

Brain Marker Links Stress and Nicotine Abstinence

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Abstract

Background: Subjective stress is a well-documented predictor of early smoking relapse, yet our understanding of stress and tobacco use is limited by reliance on self-reported measures of stress. We utilized a validated functional neuroimaging paradigm to examine whether stress exposure during early abstinence alters objective measures of brain function.

Methods: Seventy-five participants underwent blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) during the Montreal Imaging Stress Task (MIST) on two occasions: once during smoking satiety and once following biochemically confirmed 24-hour abstinence (order counterbalanced). The primary outcome measure was brain response during stress (vs. control) blocks of the MIST, assessed using whole-brain analysis corrected for multiple comparisons using clusters determined by $Z \geq 3.1$.

Results: Abstinence (vs. satiety) was associated with significantly increased activation in the left inferior frontal gyrus, a brain region associated with inhibitory control. Abstinence-induced change in brain response to stress was positively associated with change in self-reported stress.

Conclusions: This study provides objective evidence that the brain response to stress is altered during the first 24 hours of a quit attempt compared to smoking satiety.

Implications: These results point to the potential value of inoculating smokers with stress management training prior to a quit attempt.

Introduction

As many as 62% of smokers attribute their inability to stop smoking to stress.¹ Indeed, exposure to stressful life events and perceived stress prior to or following a quit attempt are linked with relapse.^{2,3} In human laboratory studies, acute stress challenges after varying lengths of abstinence lead to increases in cigarette cravings, smoking frequency and intensity.^{4,5}

Despite the observed links between stress and smoking behavior, these studies pose many challenges. First, there is no accepted gold standard for the measurement of subjective stress.⁶ Accuracy of self-reported measures is limited by social desirability bias⁷ as well as

introspection during the task.⁸ Second, subjective measures of stress exhibit modest or inconsistent associations with objective measures of biological stress response, such as cortisol, in healthy populations^{4,9,10} and in smokers.^{4,11,12} These apparent discrepancies may be interpretable after considering factors that influence cortisol response. For example, circadian fluctuation in cortisol levels causes cortisol response to vary by factors such as time since participant waking and time of day of the study, which can mask the effects of acute stress.¹³ Third, in smokers, stress reactivity as measured by cortisol response may be blunted.^{5,14,15} Other studies examining smokers during abstinence observed similar patterns of abnormal HPA axis

functioning (ie, hyporesponsivity), which suggests that abnormal cortisol responses in smokers may be independent of withdrawal state.^{12,14–16} However, studies directly comparing cortisol response during abstinence and smoking as usual are limited,¹⁷ and some studies have found conflicting results.^{4,14,15} To optimize stress reduction interventions for smoking cessation, there is a need to deepen our understanding of how early abstinence may alter stress reactivity using other measures that are sensitive to abstinence.

Neural measures of stress response, such as functional magnetic resonance imaging (fMRI), provide an objective method to interrogate abstinence-induced changes in stress reactivity and may provide insight beyond what can be obtained with cortisol or subjective measures.^{18–20} Two commonly used paradigms for stress induction in the scanner include individually calibrated scripted stress tasks,²¹ and the Montreal Imaging Stress Task (MIST), a psychosocial stress task that requires subjects to perform challenging mental arithmetic in the presence of negative social evaluation.^{22,23} Individualized stress scripts consistently increase activity in executive control and limbic regions.²⁴ The MIST also increases activity in prefrontal regions during stress blocks relative to control blocks. However, deactivation in limbic regions has also been observed.^{10,23,25} A review of investigations utilizing psychosocial stress tasks during fMRI found that only the MIST and serial subtraction tasks were able to induce a significant cortisol response (in addition to neural response).^{26,27}

To date, only two small studies have explored the effects of stress on neural responses among smokers using the MIST. Among non-abstinent smokers ($n = 15$), deactivation during stress (relative to control blocks) was observed in limbic, paralimbic, and cognitive control regions,¹¹ consistent with effects previously observed in nonsmokers.^{10,23} To identify specific regions that may contribute to abstinence-induced changes in stress reactivity, our prior pilot study ($n = 37$) compared brain response to stress following 24 hours of monitored abstinence or smoking satiety (between-subject design). Abstinence from smoking (vs. satiety) was associated with stress-related increases in activation in the inferior frontal gyrus (IFG), anterior cingulate cortex, precuneus, and supramarginal gyrus.¹⁸ Neither of these studies tested whether brain response and subjective stress response were associated.

