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Neural Stress Reactivity Relates to Smoking Outcomes and Differentiates between Mindfulness and Cognitive-Behavioral Treatments

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Abstract

Stress and negative affect are known contributors to drug use and relapse, and several known treatments for addictions include strategies for managing them. In the current study, we administered a well-established stress provocation during functional magnetic resonance imaging (fMRI) to 23 participants who completed either mindfulness training (MT; N=11) or the American Lung Association's Freedom From Smoking (FFS; N=12), which is a cognitive-behavioral treatment (CBT) for smoking cessation. Across the entire sample, we found that stress reactivity in several brain regions including the amygdala and anterior/mid insula was related to reductions in smoking after treatment, as well as at 3-month post-treatment follow-up. Moreover, conjunction analysis revealed that these same regions also differentiated between treatment groups such that the MT group showed lower stress-reactivity compared to the FFS/CBT group. This suggests that reduction in stress reactivity may be one of the mechanisms that underlie the efficacy of MT in reducing smoking over time. The findings have important implications for our understanding of stress, the neural and psychological mechanisms that underlie mindfulness-based treatments, and for smoking cessation treatments more broadly.

Keywords

Stress; fMRI; smoking; mindfulness; cognitive-behavioral therapy

Introduction

Cigarette smoking is responsible for 5.4 million deaths per year and is the most preventable cause of morbidity and mortality in developed nations (CDC, 2008a, 2008b; WHO, 2010). Measured in terms of the burden on services such as health care and law enforcement, the

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loss of productivity in the home or workplace, and premature death and disability, the estimated costs of smoking in the US is 193 billion dollars per year (CDC, 2005). Although the rates of smoking have been declining, 21% of Americans still smoke. And, although over 70% of smokers report wanting to quit, < 5% of unassisted quit attempts are successful (CDC, 2005), and relapse is the most common outcome (Fiore, Bailey, & Cohen, 2000; Fiore, Jaén, & Baker, 2008; Piasecki, 2006). These grim statistics underscore the need to understand the factors that promote relapse, including their underlying neural mechanisms, in order to improve current treatments.

The term “stress” typically refers to processes involving perception, appraisal, and response to potentially harmful, threatening, or challenging events or stimuli (Levine, 2005; Sinha, 2008). Although several types of stress have been defined (e.g., McEwen et al., 2015), here we focus on stress as an acute, negatively-valenced affective state, which is closely related to anxiety (Leuner & Shors, 2013). Several lines of research suggest that such acute stress increases drug use in general and cigarette smoking in particular: (1) Acute stress increases self-administration of drugs (including nicotine) in animal models (Buczek, Le, Wang, Stewart, & Shaham, 1999; Piazza & Moal, 1998; Shaham & Stewart, 1995; Volpicelli, 1987; Zislis, Desai, Prado, Shah, & Bruijnzeel, 2007); (2) Acute stress is associated with drug use and relapse in human prospective studies (Back et al., 2010; Baer & Lichtenstein, 1988; Brewer, Catalano, Haggerty, Gainey, & Fleming, 1998; Brown et al., 1990; Brown, Vik, Patterson, Grant, & Schuckit, 1995; Shiffman & Waters, 2004); (3) Experience-sampling studies (in which drug users provide frequent reports throughout their daily lives) link stress to increased drug use and smoking (Cooney et al., 2007; Epstein, Marrone, Heishman, Schmittner, & Preston, 2010; Preston & Epstein, 2011; Shiffman, 2005; Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996; Shiffman & Waters, 2004); (4) Studies in abstinent smokers link stress and relapse (Doherty, Kinnunen, Militello, & Garvey, 1995; Swan et al., 1988); (5) Laboratory-induced stress increases cigarette craving (Buchmann et al., 2010; Childs & de Wit, 2010) and cigarette smoking (McKee et al., 2011), and magnitude of stress responses and negative affect predict relapse (Back et al., 2010; Sinha, Fox, et al., 2011; Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006; Witkiewitz & Villarroel, 2009); (6) In retrospective reports, drug users (including smokers) often cite stressful events and psychological distress as reasons for relapse (Baer & Lichtenstein, 1988; Brandon, 1994; Brownell, Marlatt, Lichtenstein, & Wilson, 1986; Marlatt & Donovan, 2005; Marlatt & Gordon, 1980; O'Connell & Martin, 1987; Swan et al., 1988; Wallace, 1989).

Despite the demonstrated role of stress in smoking, few studies have assessed neural stress responses in smokers (for a review of neural and HPA responses to nicotine, nicotine abstinence, and nicotine cues, see Supplementary Materials). In one study of satiated smokers, stress produced deactivation in limbic (e.g., amygdala, hippocampus, striatum) and prefrontal regions (e.g., ventromedial PFC, anterior cingulate cortex) that predicted increases in subsequent cue-induced craving responses (Dagher, Tannenbaum, Hayashi, Pruessner, & McBride, 2009). On the other hand, Ashare and colleagues (Ashare et al., 2016) reported increased neural stress reactivity in four brain regions, including anterior cingulate, precuneus, and inferior frontal gyrus; further, deprived smokers exhibited significantly greater activation compared to those who were non-deprived. The latter findings are consistent with prior reports in other drug using groups showing stress-induced increases

(rather than decreases) in neural activity (e.g., Potenza et al., 2012; Sinha et al., 2005). However, to our knowledge, no previous study assessed whether neural responses to stress may relate to treatment response among smokers undergoing treatment for smoking cessation. Such a study would increase our understanding of the underlying neural mechanisms by which acute stress relates to relapse, which can improve smoking outcomes, and addiction treatment more generally.

