task-related neural activity in the left dorsolateral prefrontal cortex (DLPFC) following abstinence as compared with smoking. These effects associated with abstinence from smoking may reflect compensatory and adaptive neural functioning in order to cope with the effects of nicotine withdrawal on cognitive control, the implications of which may be an increased susceptibility to smoking relapse (Al'Absi *et al*, 2002; Domier *et al*, 2007; Snyder *et al*, 1989).

Effective everyday mental functioning requires a level of cognitive control, whereby cognition is protected from environmental response conflicts. The neural mechanisms

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by which the brain detects cognitive conflict have largely been established in healthy subjects, with consistent involvement of the anterior cingulate cortex (ACC) (Botvinick *et al*, 2004; Bush *et al*, 2000; Ridderinkhof *et al*, 2004). It has been suggested that when conflict is detected in the ACC, a cognitive control system located in the DLPFC is alerted, and subsequently engages in resolving conflict. The ability to monitor one's behavior within a certain environment during acute drug abstinence may be especially important when there is a need to detect conflicting circumstances and resolve them quickly, especially when environmental stimuli might precipitate drug relapse (Garavan and Stout, 2005). Therefore, examining the behavioral and neural responses to environmental response conflict and its resolution during acute abstinence from smoking may elucidate abnormalities in conflict adaptation that contribute to defective cognitive processing in addiction, and which may contribute to smoking relapse.

The present study aimed to extend knowledge on the neural basis of cognitive response conflict and resolution in individuals who suffer from nicotine addiction. Specifically, we aimed to clarify the effect of the resumption of smoking on cognitive response conflict and resolution in abstinent smokers. Performance- and task-related brain activity of research participants, who were regular smokers but abstained from smoking overnight (>12 h) and performed a color-word Stroop paradigm during fMRI, was assessed during two separate test sessions: one that did not include smoking before testing and another one that did. Following observations of greater task-related neural activity associated with abstinence from smoking as compared with after smoking (Xu *et al*, 2005; Xu *et al*, 2007), we hypothesized that smokers would have worse performance and greater conflict-related ACC neural activity when they were nicotine-abstinent, consistent with compromised functional efficiency during cognitive control. We also predicted that following smoking, there would be improvement in performance and conflict resolution, associated with a reduction in ACC activity, concomitant with increased neural functioning in the DLPFC.

MATERIALS AND METHODS

Participants

Twenty participants (13 women), 18–55 years of age (mean ± SE: 37.4 ± 10.6 years), who reported smoking $\geqslant$15 cigarettes per day (mean ± SE: 19.3 ± 4.4) for 2 years (mean pack–years ± SE: 18.2 ± 16.4), completed the study. Recruited through flyers and newspaper advertisements, volunteers who passed a telephone screening were invited to continue in-person. After receiving a detailed explanation of the study, qualified participants who agreed to continue, provided written informed consent, as approved by the UCLA Institutional Review Board.

During screening, recent smoking was verified by carbon monoxide (CO) levels in expired air of $\geqslant$10 ppm (Micro-smokerlyzer; Bedfont Scientific Ltd, Kent, UK) and presence of urinary cotinine (Accutest NicAlert strips; JANT Pharmacal Corporation, Encino, CA, USA). The participants also completed questionnaires covering demographic, medical, psychiatric, and smoking histories. These included the Shipley Institute of Living Scale (Zachary, 1986), Wender Utah Rating Scale (Ward *et al*, 1993), Beck Depression Inventory (Beck *et al*, 1996), and Fagerström Test for Nicotine Dependence (Heatherton *et al*, 1991).