Building upon prior work, the present study used a more powerful within-subject cross-over design to ascertain how brain response to stress changes during abstinence versus smoking satiety in a large sample of smokers ($n = 75$). We focused on the first 24 hours of abstinence, as this is the most vulnerable period for smoking relapse,²⁸ and utilized the MIST paradigm. We hypothesized that abstinence (compared to smoking satiety) would increase brain response to psychological stress in limbic regions and those involved in cognitive control. We also expected a positive association between abstinence-induced changes in brain response and subjective stress response.

Methods

Participants

Participants were 75 treatment-seeking smokers ages 18 to 65 who reported smoking ≥ 5 cigarettes/day for ≥ 6 months and were recruited through media advertisements. Exclusion criteria were: exhaled carbon monoxide (CO) breath sample < 8 ppm; current use of nicotine products other than cigarettes (such as chewing tobacco, snuff, e-cigarettes or nicotine replacement therapy); pregnancy, planned pregnancy or breastfeeding; history of DSM-IV Axis I psychiatric disorders; substance disorders (except nicotine dependence)

within the past 2 years; use of psychotropic medications; history of significant brain injury; left-handedness; fMRI contraindicated material in the body; claustrophobia; low or borderline intelligence (< 85 score on Shipley's Institute of Living Scale²⁹; breath alcohol test ≥ 0.01 ; and any impairment that would prevent task performance.

Eligibility and Intake

All procedures were approved by the University of Pennsylvania Institutional Review Board and carried out in accordance with the Declaration of Helsinki. Initial telephone screen was followed by an in-person eligibility assessment. All participants provided written informed consent, an exhaled CO breath sample to confirm smoking status, a breath alcohol measurement, a urine sample to assess for the use of study-prohibited drugs, and if applicable, participants were provided a self-administered pregnancy screening. Eligible participants completed a smoking history questionnaire (cigarettes per day); and the Fagerström Test for Nicotine Dependence.³⁰

Study Design and Measures

The neuroimaging experiment used a previously validated within-subject abstinence challenge design.¹⁹ Two blood-oxygen-level-dependent (BOLD) fMRI sessions were scheduled at least 1 week apart in a randomized counterbalanced order: (1) smoking satiety and (2) following 24-hour abstinence. All sessions were scheduled to begin between 8 AM and 10 AM. Participants with a positive urine drug screen, a breath alcohol test ≥ 0.01 , a CO reading ≥ 8 ppm for the abstinence condition, or a CO reading < 8 ppm for the smoking satiety condition were excluded. Participants then completed the Minnesota Nicotine Withdrawal Scale³¹ (MNWS) and the Questionnaire of Smoking Urges (QSU-Brief).³² For the smoking satiety condition, participants smoked a single cigarette approximately 1 hour prior to stress exposure.¹⁸

fMRI Data Acquisition

BOLD fMRI was acquired with a Siemens Prisma 3T system (Erlangen, Germany) using a whole-brain, single-shot gradient echo (GE) echoplanar sequence with the following parameters: TR/TE = 1000/30 ms, FOV = 192 mm, matrix = 64×64 , slice thickness/gap = 2.0/0 mm, 78 slices, effective voxel resolution of $2 \times 2 \times 2$ mm. RF transmission utilized a quadrature body-coil and reception used a 64-channel head coil. Prior to BOLD fMRI, 5-minute magnetization-prepared, rapid acquisition gradient echo T1-weighted image (MPRAGE, TR 2200 ms, TE 4.67 ms, FOV 240 mm, matrix 192×256 , effective voxel resolution of $1 \times 1 \times 1$ mm) was acquired for anatomic overlays of functional data and to aid spatial normalization to standard atlas space.