Given the role of stress in smoking and relapse, several smoking cessation treatments include components directed at reducing it. For example, cognitive-behavioral treatments (CBTs) may recommend reinterpretation of negative events as more positive, or engaging in a distracting or pleasurable activity to cope with stress (Carroll, 1998; Lando, McGovern, Barrios, & Etringer, 1990). Conversely, mindfulness-based treatments (MBTs) may recommend using mindfulness- and acceptance-based strategies, such as noticing and accepting negative emotions (letting those emotions be exactly as they are, without reacting to them; (Bowen, Chawla, & Marlatt, 2011). The difference between these two orientations in the treatment of substance use and smoking may be important. For example, it is known that using cognitive strategies to regulate negative emotions depends on recruitment of prefrontal cortex (PFC; Buhle et al., 2014), which may be compromised by stress (Arnsten, 2009; Raio, Orederu, Palazzolo, Shurick, & Phelps, 2013). Prefrontal function may also be compromised in some forms of psychopathology, including addictions (e.g., Kober, DeVito, DeLeone, Carroll, & Potenza, 2014; Koenigsberg et al., 2009). In contrast, it has been suggested that mindfully accepting craving and negative emotion may not depend on PFC recruitment, and may therefore be more effective, especially in vulnerable populations, or in vulnerable moments of stress when PFC function may be disrupted (Kober, Buhle, Weber, Ochsner, & Wager, under review; Westbrook et al., 2013). This raises the intriguing possibility that mindfulness-based interventions for substance use and smoking may be particularly effective at reducing stress, which in turn could improve outcomes (Creswell & Lindsay, 2014). Indeed, one of the first mindfulness-based treatments was designed for stress reduction (Kabat-Zinn et al., 1992), and such treatments have been associated with reductions in anxiety and negative affect in anxiety and mood disorders (Goldin & Gross, 2010; Kabat-Zinn et al., 1992; Teasdale, Segal, Ridgeway, & Soulsby, 2000) as well as in healthy adults (e.g., Chambers, Lo, & Allen, 2008). In fact, several recent meta-analyses have established mindfulness' efficacy in reducing negative mood and anxiety symptoms in diverse clinical samples (Goyal et al., 2014; Hofmann, Sawyer, Witt, & Oh, 2010). Thus, examining differences in responses to stress following such treatments for smoking cessation, especially as they relate to smoking outcomes, may provide a route to understanding their mechanisms of action.

Recently, we reported results from a randomized controlled trial (RCT) for smoking cessation, comparing Freedom From Smoking (FFS) – a common cognitive-behavioral treatment (CBT) for smoking cessation issued by the American Lung Association (Lando et al., 1990) – and mindfulness training for smoking (MT; Brewer, Mallik, et al., 2011). Both treatments were effective in reducing smoking, but the MT group demonstrated a greater rate of reduction in cigarette use during treatment, which was maintained during 3 month post-treatment follow-up (RCT N = 87; $F_{(1,1082)} = 11.11$, $p = .001$). Furthermore, the MT group showed a trend toward greater 1-week point prevalence abstinence at the end of treatment

(36% vs. 15%, $\chi^2_{(1)} = 3.45$, $p = .06$). This difference became statistically significant at the 17-week follow-up endpoint (31% vs. 6%, $\chi^2_{(1)} = 6.32$, $p = .01$; Brewer, Mallik, et al., 2011).

In the current manuscript, we report data from a neuroimaging probe administered to a sub-sample of participants from that clinical trial, immediately following treatment completion. We were especially interested in stress reactivity, and exposed participants to a well-established procedure of individualized script-based stressful scenarios, following our prior work (e.g., Brewer et al., 2009; McKee et al., 2011; Seo et al., 2011; Seo, Tsou, Ansell, Potenza, & Sinha, 2014; Sinha, 2001; Sinha, Catapano, & O'Malley, 1999; Rajita Sinha, Fuse, Aubin, & O'Malley, 2000; Sinha, Lacadie, Skudlarski, & Wexler, 2004; Sinha et al., 2005; Sinha & Tuit, 2012; for review see Sinha, 2009). We then (1) tested whether stress reactivity related to smoking after treatment as well as at the 3-month post-treatment follow-up, and also (2) compared neural activity during stressful scenarios between treatment groups. Given the role of stress in precipitating smoking (McKee et al., 2011), and prior findings that stress reactivity predicts relapse after treatment for other addictions (e.g., Seo et al., 2013; Sinha, Fox, et al., 2011; Sinha et al., 2006), we hypothesized that greater neural stress reactivity will be related to more smoking after treatment. Furthermore, we expected that neural stress-reactivity may be lower in the MT compared to FFS group, given prior work linking mindfulness-based treatments to reductions in stress (Goyal et al., 2014; Hofmann et al., 2010; Kabat-Zinn et al., 1992).

Method

Participants

Twenty-six participants underwent fMRI scanning in this protocol; three participants received only one (of two) negative/stress story or only one neutral/relaxing story and were therefore excluded from analyses. This was due to technical or other difficulties (e.g., scanner error; bathroom break) that limited the length of the scanning session and precluded presentation of all four stories. Therefore, data from 23 participants were considered usable and included in analyses in this paper. All participants were recruited from a smoking-cessation RCT (Brewer, Mallik, et al., 2011). RCT participants were English-speaking adults between 18-60 years of age, smoked ≥10 cigarettes per day, had fewer than 3 months of abstinence in the prior year, and reported interest in quitting smoking. Over 90% of them completed at least high school level education (see Table 1). Participants were excluded from the RCT if they could not read and understand the entire consent form, used psychoactive medications, had a serious or unstable medical condition in the prior 6 months, or met DSM-IV criteria for other substance dependence in the past year. RCT participants were offered participation in the fMRI component if they reported no claustrophobia, colorblindness, history of severe head trauma with loss of consciousness, neurological disorders, or any MRI-contraindicated conditions (e.g., metallic implants). fMRI scanning was conducted within 8 days of the last session of treatment. All participants provided written informed consent in accordance with Yale's Institutional Review Board.

Clinical Assessments

During treatment and at each of the follow-up sessions, self-reported smoking was assessed using the timeline follow-back method (Robinson, Sobell, Sobell, & Leo, 2014; Sobell & Sobell, 1992). Self-reported abstinence was then verified using exhaled carbon monoxide (CO) at CO ≤10 parts per million. The primary outcome measure was average number of cigarettes per day (CPD) across the 4 treatment weeks and through week 17 follow-up (3 month post treatment). Reduction in CPD from pre- to post-treatment and through follow-up was significant for both groups (effect of time: $F_{(1,1115)} = 480.79$, $p < .0001$; Brewer, Mallik, et al., 2011). For consistency, we used reduction in CPD from pre- to post-treatment and from pre-treatment to 3-month post-treatment follow-up as the clinical outcome variables in the current manuscript. Pre-treatment stress reactivity was assessed using the Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983).

Interventions

In the RCT, 84 participants were urn-randomized (Lachin, Matts, & Wei, 1988; Stout, Wirtz, Carbonari, & Del Boca, 1994; Wei & Lachin, 1988) to receive one of two active treatments based on gender (male vs. female), age (>40 years vs. ≤40 years old), race (white vs. non-white), and CPD (>20 vs. ≤20). Both treatments consisted of two weekly group sessions for 4 weeks (8 total sessions) that were manualized and delivered by trained instructors (for a detailed description, see (J. A. Brewer, Mallik, et al., 2011).