English language fluency and right-handedness, as indicated by a score >40 on the Edinburgh Handedness Questionnaire (Oldfield, 1971), were inclusion requirements. English language proficiency was tested using the Verbal Fluency Test (scores $\leqslant$10 exclusionary) for those participants whose first language was not English, and intelligence was assessed using the Shipley Institute for Living Scale (scores $\leqslant$85 exclusionary). Other exclusion criteria included current use of any medications that affect cognitive functioning, prior hospitalization for psychiatric illness, and history of head trauma involving loss of consciousness and/or requiring hospitalization. Psychiatric diagnoses were determined using the Structured Clinical Interview for DSM-IV to exclude participants with current psychiatric disorders (other than nicotine dependence). Detailed drug use data were obtained using the Addiction Severity Index (McLellan *et al*, 1992). Any participant with a significant drug use history was excluded from study participation. Participants who reported light use of marijuana (<1 joint per week) were allowed to participate, but were instructed to avoid marijuana for the 48 h prior to testing.

Tests of drug abuse were conducted by urine screening for cocaine, methamphetamine, opioids, Δ^9-tetrahydrocannabinol, and benzodiazepines. Any positive drug test resulted in exclusion from study participation.

Experimental Design

Each participant completed two counterbalanced fMRI test sessions (between 1400 and 1700 h), each preceded by overnight abstinence from smoking (>12 h). During each test session, participants underwent fMRI while performing the Stroop Color-Word Interference Task (see below). One session required continued abstinence before fMRI. In the other, participants each smoked two standard cigarettes, which delivered 0.59 ± 0.06 mg nicotine each (9.0 ± 1.0 mg tar, total dose ~1.2 mg nicotine) (Becker *et al*, 2008) (Quest 1; Vector Tobacco Inc., Durham, NC, USA). Before fMRI, all participants endorsed having maintained overnight smoking abstinence, which was verified by CO content in exhaled air ($\leqslant$5 ppm). In the session that involved smoking, scanning began approximately 15 min after each participant had smoked the second cigarette.

On scanning days, self-report measures of cigarette craving and nicotine withdrawal were taken three times: (1) at arrival; (2) 10–15 min after completing smoking (immediately before fMRI); and (3) immediately after fMRI (30–35 min after completing smoking). Participants were tested for cigarette craving on the Urge to Smoke (UTS) Scale (Jarvik *et al*, 2000) and for nicotine withdrawal on the Shiffman/Jarvik Withdrawal Scale (SJWS) (Shiffman and Jarvik, 1976). On the SJWS and UTS, we calculated the mean self-report score (from scores immediately before and immediately after fMRI) in order to assess how participants were feeling during the fMRI session. We also did this for recorded CO levels (ppm) in each participant.

Stroop Color-Word Interference Task

Four color words (RED, BLUE, GREEN, and YELLOW) served as the stimuli in congruent (eg, the word RED displayed in red) and incongruent (eg, the word RED displayed in blue) conditions. The stimuli were presented via magnet-compatible VGA goggles (Resonance Technology, Northridge, CA, USA), which have a field view of approximately 20 degrees vertically and 30 degrees horizontally, and display computer images at 800×600 pixel resolution. Words were presented one at a time at the center of the screen in Helvetica style font, size 72.

The study used a block design with congruent, incongruent, and rest blocks, presented over two runs (counterbalanced across subjects). Each run consisted of eight congruent, eight incongruent, and 15 rest blocks, with 12 trials per block. During congruent/incongruent blocks, subjects identified the font color of each stimulus word. Subjects were instructed to respond, as quickly as possible, by pressing a button using their right hand. Buttons were pressed with the right index, middle, ring, and baby fingers, corresponding to red, blue, green, and yellow, respectively. Responses were registered using a magnet-compatible, four-button response box. Participants were trained on the correct finger positions before the first run of the task. During rest blocks, they viewed a fixation cross at the center of the screen. Before each block, instructions ('Identify the Color' or 'Rest') were presented for a 2-s period. Within a block, each stimulus was presented for 1200 ms, with an inter-stimulus interval of 300 ms. Each task block lasted 18 s, and each rest block lasted 9 s. Each run of the task lasted approximately 7 min. Dependent measures for the task were the mean number of errors committed and the mean reaction time (RT) for the congruent and incongruent conditions. Trials in which RTs were $\leqslant 200$ ms or $\geqslant 1500$ ms were excluded from analyses, as they were likely to indicate distraction or loss of attention ($>50\%$ of responses below or above these criteria were incorrect). Only RTs for correct responses were included in the analyses. Errors were rare and occurred in $<5\%$ of overall trials. We calculated the Stroop effect for each subject (incongruent RT−congruent RT) as an index of cognitive response conflict.