Stress Reactivity Task

The MIST is a validated fMRI-based stress-induction task which requires participants to complete mental arithmetic with increasing difficulty to a level beyond the person's capacity.^{10,18,22,23} This 10-minute fMRI paradigm presents 1-minute blocks (stress and control) pseudo randomly during two 5-minute acquisition periods. Participants completed a short practice session to become familiar with the task and response device prior to the scan. During the stress blocks, the screen displays a visual rotary dial for response selection, a feedback window ("correct," "incorrect" or "timeout") and two scripted performance indicators: (1) individual subject's overall performance and (2) "average" performance for all subjects

(Supplementary Figure S1). In the stress blocks, the time limit is dynamically calculated to be 10% shorter than the subject's average required time on previous trials and this limit is represented by a progress bar. For the control blocks, mental arithmetic is performed at a comparable level of difficulty but without time restriction and neither individual nor average performance is displayed. To elevate stress of the overall task, participants are provided with scripted negative feedback regarding their performance between acquisition blocks (eg, "I have to say you are not performing as well as we were expecting you to"). To assess subjective stress and craving before and after the MIST, participants completed a validated 2-item questionnaire to assess craving and urge to smoke^{20,33} as well as a stress rating question (ie, "How stressed are you?" on a scale of 1–10.¹⁰ We chose these short assessments in order to minimize participant time in the scanner. After the second fMRI scan, participants were debriefed and informed that the task was designed to induce stress and was not a true reflection of their ability to do mental arithmetic. One participant had incomplete data for post-MIST subjective measures resulting in a final sample of $n = 74$ for subjective stress analyses. Salivary cortisol samples (Salimetrics, LLC in State College, PA) were used to measure the physiological stress response produced by the MIST. Samples were obtained immediately prior to and immediately following the task (approximately 15 minutes apart); additional samples were collected at 15 and 30 minutes after the task to assess the time course of the response²² (Supplementary Figure S2). The post-MIST and pre-MIST salivary cortisol measurements were differenced and abstinence-induced (abstinence minus smoking satiety session) cortisol response was measured and used for subsequent analysis. Participants were excluded from cortisol analyses if their baseline cortisol measurement was greater than 3 SD from the mean at the smoking satiety condition ($n = 1$) or if a sufficient sample was not collected before or after the MIST ($n = 4$), resulting in a final sample of $n = 70$ for cortisol analyses.

Image Preprocessing and Time Series Analysis

BOLD time series data were pre-processed using standard image analysis procedures executed with fMRI Expert Analysis Tool (FEAT of FSL [FMRIB's Software Library, Oxford, UK]). Preprocessing included motion correction (MCFLIRT),³⁴ slice time correction, skull stripping using BET,³⁵ spatial smoothing (6 mm), and high-pass filtering (100 seconds). The median functional volume was co-registered to the anatomical T1-weighted structural volume and transformed into standard anatomical space (T1 MNI template) with FLIRT.³⁴ Pre-processed data were analyzed using FILM (FMRIB's Improved General Linear Model). Blocks (stress and control) were convolved with a double-gamma hemodynamic response function. The temporal derivative and nuisance regressors for standard plus extended motion parameters were also included and individual time series for each acquisition were averaged. The contrast of interest was stress minus control. All analyses were completed in subject space and transformation parameters were later applied to statistical maps for group-level analyses.

Image Quality Assessment

Overall signal quality was measured by calculating mean temporal signal to noise ratio (tSNR) and participant motion was assessed with mean relative displacement. Participants with low tSNR (>3 SD below the mean) or high mean relative displacement (>3 SD from the mean) were identified for further evaluation. Using these procedures, three participants were excluded for relative motion greater than 0.57 mm, resulting in a final sample of 75 participants.