Freedom From Smoking (FFS; Lando et al., 1990), is a cognitive-behavioral treatment issued by the American Lung Association, that includes cognitive strategies for coping with cravings and stress/negative emotions, behavior modification, and relapse prevention. It is divided into three stages: preparation, action, and maintenance. In the preparation stage (sessions 1–3), participants examine smoking patterns through self-monitoring, identify triggers, and develop a personalized quit plan. On quit day (session 4), participants affirm their decision to be smoke-free and practice personalized coping strategies for stress and craving (e.g., avoiding high-risk situations). In the maintenance stage (sessions 5-8), participants identify ways to remain smoke-free by maintaining a healthy lifestyle (e.g., exercise, weight management), and discuss relapse prevention and the importance of social support and cognitive and behavioral coping strategies. Homework is recommended after each session, including formal practices (e.g., guided relaxation) and informal techniques (e.g., smoking diaries).

Mindfulness Training (MT) was developed for active smoking cessation based on mindfulness-based relapse prevention (Bowen et al., 2011) and has been described in detail previously (Brewer, Mallik, et al., 2011). Briefly, it includes training in mindfulness as a two component process: (1) attention to present moment experience, even if it includes craving or negative emotion; and (2) an accepting attitude towards this experience (letting it be exactly as it is, without judging it or reacting to it; Bishop et al., 2004; Ludwig & Kabat-Zinn, 2008). Early sessions (1-2) include an introduction to the concept of cue-induced craving, as well as strategies for mindfully working with craving and practicing mindfulness meditation. Session 3 discusses mindfully working with stress and negative emotion, and introduces loving-kindness meditation as a way to work with them through direct well-

wishing (e.g., “may I be happy”; Gunaratana, 1991). On quit day (session 4) participants practice mindfulness techniques to cope with craving, and commit to an aspiration to remain smoke free. In subsequent sessions 5-7, participants learn about possible triggers for habitual behavior and additional mindfulness practices (e.g., walking meditation, noting/labeling thoughts and feelings), while acceptance is reinforced as a tool for working with negative emotions and changing habits. The last session summarizes the course and offers ways of maintaining change. Homework is recommended after each session throughout the treatment period, including formal practices (e.g., body scan, loving-kindness meditation) and informal techniques (e.g., mindfulness of craving, smoking, stress, and daily activities).

fMRI Stress Task

During the scanning session, participants listened to two individualized stressful/negative scripts and two individualized neutral/relaxing scripts, based on our prior work (e.g., Brewer et al., 2009; McKee et al., 2011; Seo et al., 2011; Seo et al., 2014; Sinha, 2001; Sinha et al., 1999; Sinha et al., 2000; Sinha et al., 2004; Sinha et al., 2005; for review, see Sinha, 2009; for the published manual, see Sinha & Tuit, 2012). This method was initially adapted from Peter Lang's emotional imagery work and emotional network theory of threat, fear and anxiety (e.g., Lang, 1979; Lang, Levin, Miller, & Kozak, 1983; Sinha, 2009). Such individually-calibrated stressful scenarios were previously shown to elicit neurobiological stress responses in healthy adults as well as individuals with substance use and addiction disorders. Such stress responses include HPA activity, and neural activity in regions associated with negative affect, salience, and arousal, such as amygdala, hippocampus/parahippocampus, insula, thalamus, and striatum (e.g., Seo et al., 2011; Seo et al., 2014; for additional discussion, see supplementary materials).

Scripts were developed for each participant in a prior session, using a scene development interview, as previously described (Sinha, 2009; Sinha & Tuit, 2012). Briefly, each stressful script was based on a recent personal event that was experienced as very stressful, as indicated by a rating of 8 or greater on a 10-point likert scale ranging from 1 (“not at all stressful”) to 10 (“the most stressful event in my entire life”). Such stressful scenarios included breaking with a significant other, hearing about the loss of a family member, legal problems, and marital conflict situations (see Supplementary Materials for sample scripts). The neutral scripts were developed from the participants' description of a personal neutral or relaxing situation. Participants related the details of each scenario to an interviewer and reported physiologic, emotional, and cognitive responses during the event on a response checklist (e.g., “your heart skipped a beat,” “this can't be happening, you think,” “you can't take it anymore”). The interviewer integrated all the data and developed the personalized scripts using standard techniques (Sinha, 2009; Sinha & Tuit, 2012). All scripts were then recorded by one of the researchers for use during the fMRI scanning. During each of 4 functional runs, participants first provided a resting baseline for 30 seconds, and then heard the instruction “close your eyes and imagine the following situation as if it were happening right now.” Then, one of the individualized scenarios was played via headphones (the order of scenarios was randomized). Each scenario lasted about 3 minutes, and was followed by the instruction “please stop imagining and lay still,” followed by a cooldown period (See Figure 1 for schematic representation). Before and after each run, participants rated the

vividness of the imagined scenario, as well as their stress and craving on the same 10-point scale as before.

fMRI Data Acquisition, Preprocessing, and Analysis

Data Acquisition—Images were obtained using a 1.5 Tesla Sonata MRI scanner with standard eight-channel head coil (Siemens AG, Erlangen, Germany). Functional images were collected via T2*-weighted gradient-recalled single-shot echo-planar pulse sequence (TR/TE = 2000/35ms; flip angle = 85°; field of view = 220×220mm; 28 × 4mm slices). High-resolution 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) structural images were also collected (TR/TE = 2400/3.54ms; flip angle = 8°, FOV = 192 × 192; 160 × 1.2mm slices).

Preprocessing—All functional images were inspected for signal-to-noise ratio and motion in excess of one voxel; no participants were excluded from analyses for poor quality or excessive motion. Three initial volumes from each run were removed prior to preprocessing to allow for signal stabilization. Functional images were preprocessed using SPM8 (Wellcome Functional Imaging Laboratory, London, UK), following our prior work (e.g., Kober et al., 2010). This included slice-time correction to the first slice of each volume; motion correction; normalization of the mean functional image to the SPM functional template in Montreal Neurological Institute (MNI) space; warping of functional images to template space; reslicing into isometric 3×3×3 mm^3 voxels; and smoothing of functional images using a 6mm Gaussian kernel.