Analyses of Behavioral and Self-Report Data

Behavioral analyses for Stroop errors and RT were conducted using a two-condition (congruent and incongruent) $\times$ two-session (no-smoking vs. smoking) linear mixed-models analysis, allowing us to test for an effect of condition, session, and a condition $\times$ session interaction. Between-sessions analyses for the Stroop effect were conducted using a one-way (no-smoking vs. smoking) linear mixed-models analysis.

The self-report measures were analyzed using a two-condition (arrival *vs* immediately before and after fMRI collapsed) $\times$ two-session (no-smoking *vs* smoking) linear mixed-models analysis. In observation of significant condition $\times$ session interactions, follow-up planned comparisons were conducted.

Scanning Parameters

Functional images were acquired with a 3T Siemens Allegra (Erlangen, Germany) head-only MRI scanner. Localizing scans were acquired first to verify the head position and to identify the AC-PC line for the purpose of establishing the acquisition plane. We then acquired a set of T2-weighted, high-resolution, echo-planar anatomical images (26 slices, aligned to AC-PC line, 4 mm thick/1 mm skip, pixel 1.56 mm^2) covering the entire brain volume, to be used for spatial alignment and to help define the location of the BOLD signal. Functional images were acquired using a gradient-echo-planar image (EPI) sequence (TR: 1500 ms; TE: 30 ms, flip angle: 80 degrees; 26 slices; slice thickness 4 mm with a 1.0-mm inter-slice interval; matrix 64×64; in-plane pixel resolution: 3.12 mm^2). Two hundred eighty-two entire brain volumes (26 axial slices) were collected during each run of the Stroop task.

fMRI Data Analyses

Data were pre-processed using FEAT (fMRI Expert Analysis Tool) from the FMRIB Software Library (www.fmrib.ox.ac.uk/fsl). Pre-statistical processing was as follows: motion correction using the FMRIB's Linear Image Registration Tool (MCFLIRT) (Jenkinson and Smith, 2001); non-brain removal using Brain Extraction Tool (BET) (Smith, 2002); spatial smoothing with a 6-mm full-width half-maximum Gaussian kernel; mean-based intensity normalization; and non-linear high-pass temporal filtering (Gaussian-weighted least-squares straight line fit, with sigma = 25.0 s). Statistical analysis was performed by modeling the incongruent > congruent contrast (boxcar functions convolved with the hemodynamic response function) as explanatory variables within the context of the general linear model on a voxel-by-voxel basis. *Z* (Gaussianized T/F) statistical images were thresholded using clusters determined by $Z = 2.3$ and corrected cluster significance level of $p = 0.05$. Registration to high-resolution structural images of each individual subject was performed using FLIRT (Jenkinson *et al*, 2002) and all high-resolution structural images were co-registered to standard (Montreal Neurological Institute) space. Higher-level analyses were performed using FLAME (FMRIB's Local Analysis of Mixed Effects) (Beckmann *et al*, 2003; Woolrich *et al*, 2004). Z (Gaussianised T/F) statistical images were first thresholded with a mask containing regions of interest predefined *a priori*. These included the left and right ACC; DLPFC; inferior frontal gyrus (IFG); and posterior cingulate cortex (PCC). These regions were obtained from the Harvard-Oxford cortical structural atlas in FSL and were combined to form the mask. These regions were chosen based on previous findings that the Stroop effect and cognitive control commonly activate these areas (Carter *et al*, 1998; Durston *et al*, 2003; Garavan *et al*, 1999; MacDonald *et al*, 2000; Milham *et al*, 2001; Ullsperger and von Cramon, 2004). Using clusters determined by $Z = 2.3$ and a corrected cluster significance threshold of $p = 0.05$ (Worsley *et al*, 1992), voxel-by-voxel paired *t*-tests (no-smoking *vs* smoking sessions) were then performed as part of this higher-level mixed-effects analysis. Although session order (ie, whether smoking or no-smoking scan occurred first) was randomized across subjects, to determine potential session order effects, we performed an additional analysis using the same statistical model using session order as a covariate of no interest. Results from this model did not