Whole-Brain Image Analysis

Group analyses were conducted using FSL's local analysis of mixed effects method³⁶ (FSL FLAME1). First, mean task activation during the smoking satiety session was generated to characterize the neural stress reactivity network in smokers. Next, we tested between session effects (abstinence vs. smoking satiety) for stress response using a whole-brain, voxelwise paired *t*-test. Using random field theory, the resulting *Z* statistic images were corrected for multiple comparisons with a threshold of $Z \geq 3.1$ and cluster probability of $p \leq .05$.^{37,38} Appropriate anatomical assignment for peak activation was determined using the Talairach atlas.³⁹

Salivary Cortisol Analysis

Samples were stored at -80°C prior to analysis. Samples were delivered on dry ice for assay at the Children's Hospital of Pennsylvania in three cohorts. Lot-to-lot testing and validation was performed between all cohorts and kits used for analysis. On the day of testing, all samples were thawed and centrifuged at 3000 rpm for 15 minutes to remove mucins. Samples were assayed for cortisol using the cortisol enzyme immunoassay kit (Salimetrics, LLC in State College, PA) following the manufacturer's recommended protocol. The cortisol assay used 25 μL of saliva for singlet determinations and had a range of sensitivity from 0.012 to 3.00 $\mu\text{g}/\text{dL}$. Samples were assayed in duplicate and the average of the duplicate assays were used in the statistical analyses. On average, intra- and inter-assay coefficients of variation were less than 5% and 10%. Cortisol data were transformed to nmol/L.

Outcome Measure

The outcome measure was an abstinence-induced change in BOLD percent signal (abstinence minus smoking satiety) for the region identified by our primary contrast, abstinence > smoking satiety for neural stress reactivity (stress > control blocks).

Statistical Analysis

Descriptive statistics were obtained for all variables. As a manipulation check, paired *t*-tests were used to assess expected abstinence challenge effects on subjective stress, and to test the effects of the stress reactivity task on subjective stress (post-MIST – pre-MIST). Linear regression (Stata reg, College Station, TX) was used to assess the relationship of abstinence-induced neural stress reactivity and abstinence-induced subjective stress reactivity using the difference of the extracted mean percent BOLD signal in the region significantly activated during abstinence and during smoking satiety. Abstinence-induced changes in craving (post-MIST – pre-MIST), sex, age, and baseline cigarettes per day and baseline CO were entered as covariates to reduce potential confounding.¹⁹ No outliers (>3 SD from the mean) were observed for change in subjective stress (post-MIST – pre-MIST) or BOLD percent signal change (stress > control) in either condition.

Results

Descriptive Data

Eighty-eight people completed the first scan session; 10 participants withdrew before the second scan and three were excluded due to motion in the fMRI, resulting in a final sample of 75 participants included in the analysis. Of these, 40 (53.3%) were male, 42 (56.0%) were African American, and 43 (57.3%) had completed

some education beyond high school. The mean age was 43.1 years (SD 13.2), the mean cigarettes per day was 13.7 (SD 5.8), the mean Fagerström Test for Nicotine Dependence score was 4.6 (SD 1.8), and mean CO at intake was 14.8 ppm. Exhaled CO was significantly lower during abstinence (mean 2.6 ppm, SD 2.4 ppm) compared to the smoking satiety condition (mean 16.4 ppm, SD 6.9 ppm, $p < .0001$), indicating compliance with the abstinence requirement. Subjective craving (QSU) and withdrawal (MNWS) were significantly higher during the abstinence condition (craving mean 45.5, SD 14.9; withdrawal mean 15.4, SD 8.6) compared to the smoking satiety condition (craving mean 30.4, SD 13.6; withdrawal mean 7.8, SD 6.7; $ps < .00001$). Subjective stress was significantly higher following the MIST (pre-MIST $M = 2.7$, $SD = 2.5$; post-MIST $M = 4.2$, $SD = 2.6$; $p < .001$). Following the MIST, cortisol level was significantly lower during smoking satiety ($df = 69$, $t = 1.73$, $p = .04$), but was unchanged during abstinence ($df = 69$, $t = -0.13$, $p > .05$). Change in cortisol (post-MIST – pre-MIST) trended towards more positive ($df = 69$; $t = 1.65$; $p = .052$) in the abstinent condition ($M = 0.019$ nmol/L, $SD = 1.31$) compared to smoking satiety condition ($M = -0.36$ nmol/L, $SD = 0.21$; $p = .07$).