Analysis—First-level robust regression was implemented in MATLAB 7.3 (Mathworks, Natick, MA), via the NeuroElf platform (NeuroElf.net). This procedure uses the standard general linear model but with iteratively reweighted least squares using the bisquare weighting function to reduce the effects of outliers (Wager, Keller, Lacey, & Jonides, 2005), following our prior work (Brewer, Worhunsky, et al., 2011; Buhle et al., 2013; Kober et al., under review; Kober et al., 2014). Neutral and stressful scenarios were modeled as blocks, as were the instruction periods. Motion parameters were modeled as regressors of no interest. Subsequently, we performed a second-level, random-effects analysis to compare activity during stress and neutral scenarios between groups, using NeuroElf (e.g., Brewer, Worhunsky, et al., 2011; Buhle et al., 2013; Kober et al., under review; Kober et al., 2014). Results were familywise-error (FWE) corrected at $p < .05$ using the procedure first established, tested, and popularized by AFNI (“AlphaSim”; Cox, 1996). This process currently entails two steps. First, smoothness is estimated directly from the residual maps. Then, Monte Carlo simulation is used to estimate cluster size for the intensity threshold (Xiong, Gao, Lancaster, & Fox, 1995) to reach a combined familywise-error threshold.

To assess the relationship between stress-related brain activity and smoking, we computed whole-brain correlations between neural activity during stress scenarios and % reduction in CPD from pre- to post-treatment, as well as from pre-treatment to the 3 month post-treatment follow up, as reported in the original clinical trial (Brewer, Mallik, et al., 2011). Results were similarly FWE corrected at $p < .05$. To assess whether any stress-responsive regions were associated with smoking at both timepoints, we conducted a formal

conjunction analysis between the two correlation maps. To assess whether any stress-responsive regions both differentiated between treatment groups and were associated with smoking at both timepoints, we performed another conjunction between the contrast map [stress (FFS>MT)] and the two correlations.

Results

Participants

Eleven participants from the mindfulness and 12 participants from the CBT/FFS treatment groups participated in the fMRI scan. Demographic and participant characteristics are summarized in Table 1. Participants in the two treatment groups did not differ in age, education, race, BMI, alcohol use, or stress reactivity. Importantly, although the MT group smoked more pre-treatment, this difference was not statistically significant (similar to the main RCT; Brewer, Mallik, et al., 2011).

Smoking Outcomes

Although the fMRI subsample is smaller than that of the full RCT (Brewer, Mallik, et al., 2011), we replicated the analyses from the primary paper, for consistency, and found that smoking outcomes mirrored those in the full RCT. Specifically, both treatments reduced smoking, but the MT group demonstrated a greater rate of reduction in cigarette use during treatment, which was maintained during 3 month post-treatment follow-up (group * time $F_{(1,372)} = 21.00$, $p < .001$). Furthermore, the MT group showed a trend toward greater 1-week point prevalence abstinence at the end of treatment (55% vs. 23%, $\chi^2_{(1)} = 2.42$, $p = .11$, $d = .70$). This difference became statistically significant at the 17-week follow-up (44% vs. 7%, $\chi^2_{(1)} = 4.09$, $p = .04$, $d = .95$).

Behavioral Results

During scanning, participants reported being able to vividly imagine all scenarios ($M_{VIVIDNESS} = 8.58$, SD = 1.16; ratings were only available for 17 participants due to technical errors). First, as a manipulation check, we assessed the changes in ratings of stress and craving from pre- to post- stress and neutral scenarios. As expected, stress/negative scenarios increased ratings of stress ($t_{(16)} = 3.78$, $p = .002$, $d = .6$), whereas neutral scenarios did not ($t_{(16)} = 1.33$, $p > .2$). Similarly, stress scenarios increased ratings of craving ($t_{(16)}=2.58$, $p =.02$, $d = .36$) whereas neutral scenarios did not ($t_{(16)} = -1.69$, $p > .1$). Then, we compared post-scenario ratings between stressful and neutral scenarios. As expected, stress and craving ratings following stress stories were significantly higher than ratings following neutral stories (anxiety: $t_{(16)} = 2.42$, $p = .028$, $d = .3$; craving: $t_{(16)} = 2.72$, $p =.015$, $d = .36$). The MT and FFS groups did not differ on any of these self-report measures (all ps > .2).

fMRI Results

Correlations with Smoking—Across all participants, neural activity during the stressful scenarios was negatively correlated with post-treatment CPD reduction in a large cluster that included peaks in bilateral amygdala, anterior insula, mid insula, hippocampus, parahippocampal gyrus, thalamus, middle occipital gyrus, midbrain, cerebellum, and right

posterior insula, as well as a second region spanning the midline across cuneus/precuneus and posterior cingulate cortex (Table 2A; see Supplementary Figures S1-S2 for full results). The negative correlation indicates that those individuals with the greatest stress reactivity in those regions showed the lowest reduction in smoking from pre- to post- treatment.

Further, neural activity during the stressful scenarios was negatively correlated with CPD reduction at the 3-month follow-up in several regions including left amygdala, anterior/mid insula, posterior insula, parahippocampal gyrus, caudate and middle occipital gyrus, right hippocampus, hippocampal gyrus, inferior temporal gyrus and middle occipital gyrus, and bilateral portions of thalamus and cerebellum (Table 2B; Supplementary Figures S3-S4 for full results). Again, the negative correlation indicates that those individuals with the greatest stress reactivity in those regions showed the lowest reduction in smoking from pre-treatment to 3-month follow-up.

Differences between treatment groups—Next, we compared neural activity during neutral and stressful scenarios between groups. There were no significant group differences in brain activity during neutral scenarios. During stressful scenarios, participants in the FFS group (vs. MT) exhibited increased neural reactivity in several brain regions including left amygdala, anterior, middle, and posterior insula, and bilateral portions of parahippocampal gyrus and hippocampus, putamen, thalamus, midbrain and cerebellum (See Table 2C; Figure 2; Supplementary Figures S5-6 for full results). The MT group did not show greater neural reactivity in any region during stressful stories.

Identifying commonalities—A formal conjunction analysis between the two correlation maps revealed a set of regions that were responsive to stressful scenarios, and correlated with CPD reduction at both timepoints. Those included the left amygdala, extending into the anterior/mid insula and parahippocampal gyrus, as well as right hippocampus, parahippocampal gyrus, and posterior insula (Table 2D; Figure 3; Supplementary Figures S7-8 for full results). A second conjunction between the two correlation maps and the between-group contrast [stress (FFS>MT)] identified a few small regions that were related to smoking outcome and differed significantly between the two groups. Those included left amygdala and anterior/mid insula and right posterior parahippocampal gyrus (Table 2E; Supplementary Figures S9-10 for full results). Notably, in these regions, the MT group showed lower stress reactivity, and lower activity was related to better outcomes (greater reduction in smoking) after treatment and at 3-month follow-up.