differ from those from the original model; thus, no session order effects were found.

RESULTS

Self-Report Measures and CO Levels

Table 1 shows the effects of overnight abstinence and smoking on cigarette craving and nicotine withdrawal during the two sessions. For UTS scores, there was a significant effect of measurement time ($F = 12.2$, $df = 1, 76$, $p < 0.01$; at arrival > during scan); session ($F = 4.9$, $df = 1, 76$, $p < 0.05$; no-smoking > smoking); and a measurement time × session interaction ($F = 9.8$, $df = 1, 76$, $p < 0.01$). Follow-up planned comparisons for the interaction showed significant difference between the no-smoking and smoking sessions for UTS scores during the scan period ($p < 0.01$). On the craving item of the SJWS, there was a significant effect of measurement time ($F = 11.9$, $df = 1, 76$, $p < 0.01$; at arrival > during scan); no significant effect of session ($F = 3.8$, $df = 1, 76$, $p = 0.06$); but a significant measurement time × session interaction ($F = 8.4$, $df = 1, 76$, $p < 0.01$). Planned comparisons demonstrated a significant difference between the no-smoking and smoking sessions for cigarette craving during the scan period ($p < 0.01$). There was only a significant effect of measurement time for psychological symptoms ($F = 5.6$, $df = 1, 76$, $p < 0.05$; at arrival > during scan), with no other main effects or interactions observed for the physical, sedation or appetite items of the SJWS. Finally, for CO levels (ppm), there was a significant effect of measurement time ($F = 47.8$, $df = 1, 76$, $p < 0.001$; at arrival > during scan); session ($F = 50.6$, $df = 1, 76$, $p < 0.001$; no-smoking > smoking); and a measurement time × session interaction ($F = 50.6$, $df = 1, 76$, $p < 0.001$). Follow-up planned comparisons for the interaction showed a significant difference between the no-smoking arrival and smoking during scan ($p < 0.001$) and between the smoking arrival and smoking during scan ($p < 0.001$) sessions.

Behavioral Measures

For mean errors on the Stroop Task (see Figure 1a), there was a significant effect of task condition ($F = 5.0$, $df = 1, 76$, $p < 0.05$; incongruent > congruent); no effect of session ($F = 2.9$, $df = 1, 76$, $p = 0.09$); and no condition × session interaction ($F = 0.4$, $df = 1, 76$, $p = 0.5$). For reaction time (see Figure 1b) there was a significant effect of condition ($F = 28.1$, $df = 1, 76$, $p < 0.001$; incongruent > congruent); a significant effect of session ($F = 9.0$, $df = 1, 76$, $p < 0.01$; no-smoking > smoking); but no condition × session interaction ($F = 0.1$, $df = 1, 76$, $p = 0.7$). The Stroop effect (see Figure 1c) showed no effect of session ($F = 1.0$, $df = 1, 38$, $p = 0.3$).