Abstinence Challenge Effects on Neural Stress Reactivity

The stress minus control fMRI block contrast revealed a pattern of brain activation consistent with previous neuroimaging studies (Table 1).^{11,18,22} The abstinence challenge (abstinence > smoking) produced greater activation in the left IFG ($Z > 3.1$, $p < .05$; Figure 1). Peak activation of this region was confirmed to be part of the task network during smoking satiety at a more liberal threshold (Supplementary Figure S3). There were no regions with greater activation for the smoking satiety condition (vs. abstinence) or for the control minus stress block contrast ($Z > 3.1$, $p < .05$).

Relationship of Neural Response and Subjective Stress

The abstinence-induced increase in neural stress reactivity in the left IFG was positively associated ($r = 0.26$) with abstinence-induced increase in subjective stress ($\beta = 2.1$; 95% CI = 0.18–4.05; $p = .033$). Significant covariates included change in craving ($\beta = 0.38$; $p = .004$) and age ($\beta = 0.07$; $p = .005$). Sex was not a significant covariate ($\beta = 0.03$; 95% CI = -0.12 to 0.19; $p = .64$).

Discussion

This study provides objective evidence for change in neural stress reactivity during the first 24 hours of smoking cessation. Abstinence (vs. smoking satiety) resulted in a significant increase in activation in the IFG during stress (vs. control exposure). Abstinence-induced change in IFG activation was positively associated with abstinence-induced change in subjective stress; increase in neural reactivity may underlie the heightened subjective stress experienced during smoking cessation (compared to smoking satiety). These findings validate and extend our prior pilot study¹⁸ by documenting effects of abstinence on stress-induced IFG activation in a larger sample of smokers and linking brain response to subjective stress. In addition, our results support prior observations that cortisol response to stress is not sensitive to abstinence and suggest that fMRI may provide a more sensitive measure of abstinence-induced changes in stress response.

Our finding of increased stress-induced activation in the IFG during abstinence is consistent with results of our prior between-subject study and suggests that abstinence-induced changes in IFG activation may contribute to the heightened stress response experienced during nicotine withdrawal.¹⁸ Although our study was not designed to probe the specific contribution of the IFG to subjective stress, we can speculate. The IFG is commonly activated during both physiological and psychological stress responses.^{10,40} IFG activation is also associated with response inhibition, attentional control suppression of intrusive thoughts, and regulation of emotion.^{41–43} Further, abstinence-induced increases in IFG activation have been observed during tasks involving response inhibition,⁴⁴ viewing of smoking cues,²⁰ and resisting craving.⁴⁵ It is therefore possible that greater activation of the IFG during abstinence reflects greater effort to control or downregulate the stress response.⁴⁶ However, in our sample, a greater increase in IFG activation was associated with a greater increase in subjective stress, suggesting that IFG activation may be contributing to greater subjective stress during abstinence. Interestingly, IFG activation is also sensitive to smoking cessation treatment; specifically, the efficacious smoking cessation medication varenicline decreases working-memory-related BOLD activation in the IFG during abstinence compared to placebo.⁴⁷ This suggests that treatments that reduce abstinence-induced increases in IFG activation may be beneficial for smoking cessation.