Discussion

We found that lower neural reactivity to stressful scenarios in amygdala, mid-insula, and hippocampal regions related to greater reduction in smoking after treatment and at 3-month follow-up. Moreover, we found that reactivity in the same regions was significantly lower in individuals who underwent MT compared to FFS. In addition, we reported that the MT group showed a greater reduction in smoking in both timepoints following treatment, and a significantly higher rate of point-prevalence abstinence at follow-up. Taken together, these results suggest that MT reduces stress reactivity in these brain regions, and that this reduction is one of the clinically-relevant mechanisms that may underlie its efficacy as a

smoking cessation treatment. This is the first demonstration of this kind, and has important implications for our understanding of stress, the neural and psychological mechanisms that underlie mindfulness-based treatments, and for smoking cessation treatments more broadly.

Stress Reactivity and Smoking

First, these results join prior reports linking stress reactivity to drug use in general (Back et al., 2010; Brewer et al., 1998; Brown et al., 1990; Brown et al., 1995; Preston & Epstein, 2011; Sinha, 2001; Witkiewitz & Villarroel, 2009) and smoking in particular (Baer & Lichtenstein, 1988; Cooney et al., 2007; Epstein et al., 2010; McKee et al., 2011; Shiffman, 2005; Shiffman et al., 1996; Shiffman & Waters, 2004). Some of these studies have specifically shown that physiological and neural responses to stress relate to or predict drug use and relapse (Back et al., 2010; Seo et al., 2013; Sinha, Fox, et al., 2011; Sinha et al., 2006). Importantly, to our knowledge, this is the first demonstration of this relationship in smokers, whereby neural stress reactivity is negatively correlated with smoking outcomes, suggesting a broad role for stress reactivity across various substances, including nicotine cigarettes.

More specifically, we found that stress reactivity related to outcome in the amygdala and insula. The amygdala is an almond-shaped structure comprised of several subnuclei, which have distinct anatomical projections and serve different functions (Amaral, Price, Pitkanen, & Carmichael, 1992; Freese & Amaral, 2009). Nevertheless, the responsivity of amygdala to stress provocation in this study is not surprising given its role in detecting motivationally-salient stimuli (Kim et al., 2011), and in implementing core affect and emotion (for meta-analytic reviews, see Kober et al., 2008; Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012). Similarly, the insula may be conceptualized as a core affect region involved in awareness of affective feelings and bodily sensations (Craig, 2002, 2009; Lindquist et al., 2012). Consistently, both amygdala and insula have been implicated in the pathophysiology of anxiety and anxiety disorders (Damsa, Kosel, & Moussally, 2009; Etkin & Wager, 2007). In addition, functional and structural neuroplastic changes have previously been shown in both insula and amygdala following mindfulness meditation training (e.g., Farb et al., 2007; Goldin & Gross, 2010; Hölzel et al., 2011; Lazar et al., 2005; Lutz et al., 2014), with one study specifically linking reduction in amygdala density with stress reduction (Holzel et al., 2010).

Stress Induced Craving

Interestingly, the amygdala and insula have also both been implicated in drug craving (Chase, Eickhoff, Laird, & Hogarth, 2011; Garavan, 2010; Jasinska, Stein, Kaiser, Naumer, & Yalachkov, 2014; Mihov & Hurlemann, 2012), including cigarette craving (Engelmann et al., 2012; Kober et al., 2010; Kuhn & Gallinat, 2011; Naqvi, Rudrauf, Damasio, & Bechara, 2007). This is relevant to the present study, as it has been suggested that stress increases drug use specifically via stress-induced increases in craving (Li & Sinha, 2008; Potenza et al., 2012; Sinha, 2007, 2008; Sinha, Shaham, & Heilig, 2011). This link was demonstrated in laboratory studies in which stress and negative affect cues were found to increase negative affect, cortisol, heart rate, self-reported craving and cue reactivity (Childress et al., 1994; Coffey et al., 2002; Cooney, Litt, Morse, Bauer, & Gaupp, 1997; Fox, Hong, Siedlarz, &

Sinha, 2008; Hyman, Fox, Hong, Doebrick, & Sinha, 2007; Sinha, 2001; Sinha et al., 1999; Sinha et al., 2006; Sinha et al., 2005; Sinha & Li, 2007; for review, see Sinha, Shaham, et al., 2011). Prospective clinical studies have also related acute stress to craving for cigarettes (Doherty et al., 1995; McKee et al., 2011) and other drugs (Sinha, Fox, et al., 2011; Sinha et al., 2006) and further linked such stress-induced craving to drug use and relapse (McKee et al., 2011; Sinha et al., 2006). In the present study, participants across groups also reported increased craving following stressful scenarios, along with increased stress-related neural activity. However, compared to FFS, the MT group showed lower stress-related neural activity, and it is possible that the reduction in smoking seen with MT may be attributable to relative reduction in such stress-induced reactivity (Witkiewitz et al., 2014). Alternatively, reductions in these regions may reflect the decoupling of craving and smoking behavior; in the larger clinical trial, we found strong correlations between craving and smoking at baseline that were attenuated at the end of treatment in the MT group (Brewer, Mallik, et al., 2011). Further, this decoupling of craving and smoking was moderated by informal mindfulness practice (Elwafi, Witkiewitz, Mallik, & Brewer, 2013). While both interpretations are plausible, future studies are needed to specifically compare between them.

Implications for our Understanding of Mindfulness

It has long been known that mindfulness-based treatments reduce stress and anxiety, including in anxiety and mood disorders (as exemplified by Mindfulness-Based Stress Reduction; Goldin & Gross, 2010; Kabat-Zinn et al., 1992; Teasdale et al., 2000) and healthy adults (e.g., Chambers et al., 2008). In terms of neural activity, several studies have linked mindfulness to reduced neural reactivity to affective stimuli. In mindfulness-based emotion regulation studies comparing mindfulness (as an instructed transient mindful state) to non-mindfulness trials, mindfulness was associated with reduced amygdala and parahippocampal reactivity during perception of negative images (Lutz et al., 2014) and reduced reactivity to cigarette cues in subgenual anterior cingulate (in cigarette smokers Westbrook et al., 2013). Following 8 weeks of mindfulness training, Goldin and Gross (2010) reported faster decrease in amygdala activity to negative self-beliefs in socially anxious patients. Similarly, reductions in amygdala activity to negative emotional images was reported in healthy adults following training (Desbordes et al., 2012). Studies with trait mindfulness are also consistent with reduced reactivity to affective stimuli: higher trait mindfulness is associated with lower amygdala reactivity to negative faces (Creswell, Way, Eisenberger, & Lieberman, 2007), lower resting-state amygdala activity (Way, Creswell, Eisenberger, & Lieberman, 2010) and smaller amygdala volume (Taren, Creswell, & Gianaros, 2013). A recent EEG study also found lowered late positive potential to negative and erotic images in individuals with higher trait mindfulness (Brown, Goodman, & Inzlicht, 2013); for extended discussion, see Supplementary Materials).