fMRI Measures

During both the no-smoking and smoking sessions, participants demonstrated robust BOLD activations across a number of regions (see Figure 2a and b), including the bilateral anterior and posterior cingulated, and inferior frontal and DLPFCs (Brodmann areas 46 and 9). Table 2 shows the results from the small-volume correction analysis when comparing the no-smoking and smoking sessions on activity in the regions mentioned above related to the Stroop effect (inconcongruent > congruent contrast). For this contrast, we identified a cluster of 154 voxels in the ACC (see Figure 3a), with the local maxima of activity located in the right ACC (see Figure 3b) where participants exhibited a significantly greater BOLD response during the no-smoking session as compared to the smoking session ($p < 0.02$). There was also a cluster of 240 voxels in the right middle frontal gyrus (MFG, see Figure 4a and b) where participants showed a significantly greater BOLD response

Table 1 Effects of Abstinence and Smoking on Craving and Nicotine Withdrawal

	Test session			
	No-smoking		Smoking	
	Arrival time[a]	During scan[b]	Arrival time	During scan
Urge to Smoke[c]	5.3 ± 0.4	5.2 ± 0.4**	5.6 ± 0.3	3.3 ± 0.3
Shiffman/Jarvik Withdrawal Scale				
Craving[d]	5.6 ± 0.3	5.5 ± 0.3**	5.8 ± 0.3	4.2 ± 0.3
Psychological symptoms	3.5 ± 0.2	3.4 ± 0.2	3.8 ± 0.2	3.0 ± 0.1
Physical symptoms	2.0 ± 0.2	2.2 ± 0.3	2.1 ± 0.3	1.9 ± 0.2
Sedation	2.9 ± 0.4	3.0 ± 0.2	2.6 ± 0.3	2.6 ± 0.2
Appetite	3.9 ± 0.2	3.8 ± 0.2	4.3 ± 0.3	3.9 ± 0.2

Data expressed as means and SE.
[a]Assessments at the beginning of each test day (14:00–17:00 h) after overnight abstinence (≥12 h).
[b]Mean of two assessments: (1) 10–15 min after smoking (immediately before scan) and (2) immediately after scan (30–35 min after smoking) for SJWS and UTS.
[c]Significant measurement time × session interaction ($F = 9.8$, $df = 1, 76$, $p < 0.01$); **$p < 0.01$ (follow-up planned comparisons) for a difference between the two smoking sessions during the scan period.
[d]Significant measurement time × session interaction ($F = 8.4$, $df = 1, 76$, $p < 0.01$); **$p < 0.01$ (follow-up planned comparisons) for a difference between the two smoking sessions during the scan period.