In contrast to the subjective stress measure, there were no associations between neural stress reactivity and cortisol response, and we did not observe significant differences in change in cortisol level

Table 1. Areas of Activation for Mean Experimental > Control Contrast During Smoking Satiety

Region ^a	BA ^b	Hem ^c	Z-MAX ^d	X (mm) ^e	Y (mm)	Z (mm)
Middle temporal gyrus	39	R	11.3	50	-68	10
Mid occipital gyrus	19	L	6.8	-32	-84	12
Middle temporal gyrus	39	L	6.4	-44	-66	10
Middle frontal gyrus	6	R	6.0	36	0	50
Medial frontal gyrus	10	R	6.1	16	44	12
Caudate tail		L	5.8	-12	-22	24
Caudate tail		R	3.5	6	28	22
Caudate body		R	6.4	2	10	8
Cingulate gyrus	24	R	3.3	16	8	26

^aVoxelwise corrected $Z \geq 4.7$.

^bBA = Brodmann Area.

^cHEM = cerebral hemisphere.

^dZ-MAX values represent peak activation for cluster.

^eMNI coordinates. Regions listed are for areas larger than 100 voxels.

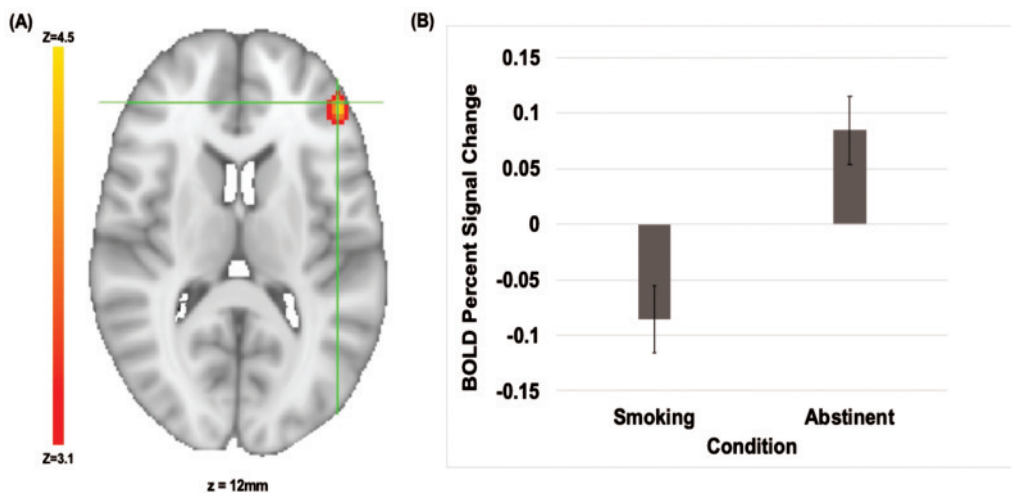


Figure 1. Abstinence significantly alters neural stress reactivity in the left inferior frontal gyrus. (A) The whole-brain analysis of the abstinence versus smoking satiety condition revealed significant activation in the left inferior frontal gyrus during the stress task (cluster corrected $Z > 3.1$, $p < .05$). (B) Neural stress reactivity is significantly increased during the abstinent condition compared to the smoking satiety condition.

(post-MIST – pre-MIST) by condition. Although we did observe a significant decrease in cortisol over time during smoking satiety, and cortisol levels remained relatively constant during abstinence, the interaction was nonsignificant. Prior associations between cortisol and neural responses to stress have been observed primarily in post hoc analyses of healthy participants stratified by direction of cortisol response.²³ Our results are consistent with previous findings reporting no change in cortisol response during smoking abstinence and suggests that cortisol response to a stressor may be independent of nicotine withdrawal state.¹⁴ It is possible that higher basal cortisol concentrations following chronic nicotine exposure result in enhanced negative feedback during exposure to a stressor. Although nicotine administration is associated with an increase in cortisol level, frequent and prolonged stimulation of the HPA axis by nicotine may also lead to reduced sensitivity to effects of other stimuli (such as stressful situations).⁴⁸ Further investigation into mechanistic changes in the HPA axis following chronic nicotine exposure may clarify the effects of these changes on cortisol response to a stressor. For these reasons, changes in neural activation may be a more reliable and sensitive measure of changes that occur during acute abstinence and contribute to the heightened subjective stress experienced during an acute stressor.

