

## Effects of acute smoking on brain activity vary with abstinence in smokers performing the N-Back Task: A preliminary study

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### Abstract

We previously reported that compared with a non-deprivation state, overnight abstinence from cigarette smoking was associated with higher brain activity in the left dorsolateral prefrontal cortex (L-DLPFC) during a low demanding working memory challenge, and little increase beyond this activity level during more taxing working memory conditions. In the present study, we aimed to assess how recent smoking (overnight abstinence vs. smoking *ad libitum*) influenced the effect of smoking a cigarette on brain activity related to a working memory challenge. Six smokers performed the N-Back working memory task during functional magnetic resonance imaging (fMRI) both before and after smoking a cigarette in each of two test sessions: one following overnight abstinence from smoking (~13 h) and the other following *ad libitum* smoking. Task-related activity in L-DLPFC showed a significant interaction between the effects of acute smoking, test session, and task load. After overnight abstinence, post-smoking brain activity in L-DLPFC was lower than before smoking at low task load and higher at high task load; corresponding activity on a day of *ad libitum* smoking was higher at low load and lower at high task load after smoking during the session. These data suggest that the effect of acute smoking on working memory processing depends on recent prior smoking and task load. In particular, they provide preliminary evidence that functional efficiency of working memory is improved by smoking a cigarette during abstinence, while the effect of a cigarette in a non-deprived state varies with the nature and difficulty of the working memory challenge. This interaction merits further examination in larger studies specifically designed to consider this issue.  
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## 1. Introduction

Among nicotine-dependent individuals, abrupt initiation of abstinence from smoking produces both psychological and somatic withdrawal symptoms (DSM-IV). Impairment of cognitive functioning is among these symptoms, and smokers may continue to smoke in part to relieve it (Snyder et al., 1989; Snyder and Henningfield, 1989; Pineda et al., 1998; al'Absi et al., 2002; Mendrek et al., 2005). Indeed behavioral testing indicates that after acute abstinence, resumption of smoking does improve cognitive performance. For example, after resuming smoking, abstinent smokers showed reduced latency during a serial-probe working memory task (Pineda et al., 1998) and during a Sternberg-type working memory test (Houlihan et al., 2001).

Neuroimaging has been used to assess the effects of smoking and of nicotine *per se* on working memory (Ernst et al., 2001; Kumari et al., 2003; Jacobsen et al., 2004), but with inconsistent findings. In one study, abstinent smokers performing a 2-back task showed less activation in the frontoparietal cortex and shorter response latency after chewing nicotine gum relative to placebo (Ernst et al., 2001). In another study, abstinent smokers showed increased activation of the right occipitotemporal cortex and decreased activation of the right globus pallidus with reduced accuracy on an auditory 2-back task after receiving transdermal nicotine (Jacobsen et al., 2004). In a third study, after subcutaneous injection of nicotine, nonsmokers showed increased activation in frontoparietal cortex at 1-, 2-, and 3-back condition, and decreased activation in the right parietal cortex at 3-back with decreased response latency and increased accuracy (Kumari et al., 2003).

In a fourth study, we tested the effect of smoking abstinence (>13 h) on working memory using a parametric N-Back task (including 0-, 1-, 2-, and 3-back conditions). On a day that smokers had smoked *ad libitum*, task-related activity in the left dorsolateral prefrontal cortex (L-DLPFC) was relatively low for an easy task condition (1-back), and increased as task difficulty increased; but when smokers were abstinent overnight, activity in the L-DLPFC was approximately as high at low task level as it was at more difficult levels (Xu et al., 2005). We interpreted this pattern of task-related activity in abstinent smokers as reflecting decreased functional efficiency of working memory-related brain function.

A subset of the participants in the aforementioned study repeated the N-Back Task after smoking one cigarette during both test sessions: one that began after *ad libitum* smoking and another began after overnight

abstinence, and these data were not included in our earlier report. Here we report on this assessment, which was made to gather preliminary data on the possible contribution of deprivation state to the effect of smoking a cigarette on brain activity related to working memory. Given our previous finding that the effect of smoking abstinence on brain activity varied with task difficulty (load), we anticipated that the effects of acute smoking might vary both with task load and recent smoking. In particular, we expected that smoking a cigarette would produce a greater decrease in task-related activity at low task loads after abstinence than during a non-deprived state. Such a difference would suggest a normalization of the pattern of activity observed in abstinent smokers.