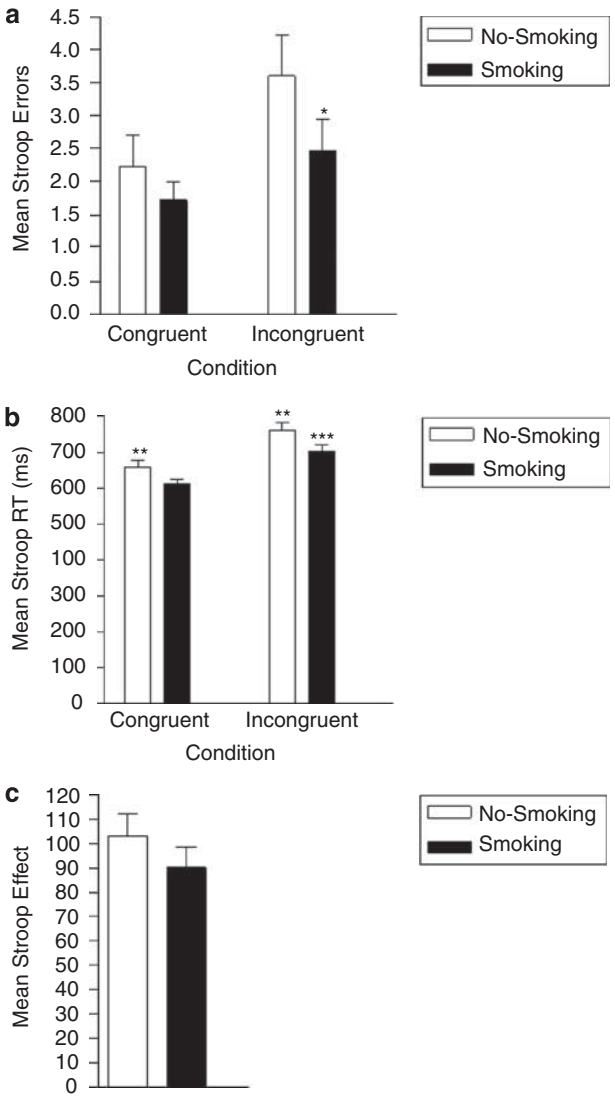

Figure 1 For the no-smoking and smoking sessions showing: (a) Mean Stroop errors (*$p<0.05$ incongruent > congruent); (b) Stroop reaction time (***$p<0.001$ incongruent > congruent; **$p<0.01$ non-smoking > smoking); and (c) mean Stroop effect.

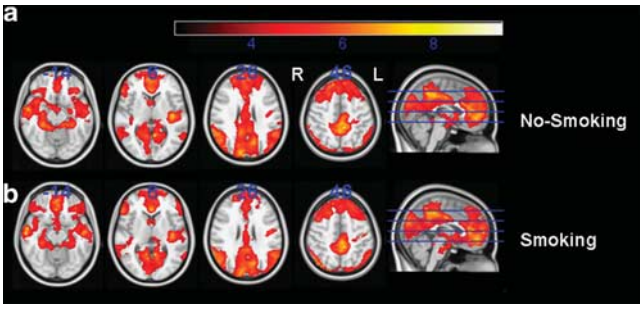

Figure 2 Showing average BOLD activation across the whole brain for the Stroop effect in (a) the no-smoking session and (b) the smoking session. *Z* (Gaussianized T/F) statistic images were thresholded using clusters determined by $Z=2.3$ and corrected cluster significance level of $p=0.05$. The scale represents the color (from dark to light yellow) of the cluster corresponding to the increasing *Z*-statistic. The structural image represents the MNI152 average normal brain with corresponding horizontal coordinates (inferior-superior).

during the smoking session as compared to the no-smoking session ($p<0.003$).

Correlations

There were no correlations between FTND and UTS scores and Stroop performance (ie, errors, reaction time, Stroop effect) in either fMRI test session; nor were there any correlations between nicotine use demographics (ie, pack–years, cigarettes per day) and Stroop performance in either fMRI test session.

DISCUSSION

The study presented here tested the hypothesis that smoking would reduce response conflict and enhance conflict resolution in chronic cigarette smokers who had abstained from smoking for >12 h. Although we did observe an effect of resumption of smoking on Stroop reaction time, whereby there was a smaller latency to respond in the smoking session, we did not detect any between-session difference in the Stroop effect, which is considered to be an important index of cognitive response conflict. We have previously demonstrated that smoking reduces the Stroop effect in a larger sample of smokers following overnight abstinence (Domier *et al*, 2007), and there is evidence that nicotine enhances Stroop performance in both smokers and non-smokers (Provost and Woodward, 1991; Warburton, 1992). Although contradictory findings have been reported concerning this effect (Foulds *et al*, 1996), the lack of an effect of smoking in abstinent smokers observed here may merely reflect inadequate statistical power given the small sample size.