Finally, the neural stress reactivity patterns we observed during smoking satiety are consistent with our previous report¹⁸ and with reports of stress reactivity networks in healthy populations.^{10,23} During smoking satiety, significant activation was observed in the medial frontal gyrus, caudate, cingulate gyrus, middle occipital gyrus, and middle temporal gyrus.³⁸ This pattern supports a model of stress reactivity that involves recruitment of neurocircuitry in frontal, limbic, and cortical regions.²⁶ For example, it is proposed that the medial frontal and cingulate gyri are key regions involved in stress response and mood regulation and may act as an interface between limbic and cortical structures.^{49,50} These regions have been associated with top-down inhibitory control and self-evaluative processes, and therefore increased activation during stress may reflect increased recruitment of self-regulatory processes.⁵¹ The caudate has also been associated with stress-induced increases in neural activation in healthy participants,¹⁰ participants with anxiety,⁵² and in smokers,¹⁸ and may be associated with increased effort required to maintain goal-directed

behavior following the stressor.⁵³ Increased activation of the middle occipital gyrus and middle temporal gyrus during the stress condition has been proposed to reflect processing of task stimuli.²² Taken together, these findings suggest that the stress-reactive network in smokers who are smoking as usual is substantially similar to the network observed in healthy subjects.

To our knowledge, this is the largest fMRI study of abstinence-induced changes in stress reactivity in smokers. The use of a well-validated within-subject abstinence challenge paradigm allowed us to objectively measure neurobiological differences that occur specifically during abstinence.^{19,20} The MIST produced neural activation patterns and subjective stress responses in our sample that are consistent with those observed in other studies utilizing this task, which suggests that our stress manipulation was effective.^{10,54,55} However, this study also has limitations. Because the time course of stress response during abstinence is not fully understood, it is possible that changes in stress response may be more robust at longer windows of abstinence.⁵⁶ It is also possible that some participants may experience anticipatory stress about the fMRI scan which could heighten stress response to the stressor.⁵⁷ However, the within-subject design controls for such individual differences. On the other hand, our sample size did not enable testing for individual differences in stress response (such as gender differences) which have been noted in the literature.⁵² In addition, we did not include a sample of healthy control participants to directly compare stress reactivity in smokers to stress reactivity in healthy populations. We, therefore, cannot discern whether changes in neural activation during abstinence represent further disruption in activation compared to healthy controls, or a return to “normal” responses. Finally, our study was not designed to probe the causality of the relationships between neural activation and subjective responses. Future research designed to probe this question could provide more information for optimizing smoking cessation treatment.

The findings of this study suggest that the first 24 hours of a quit attempt is a vulnerable period for abstinence-induced neural stress response, supporting the use of effective stress management interventions such as mindfulness training or cognitive behavioral therapy prior to a quit attempt. Mindfulness training and cognitive behavioral therapy (with stress management) can reduce subjective

stress in clinical populations as well as healthy adults,^{58,59} and improve cessation rates among smokers.⁶⁰ An important next step in this regard would be to identify those strategies which decrease neural activation during an acute stressor. To that end, in a small ($n = 23$) randomized trial of smokers, Kober et al.⁶¹ found that mindfulness training, relative to cognitive behavioral therapy, was associated with lower neural stress response to individualized stress scripts; stress reactivity, in turn, was associated with smoking reduction. Collectively, these findings support further development of treatment approaches which target neural stress reactivity during the first 24 hours of smoking cessation, and suggest that fMRI may provide a useful tool for intervention optimization.

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Declaration of Interests

None declared.

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