## 2. Methods

### 2.1. Study participants

As described previously (Xu et al., 2005), healthy participants provided written informed consent after receiving a detailed explanation of the research protocol, which was approved by the Institutional Review Board of University of California Los Angeles. They completed questionnaires covering medical and smoking histories, childhood attention deficit hyperactivity disorder, and depressive symptoms.

Data were acquired from six smokers (20–40 years of age, 3 women), who were among the eight participants in the study we reported previously (Xu et al., 2005). They smoked 13–20 cigarettes/day, having smoked regularly for 2–26 years (mean=10.8 years, S.D.=9.4). Their scores on the Fagerström Test for Nicotine Dependence (Heatherton et al., 1991), ranged from 3–7 (mean=4.2, S.D.=1.3), indicating moderate dependence.

### 2.2. Experimental design

Each participant completed four test sessions of the N-Back working memory task. Of the four test sessions, two involved behavioral testing and two involved fMRI. One of each type of session (i.e., behavioral or fMRI) began after ~13 h abstinence from smoking, and the other began after smoking *ad libitum*. In both behavioral and fMRI testing, the abstinence session was first for three participants, and the session following *ad libitum* smoking was first for the other three participants. Each test session was conducted in two blocks, with participants always smoking one cigarette before beginning the second block. The period during which each participant finished the four test sessions ranged from 5 to 14 days (mean=9 days, S.D.=3.3). The period

between the two sessions that followed overnight abstinence ranged from 2–8 days (mean=4.3 day, S.D.=2.5).

On each fMRI day, two fMRI testing blocks were administered with a 15-min break between the two blocks. During the break, each participant exited the scanner and smoked one cigarette of his/her usual brand. On the test day that allowed *ad libitum* smoking, 20–45 min elapsed between smoking and the beginning of first fMRI scanning block. On each of the fMRI test days, the time between acute smoking and the beginning of second fMRI scanning test block was about 20 min. Before each test block, the participants completed the Shiffman/Jarvik Withdrawal Scale (Jarvik et al., 2000). The score of each subscale of SJWS ranges from “1” to “7”, with scores of “1”, “4”, and “7”, corresponding to “definitely no withdrawal or craving symptom”, “possibly withdrawal or craving symptom”, and “definitely withdrawal or craving symptom”, respectively.

### 2.3. Task design

We used a 4-step letter version of the N-Back Task. During fMRI, stimuli were displayed through video goggles (Resonance Technology Corporation, Northridge, CA). The test stimuli were letters, presented one at a time. Each letter appeared for 400 ms, and the inter-stimulus interval (ISI) was 1600 ms. In the 0-back condition, subjects pressed a “target key” when the letter “X” appeared, and the “non-target key” when any other letter appeared. In the 1-back, 2-back, and 3-back conditions, participants pressed the “target key” when the letter presented was identical to the letter 1, 2, or 3 letters preceding it, respectively. Otherwise, they were to press the “non-target key.”

The N-Back conditions were presented individually in 42-s blocks. In each block, 21 trials were presented, each containing 7 (33%) targets and 14 non-targets. There was a 3-s instruction screen before each task block and a 15-s block of rest after each task block. During rest, subjects fixed their eyes on a cross that was displayed at the center of the screen. The task blocks were programmed into four scripts. In each script, each of the four N-Back conditions was presented twice in one of four pseudorandom orders, resulting in an 8-min run of the entire task. Each subject completed two test blocks (before and after the break) on each day, with two 8-min runs in each block. The sequence of presentation of the scripts was counterbalanced among subjects. Performance data were not acquired during scanning due to a programming error. We therefore report on the N-Back performance data collected outside the scanner.

#### 2.3.1. Scanning parameters

Functional images were acquired on a 3T MRI scanner (GE, Signa with an EPI upgrade from Advanced NMR Systems), using T2\* weighted gradient-recalled EPI, with blood oxygen level-dependent (BOLD) contrast (TR=3000 ms, TE=42 ms, flip angle=80°, slice thickness=4 mm with a 1-mm inter-slice interval, matrix of 64 × 64, in-plane resolution=3.12 × 3.12 mm<sup>2</sup>). One hundred sixty images were acquired for each of 16 axial slices through the brain during the presentation of N-Back script. High-resolution T2-weighted EPI anatomical images of the whole brain (23–25 slices, 4-mm thick) were acquired in each scanning session to help define the locations of the BOLD signal changes.