The neural mechanisms by which the brain detects cognitive conflict have been established, with consistent evidence implicating the ACC in this function (Botvinick *et al*, 2004; Bush *et al*, 2000; Ridderinkhof *et al*, 2004). Our results revealed that for the Stroop effect, there was a significantly smaller BOLD response in the right ACC during the smoking session than during the no-smoking session, suggesting that smoking enhanced cognitive efficiency in abstinent smokers. Cognitive efficiency refers to the allocation of resources toward performance, where it is hypothesized, that under optimal conditions, this allocation is minimized and processing speed and accuracy are maximized (Rypma *et al*, 2006). While some studies support the view that greater brain activation related to the Stroop effect reflects superior task performance (Bush *et al*, 1999; Kerns *et al*, 2005; Strakowski *et al*, 2005; Zang *et al*, 2005), other studies suggest that low task-related responses are associated with better cognitive functioning (Kaufmann *et al*, 2008; Mohanty *et al*, 2005). These differences are likely related to the use of different versions of the Stroop Task or differential BOLD activation patterns observed between clinical and healthy populations. ACC activity and cognitive conflict are highly correlated, with strong evidence that neural activity within the ACC increases when 'top-down' control is compromised (Botvinick *et al*, 1999). In the present study, less neural activity in the ACC during the Stroop effect was observed in individuals after smoking following overnight abstinence, perhaps suggesting that reduced neural activity in this region reflected enhanced

Table 2 Mixed-Effects, Small-Volume Correction Analysis for Incongruent > Congruent Contrast Comparing the Two (No-smoking *vs* Smoking) Test Sessions

	No. voxels/cluster	*x* (mm)	*y* (mm)	*z* (mm)	Max *Z*-statistic	*P*
No-smoking > Smoking						
Anterior cingulate cortex	154	4	22	32	4.11	<0.02
Smoking > No-smoking						
Middle frontal gyrus	240	48	24	28	4.17	<0.003

Statistical images were first thresholded using a mask containing *a priori* regions of interest, with clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $p = 0.05$ prior to voxel-by-voxel paired *t*-test analyses. Coordinates represented are in Montreal Neurological Institute (MNI) space. *P* represents the *P*-value corresponding to the maximum *Z*-statistic within each cluster. Clusters reported were in the right hemisphere.

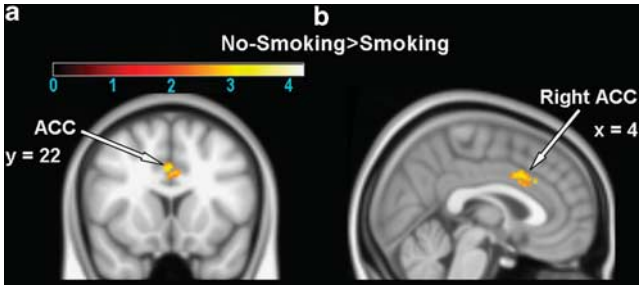

Figure 3 Small-volume correction analysis showing (a) voxel cluster of activity across both the left and right ACC, and (b) the local maxima of activity, located in the right ACC ($x = 4$, $y = 22$, $z = 32$), where smokers showed a significantly greater BOLD response during the no-smoking as compared with the smoking session for the incongruent > congruent contrast ($p < 0.02$, paired *t*-test). The scale represents the color (from dark to light yellow) of the cluster corresponding to the increasing *Z*-statistic. The structural image represents the MNI152 average normal brain with corresponding coronal (anterior-posterior) and sagittal (right-left) coordinates.

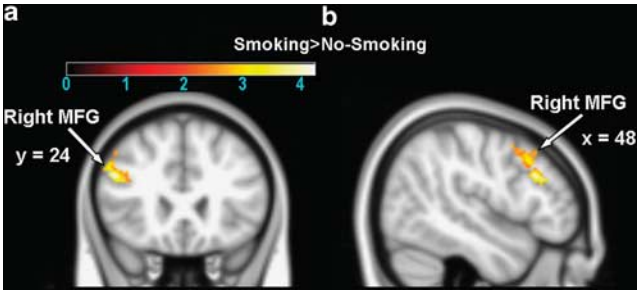

Figure 4 Small-volume correction analysis showing the (a) coronal section and (b) sagittal section voxel cluster of activity located in the right MFG ($x = 48$, $y = 24$, $z = 28$), where smokers showed a significantly greater BOLD response during the smoking as compared with the no-smoking session for the incongruent > congruent contrast ($p < 0.003$, paired *t*-test). The scale represents the color (from dark to light yellow) of the cluster corresponding to the increasing *Z*-statistic. The structural image represents the MNI152 average normal brain with corresponding coronal (anterior-posterior) and sagittal (right-left) coordinates.