In substance users, however, only a few small studies have been published on this topic. Those reported reductions in depression, anxiety, and stress (Zgierska et al., 2008), and in physiological markers of stress (Brewer et al., 2009) following mindfulness-based treatments. Here we find reduced neural stress reactivity following MT in cigarette smokers, compared to FFS, and no differences in recruitment of typical “cognitive control” regions

(e.g., dorsolateral prefrontal cortex; Buhle et al., 2014). This pattern of results is consistent with the view that mindfulness may lower emotional reactivity via “bottom up” mechanisms (rather than by increasing cognitive regulation of emotion; (Chiesa, Serretti, & Jakobsen, 2013; Kober et al., under review; Westbrook et al., 2013). This is further consistent with the Buddhist view that mindfulness prevents emotional reactivity (“the second arrow”; Teasdale & Chaskalson, 2011a).

The findings are further consistent with the “stress buffering account” of mindfulness (Creswell & Lindsay, 2014), which makes the specific prediction that mindfulness effects should be most potent in populations, such as smokers, in which stress is known to exacerbate the condition – and that this reduction would directly relate to reduced severity of the condition (i.e. smoking), as we report herein. As such, the present results may be the first direct evidence of this model, in showing that MT was associated with reduced neural reactivity to stress, which was further related to reduced smoking post treatment and at follow-up. Future studies should investigate the effects of MT on stress reactivity both pre- and post-treatment, as well as their effect on smoking and drug use outcomes.

Broad Implications for Treatment

Following previous reports implicating stress reactivity as a contributory factor in smoking relapse, this work suggests that, by reducing stress reactivity, MT may lead to improved smoking outcomes. One obvious implication would be that smoking cessation treatments should include strategies for stress-reduction. However, this is already the case: *both treatments* investigated in this RCT already included techniques for stress reduction. What is important, then, is that each treatment did so using *different psychological orientation and strategies*. Indeed, while CBT-type treatments focus on *changing the content of thought and emotions* (e.g., reappraising negative events, “finding the silver lining,” reducing negative affect), mindfulness-based treatments *change one's relationship to thoughts and emotions* (e.g., acceptance of negative events, letting thoughts be as they are, tolerating emotions; Gilpin, 2008; Shapiro, Carlson, Astin, & Freedman, 2006). This difference may be implicated in the differences in neural stress reactivity observed herein, as it has been previously proposed that awareness and acceptance (rather than avoidance and reduction) of emotional states is a mechanism of behavioral change across various disorders (e.g., Baer, 2003; Fjorback, Arendt, Ørnbøl, Fink, & Walach, 2011; Greenberg, 2002; Hayes & Feldman, 2004; Roemer & Orsillo, 2003; Teasdale & Chaskalson, 2011b).

However, thus far, only a few studies directly compared mindfulness-based to cognitive-behavioral treatments (e.g., Smith et al., 2008), and even fewer did so for substance use disorders (Bowen et al., 2014) including our prior RCT in smoking cessation (Brewer, Mallik, et al., 2011). This highlights the need for additional studies that examine the relationship between treatment type, mastery of particular strategies, neural activity, and drug use or smoking outcomes. The current results are at the very least consistent with the idea that the techniques taught in MT – including noticing and accepting negative affect and craving – are important treatment targets in smoking cessation and may be more potent than cognitive-behavioral strategies taught in FFS. This, in turn, suggests that adding mindfulness-based strategies might enhance the efficacy of active cessation treatments, as

has been shown recently in comparing standard relapse prevention and mindfulness-based relapse prevention (Bowen et al., 2014).

Strengths and limitations

One limitation of this study was the group sample sizes: there were only 12 participants in the FFS group and 11 in MT. Nevertheless, 23 participants were included in the main correlational analysis – that directly relates neural stress reactivity to treatment outcome – and this sample size exceeds the minimum standards for a study of this type (e.g., Carter, Heckers, Nichols, Pine, & Strother, 2008). The data were also collected on 1.5T scanner, which typically has lower signal-to-noise ratio (SNR) than 3T scanners. However, data were carefully quality-checked by the imaging center staff and the authors, and found to have normal SNR, and sufficient contrast-to-noise ratio (which is most important in this context). Another limitation is that self-report ratings were not available for the full sample due to technical difficulties during data acquisition. In addition, the smokers in our study participated in the fMRI session after completing smoking cessation treatment; therefore, changes from pre- to post-treatment were impossible to assess. Furthermore, because we excluded individuals taking psychoactive medications or who met DSM-IV criteria for any substance dependence, we did not collect information on substance use except cigarettes and alcohol. Nonetheless, random assignment from a community-based sample is a strength, and the groups did not differ in any pre-treatment clinical characteristics, including smoking, alcohol use, and stress reactivity (measured via the PSS). Indeed, participants were randomized into groups; thus, the post-treatment data allows for cautious consideration of treatment effects.

Conclusions

We presented results from an fMRI stress probe administered following MT or FFS treatment for smoking cessation. We found that neural reactivity in regions including amygdala and insula related to smoking outcomes after treatment and at 3-month post-treatment follow-up. Activity in these regions also differentiated between treatment groups such that those who underwent MT showed lower stress reactivity in these regions. The results implicate reduction in stress reactivity as a mechanism of MT treatment-related change, and suggest that treatments that target stress reactivity hold particular promise for smoking cessation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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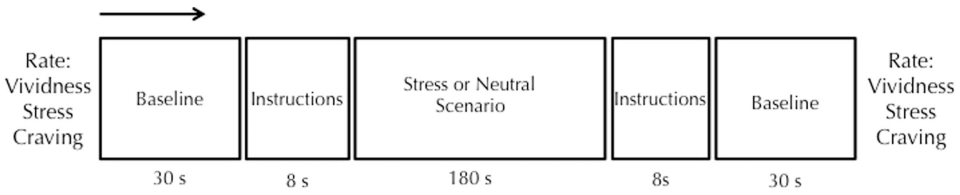

Figure 1. Schematic Representation of Each Run

During each of 4 functional runs, participants first experienced a resting baseline for 30 seconds, and then heard the instruction “close your eyes and imagine the following situation as if it were happening right now.” Then, one of four individualized scenarios was played via headphones (two stressful/negative and two neutral/peaceful scenarios, presented in random order). Each scenario lasted 3 minutes, and was followed by the instruction “please stop imagining and lay still,” followed by a cooldown period. Before and after each run, participants rated their stress and craving on a 10-point scale; and after each scenario they rated the vividness of the imagined scenario.