### 2.4. Statistical analysis

#### 2.4.1. Behavioral data

Repeated measures analyses of variance (ANOVAs) were conducted in which N-Back level (0-, 1-, 2-, and 3-back), test session (during smoking deprivation or following *ad libitum* smoking) and test block (pre- or post-smoking) were each within-subject independent factors. Separate analyses were conducted for errors and response times (RTs).

#### 2.4.2. Imaging data

The functional images of each subject were corrected for motion. We used 4 mm, the thickness of imaging slices, as the maximum motion allowed, and none of the data from the six subjects exceeded this threshold during any functional scanning. There also was no significant difference in maximum motion among the four test blocks (One-way ANOVA,  $df=3$ ,  $F=1.588$ ,  $P=0.224$ ).

After motion correction, functional series were co-registered with the high-resolution T2-weighted EPI anatomical image, spatially normalized with the study-specific template, and smoothed with a 10-mm FWHM Gaussian filter using SPM2 (Wellcome Department of Cognitive Neurology, London). We constructed model time courses for each task level by convolving a boxcar waveform representing the times of onset and duration of each task level with the canonical hemodynamic response function offered with SPM2.

Given our small sample size and the multiple comparisons in fMRI analysis, we limited the search volume in the statistical analysis. The ROI (region of interest) was defined in our earlier report (Xu et al., 2005). To define this ROI, we combined the imaging data acquired during pre-smoking test block of the two test sessions together. We then used a parametric contrast (i.e., -2 -1 1 2) to identify brain regions showing

Table 1  
Withdrawal Scale of Shiffman/Jarvik: mean scores (standard error) of craving and withdrawal

	Satiety session		Abstinence session	
	Pre-smoking	Post-smoking	Pre-smoking	Post-smoking
Craving <sup>a</sup>	3.67(0.4)	4.31(0.3)	6.36(.5)	4.17(0.6)
Psychological symptoms <sup>a</sup>	3.08(0.34)	3.10(0.6)	4.49(0.6)	3.38(0.46)
Physical symptoms	1.67(0.4)	2.11(0.8)	2.72(0.9)	2.33(0.8)
Sedation	3.25(0.7)	3.79(0.8)	3.42(0.3)	3.88(0.8)
Appetite	4.0(0.2)	4.0(0.2)	4.42(0.75)	4.67(0.8)
Total score	15.67(1.0)	17.3(2.2)	21.41(2.0)	18.44(3.4)

Repeated measures analyses of variance (ANOVAs) were used to assess the overall significance of differences.

<sup>a</sup>  $P < 0.05$ , interaction between acute smoking and test session.

significant increase in BOLD signal with increasing task load. Clusters in the left dorsal lateral prefrontal cortex (DLPFC), and bilateral pre-supplementary motor cortex and parietal cortex showed significant changes in BOLD signal at this contrast. All these significant clusters were defined as one ROI by using the SPM2-compatible ROI analysis tool Marsbar (Brett et al., 2002). The size of this ROI was 12,992 m<sup>3</sup>.

Considering our previous finding of a 2-way interaction (test session  $\times$  task load) only at the contrast of 3-back minus 1-back, we used this contrast to test for a 3-way interaction in changes of BOLD signal between task load, test session, and test block. We first used the contrast of “3-back minus 1-back” to create a SPM{T} map for each test block (i.e., pre- and post-smoking) of each test session of each participant. Then we entered these SPM{T} maps into second level (one-way ANOVA, within-subject) for random effect analysis at the group level. The contrast [(pre-smoking test block minus post-smoking test block during the session following *ad libitum* smoking) minus (pre-smoking test block minus post-smoking test block during the session that followed abstinence)] was used to assess the task load  $\times$  test session  $\times$  test block 3-way interaction of changes in BOLD signal. Only voxels that survived the voxel-level threshold of  $P < 0.001$  (uncorrected) and were within the *a priori* ROI, were further analyzed, with multiple comparison correction using the small volume correction (SVC) tool in SPM2. The threshold for cluster significance was  $P < 0.05$  (after correction). Relative to baseline (0-back), the mean signal change of significant voxels within the ROI at 1-back, 2-back, and 3-back were extracted with the Marsbar tool (Brett et al., 2002) for presentation purposes only.