processing efficiency and reduced response conflict. Exaggerated neural activity during continued abstinence, but not smoking, may therefore, reflect a compensatory mechanism by which cognitive control networks expend excessive energy to support selective attention processes in nicotine addiction. This result of increased neuronal activity appears consistent with an effect indicating possible inefficiency, which we have previously observed in nicotine-dependent subjects performing Stroop and working memory tasks (Xu *et al*, 2005, 2007).

With respect to conflict adaptation, research suggests that the ACC may be less important than other regions, particularly the DLPFC (Botvinick *et al*, 1999; Carter *et al*, 2000). It has been suggested that upon detection of conflict in the ACC, a cognitive control system located in the DLPFC is alerted and subsequently engages in the resolution of conflict. The left DLPFC has previously been associated with the implementation of cognitive control processes in preparation for high-conflict trials (MacDonald *et al*, 2000), but there is also evidence of conflict adaptation processes in the right DLPFC (Kerns *et al*, 2004). We observed significantly more neural activity in the right DLPFC (right MFG/BA 9) associated with the Stroop effect following cigarette smoking. This finding appears to be consistent with the current literature, demonstrating increased activity in this region corresponding with high-adjustment, post-conflict and post-error trials (Kerns *et al*, 2004). Computational modeling of the Stroop Task suggests that the DLPFC may be responsible for maintaining and representing context information, which includes the attentional demands of the task (Cohen *et al*, 1992). Furthermore, cognitive control is implemented in the brain by a distributed network that involves closely interacting, but dissociable, components (MacDonald *et al*, 2000). The current findings of increased DLPFC activity following smoking, therefore, suggest that re-initiation of smoking re-establishes an optimal dissociation between DLPFC conflict adaptation and ACC response conflict neural activity in smokers.

Interestingly, deficits in conflict monitoring have been observed in a number of clinical populations where cognitive control disturbances have previously been reported. Schizophrenics, for example, exhibit reduced conflict-related ACC activity (Kerns *et al*, 2005) as well as reduced conflict adaptation (Kerns *et al*, 2005) and error-related ACC activation (Alain *et al*, 2002; Kerns *et al*, 2005; Mathalon *et al*, 2002). Research into the neural characteristics of error monitoring in drug-abusing populations has also revealed deficits in ACC functioning (Bolla *et al*, 2004; Eldreth *et al*, 2004; Forman *et al*, 2004; Hester *et al*, 2009; Kaufman *et al*, 2003; London *et al*, 2005), which are contrary to the higher ACC activity observed herein during

abstinence from smoking. The ACC hyperactivity observed in our abstinent smoking group and hypoactivity reported in schizophrenics and illicit drug users may relate to the use of different cognitive control paradigms, some of which may be more sensitive to the exploits of cognitive conflict monitoring in the ACC.

We have demonstrated important neural activity differences in chronic cigarette smokers, related to nicotine withdrawal and resumption of smoking, during cognitive response conflict and resolution. Specifically, exaggerated neural activity in the ACC during nicotine withdrawal may reflect a compensatory mechanism by which cognitive control networks exhibit a discordant response to support selective attention processes. Moreover, we have shown that resumption of smoking may enhance cognitive control in nicotine addiction, which involves a reduction in ACC response conflict together with improvement in conflict resolution involving the DLPFC. Longitudinal studies, which assess treatment approaches to augmenting nicotine abstinence, may benefit from considering how cognitive control may be compromised during the initial stages of withdrawal, possibly contributing to smoking relapse.

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DISCLOSURE

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