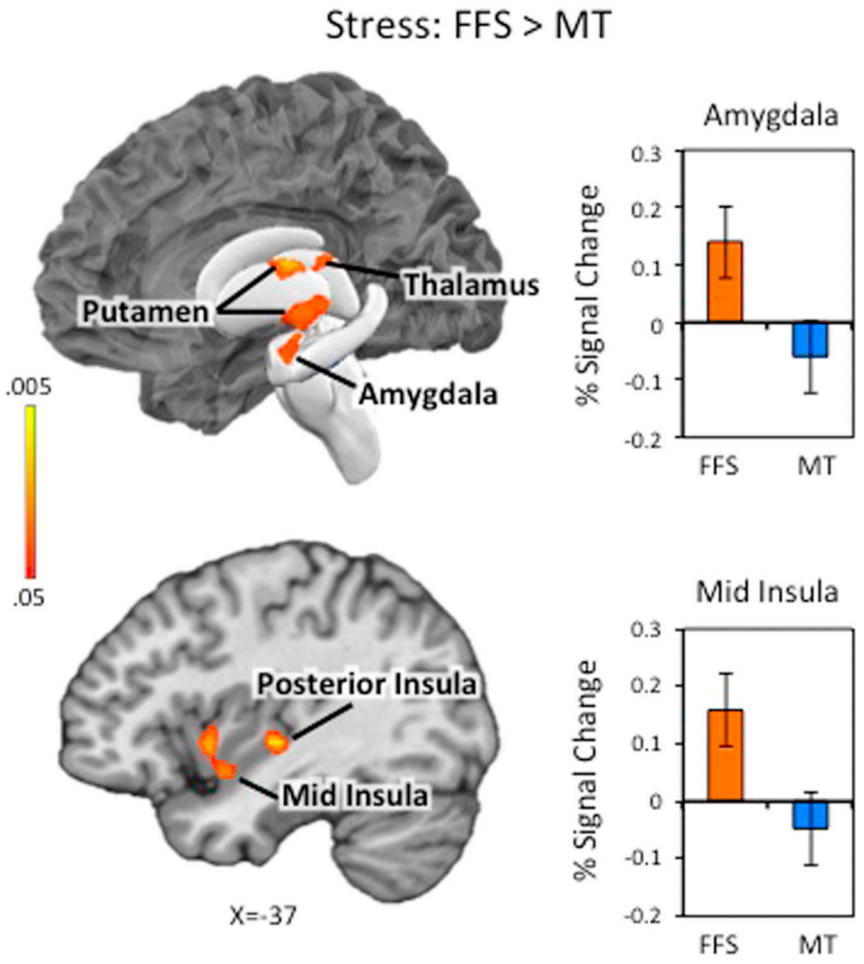

Figure 2. Stress Reactivity: Comparison Between Treatment Groups

Neural activity during stressful scenarios was contrasted between the Freedom from Smoking (FFS) group and the Mindfulness Training (MT) group [FFS_{STRESS}>MT_{STRESS}]. The FFS group exhibited greater stress-related neural activity in left amygdala, anterior, middle, and posterior insula, and bilateral portions of parahippocampal gyrus and hippocampus, putamen, thalamus, midbrain and cerebellum (See Table 2A; See Supplementary Figures S5-S6 for full results). The MT group did not show greater neural reactivity in any region during stressful stories. Bar graphs represent the extracted cluster-averaged percent signal change in amygdala (top) and insula (bottom). Error bars represent standard errors. Results are familywise-error corrected (FWE) at $p < .05$. Left side of the brain is displayed on the left.

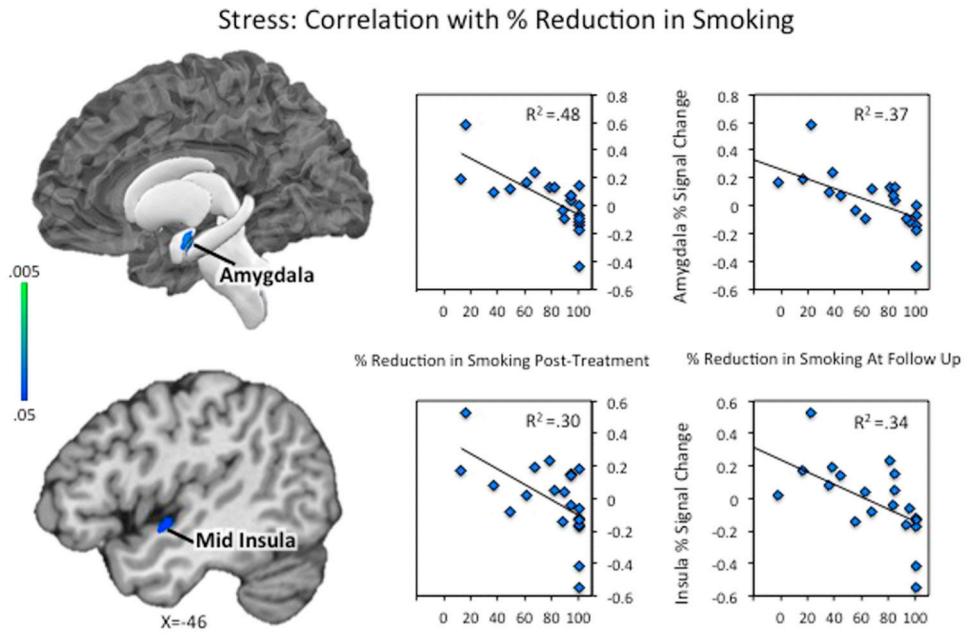

Figure 3. Stress Reactivity: Correlations with % Reduction in Smoking

Neural activity during stressful scenarios was correlated with % reduction in cigarettes per day from pre- to post-treatment (left scatter plots) and % reduction in cigarettes per day from pre-treatment to 3-month follow-up (right scatter plots). Full correlation results are displayed in Supplementary Figures S1–S4. A formal conjunction analysis between the two correlation maps revealed a set of regions that were responsive to stressful scenarios, and correlated with CPD reduction at both timepoints. Those included the left amygdala, extending into the anterior/mid insula (as shown here) and parahippocampal gyrus, as well as right hippocampus, parahippocampal gyrus, and posterior insula (shown in Supplementary Figure S7-S8). Scatter plots represent the extracted cluster-averaged percent signal change during stress scenarios in regions identified in the conjunction analysis.