### 3. Results

#### 3.1. Subjective self-reports of Shiffman–Jarvik Withdrawal Scale

A significant interaction between acute smoking and test session was observed on reported cigarette craving ( $F(1,5)=45.47$ ,  $P < 0.05$ ) and psychological withdrawal symptoms ( $F(1,5)=9.19$ ,  $P < 0.05$ ). These interactions reflected decreases in the self-ratings of symptoms after acute smoking during the abstinence session but not in the non-abstinent session (Table 1).

#### 3.2. Behavioral performance

N-Back performance data (sessions combined) showed no significant effects on reaction time RT with this small sample size, and a nonsignificant trend towards decreases in error rate from the pre- to the post-smoking test ( $F(1,5)=5.85$ ,  $P = 0.06$ ). Error rates were significantly lower after smoking at the 3-back condition in both the abstinent session ( $t = 4.0$ ,  $df = 5$ ,  $P < 0.05$ ) and the non-abstinent session ( $t = 2.6$ ,  $df = 5$ ,  $P < 0.05$ , Fig. 1). No interaction was observed between test session and test block as predictors of either error rates or RT.

#### 3.3. Task-related fMRI signal change

Group level, within-subject, one-way ANOVA analysis (SPM2) found a significant interaction between acute smoking, test session, and task load in the left DLPFC (1176 mm<sup>3</sup>, MNI  $x, y, z$  coordinates:  $-38, 6, 34$   $P < 0.001$ , Fig. 2A). This cluster was within the *a priori* ROI, and survived the correction for multiple comparisons within the ROI (SPM2 SVC,  $P < 0.05$ ). The extracted % signal change from this cluster indicating

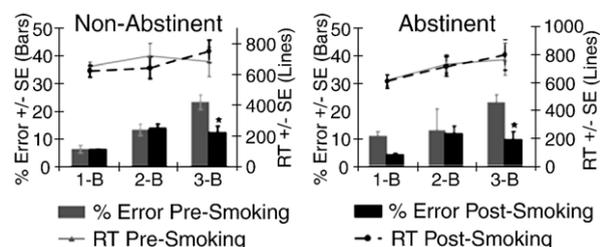


Fig. 1. N-Back performance of smokers in sessions following either smoking *ad libitum* or smoking abstinence (>13 h). Lines indicate mean RT's and bars indicate mean percent of errors, both at each N-Back level, session following smoking *ad libitum*, right panel, session following smoking abstinence. In both sessions, subjects showed significantly fewer errors at the 3-back level after acute smoking.

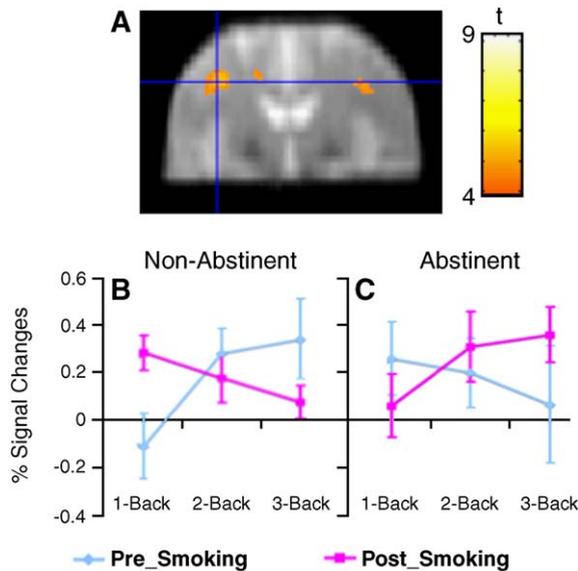


Fig. 2. A cluster in the left dorsal lateral prefrontal cortex (DLPFC) showed a 3-way interaction among acute smoking, test session, and task load on task-related activity. Colors superimposed on the gray scale image, from the study-specific structural brain template, indicate values of  $t$  according to the color bar. The line graph indicates the mean percent signal changes from the 0-back and standard deviation at each level of the N-Back Task. B. Data from session after smoking *ad libitum*, C: data from session after overnight abstinence.

that task-related BOLD signal change decreased at the 1-back condition and increased at the 3-back condition in the test session following smoking abstinence (>13 h); and increased at the 1-back condition and decreased at the 3-back condition in the test session following *ad libitum* smoking (Fig. 2B,C).

#### 4. Discussion

The findings suggest that the effect of acute smoking on activation within the left DLPFC related to working memory challenge depends on the state of abstinence. In particular, the effect observed in the left DLPFC was roughly opposite when the participants were smoking-deprived or relatively non-deprived: during abstinence, smoking was followed by decrease in activity at low task load and increased activity at high load; on the day of *ad libitum* smoking, activity increased at low task load and decreased at high task load. Notably, smoking a cigarette after overnight abstinence changed the pattern of activity in the left DLPFC to resemble the relationship between task-related activity and task difficulty that was observed in healthy nonsmokers and non-deprived smokers (i.e., low activity at low load and high activity at high load, (Jansma et al., 2000; Xu et al., 2005).

The opposite effect on changes of BOLD signal after acute smoking on a day of *ad libitum* smoking was unexpected. Since there were no changes in performance at the 1-back level and improved performance at the 3-back level (decreased error rates), this effect suggested that cigarette smoking decreased the functional efficiency of left DLPFC at the 1-back level and increased it at the 3-back level. Although not easily explained, the inconsistencies related to the state of abstinence underscore previous assertions that cigarette smoking and/or nicotine administration have complex effects on performance of cognitive tasks and related brain activity (Gilbert et al., 1989; Lambe et al., 2003; Pritchard, 1991). For example, electroencephalography (EEG) revealed that cigarette smoking increased EEG dimensional complexity (DCx) in smokers with low pre-smoking DCx, and decreased EEG DCx in smokers with high pre-smoking DCx (Houlihan et al., 2001).

Our findings are also consistent with the theory that neurochemical optima in the brain vary for different cognitive tasks (Clark et al., 2004; Lambe et al., 2003; Robbins, 2005). The 1-back task is certainly easier than 3-back task, and the two tasks arguably involve qualitatively different functions. While the 1-back requires *maintenance* alone, success on the 3-back requires extensive *manipulation* of working memory content (Ragland et al., 2002). These two task conditions, accordingly, may have different neurochemical optima. Nicotine stimulates the release of dopamine (DA), serotonin (5-HT), and norepinephrine (NE) in multiple brain regions (George et al., 1998; Rossi et al., 2005). The neurochemical effects of cigarette smoking (following *ad libitum* smoking throughout the test day) could be optimal for the 3-back condition, but not for the 1-back condition.

This preliminary report has several limitations, including the small sample size, lack of plasma nicotine levels, and failure to record task performance during fMRI. The absence of behavioral data prevented the analysis of relation between performance and changes in BOLD signal, and also prevented the analysis of the data in an event-related fashion. It is possible that performance differences across conditions contributed to observed differences in task-related activity. Another caveat is that CO and nicotine have complex effects on cerebral perfusion (Ghatan et al., 1998; Rose et al., 2003; Domino et al., 2004), possibly complicating interpretation of differences in BOLD signal. There is evidence, however, that nicotine does not alter the coupling between the BOLD signal and the activity of the visual cortex in response to photic stimulation (Jacobsen et al., 2002). Finally, it is important to consider that smoking a cigarette was confounded with test order in the present study; therefore,

differences in performance and/or task-related activity before vs. after acute smoking may reflect more than an effect of cigarette smoking alone. Order effects related to factors such as fatigue, or learning may have contributed to the differences observed on either test day. It is more reasonable to interpret *interactions* between smoking state and changes in performance after acute smoking as evidence that the effect of smoking a cigarette is influenced by recent smoking. As order effects may interact with smoking state (e.g., overnight abstinence vs. *ad libitum* smoking), however, conclusions regarding the effect of smoking manipulations should be tentative.

In conclusion, this report presents the first fMRI evidence that the effects of acute smoking on the function of the left DLPC depend on the smoking status of smokers (non-abstinent vs. abstinent), in conjunction with the working memory load. The data suggest in particular that acute smoking improves the functional efficiency of the DLPFC in abstinent smokers performing a working memory task; but the effect of acute smoking on the function of DLPFC in non-abstinent smokers may vary with the tasks. This conclusion merits further examination in larger studies specifically designed to consider this issue.

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