Table 1

Clinical and Demographic Characteristics

	Overall	MT	FFS	Test Statistics	Significance
N	23	11	12		
N Females	7	4	3	X2 = .35	NS p>.5
Age: Years (SD)	48.3 (6.98)	48.0 (7.18)	48.5 (7.10)	t(21) = .43	NS p>.6
Race				X2 = 4.43	NS p>.1
White	14	8	6		
Black	8	2	6		
Asian	1	1	0		
Hispanic	1	1	0		
Education				X2 =3.63	NS p>.3
College Grad or More	6	3	3		
Partial College	3	1	2		
High School	12	6	6		
Less Than High School	2	1	1		
Body Mass index (SD)	28.9 (4.5)	28.5 (4.34)	29.2 (4.70)	t(21) = .40	NS p>.6
Pre-Treatment Stress (PSS)	25.41 (6.84)	27.56 (4.85)	23.92 (7.77)	t(20) = 1.24	NS p>.2
Pre-Treatment Alcohol Per Day	1.14 (1.54)	1.3(1.8)	1.02(1.39)	t(21) = .41	NS p>.6
Pre-Treatment CPD	17.97 (9.65)	20.67 (10.92)	14.71 (7.45)	t(21) = 1.36	NS p>.1
Average % Reduction in CPD Post Treatment	79%	88%	71%	Group × Time reported ln text	
Average % Reduction in CPD At Follow Up	60%	71%	50%	Group × Time reported in text	

Note. The fMRI sub-sample was similar to the main RCT sample. Treatment groups did not differ significantly on any dimension pre-treatment. One individual identified as both Black and Hispanic (MT=Mindfulness Training; FFS=Freedom from Smoking; N=number of participants; SD=standard deviation; NS=not significance; PSS=Perceived Stress Scale; CPD=Cigarettes Per Day).

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Table 2

Neuroimaging Results: Stress-reactive regions that differ between treatment groups and relate to smoking outcomes.

		Peak-Coordinates							
Regions of Activation	**R/L/Bi**	***x***	***y***	***z***	***k***	***Vol(mm3)***	**Peak Statistic**	**Mean Statistic**	**Cohen *d***
A. Stress Reactivity Correlates with % Smoking Reductiion at End of Treatment (Week 4)									
Bilateral Amygdala, Anterior/Mid Insula, Hippocampus, Parahippocampal Gyrus, Thalamus, Middle Occipital Gyrus, Cerebellum, Midbrain, and Right Posterior insula, Superior/Middle Temporal Gyrus	Bi	-15	-51	-45	3250	87750	-0.77	-0.51	1.18
Cuneus, Precuneus, Posterior Cingulate	Bi	-3	-69	21	164	4428	-0.69	-0.52	1.22
B. Stress Reactivity Correlates with % Smoking Reduction at FollowUp (Week17)									
Hipoocampus, Parahippocampal Gyrus, Posterior inferior Temporal Gyrus, Middle Occipital Gyrus	R	30	-30	-6	180	4860	-0.77	-0.52	1.22
Cerebellum	L	-39	-90	-24	143	3861	-0.70	-0.50	1.15
Caudate, Superior/Middle Temporal Gyri	R	24	-39	12	165	4455	-0.69	-0.51	1.18
Middle Occipital, Parahippocampal Gyrus, Caudate	L	-27	-72	-3	152	4104	-0.67	-0.51	1.18
Amygdala, Anterior/Mid insula, Posterior insula, Superior Temporal Gyrus, Parahippocampal Gyrus	L	-39	-6	-3	208	5616	-0.66	-0.49	1.12
Thalamus. Cerebellum	Bi	-6	-42	-9	276	7452	-0.63	-0.49	1.12
C. Group Differences: Stress Scenarios (FFS>MT)									
Amygdala, Anterior/Mid insula, Posterior insula, Putamen, Thalamus, Parahippocampal Gyrus	L	-24	-6	15	344	9288	5.72	2.64	1.10
Right Thalamus, Putamen, Bilateral Midbrain, Cerebellum	Bi	9	-3	-6	371	10017	4.00	2.48	1.03
Posterior Parahippocampal/Hippocampal Gyri, Cerebellum	Bi	6	-66	-42	380	10260	3.97	2.48	1.03
D. Conjunction of A & B: Stress Reactivity Correlates with % Smoking at Weeks 4 & 17									
Hippocampus, Parahippocampal Gyrus, Posterior Insula	R	30	-27	-9	95	2565	0.0008	0.010	-
Amygdala, Anterior/Mid Insula, Parahippocampal Gyrus	L	-30	-9	-18	75	2025	0.003	0.020	-
E. Conjunction of A & B & C: Stress Reactivity Correlates with Smoking Outcomes and Differentiates Between Groups									
Posterior Cingulate/Posterior Caudate	R	21	-48	12	22	594	0.007	0.027	-
Posterior Hippocampus/Parahippocampal Gyrus	R	24	-45	-15	22	594	0.008	0.026	-
Hippocampus/Parahippocampal Gyrus	R	30	-24	-9	15	405	0.010	0.024	-
Amygdala	L	-30	-9	-18	12	324	0.016	0.030	-
Anterior/Mid insula	L	-42	-3	-12	11	297	0.026	0.036	-

Note. Peak activations xyz are in MNI coordinates. R/L/Bi refer to lateralization of activation as Right, Left, or Bilateral. K refers to number of 3×3×3 voxels in each cluster. Volume is expressed in mm^3. (a-b) Peak/mean statistics are correlation coefficient r. Results are whole-brain familywise error-corrected at $p < .05$. (c) Peak/mean statistics are t values. Results are whole-brain familywise error-corrected

at $p < .05$. (d–e) Peak statistics for conjunctions represent the maximum (i.e. least significant) p statistic following conjunction conventions (Nichols, Brett, Andersson, Wager, & Poline, 2005). Mean statistics represent the average maximum (i.e. least significant) p statistic following conjunction convention. Cohen *d* effects sizes are provided for illustration, calculated from the mean (rather than peak) statistic in each cluster. These should be interpreted with caution as effect sizes estimated from imaging data may be inflated (e.g., Vul, Harris, Winkielman, & Pashler, 2009; Yarkoni, 2009).