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Quitting-Unmotivated and Quitting-Motivated Cigarette Smokers Exhibit Different Patterns of Cue-Elicited Brain Activation When Anticipating an Opportunity to Smoke

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The authors examined the effects of smoking expectancy on cue-reactivity among those motivated and those unmotivated to quit smoking using functional MRI. Cue-elicited activation was observed in the rostral prefrontal cortex (PFC) in smokers who expected to smoke within seconds, but not in those who expected to have to wait hours before having the chance to smoke, regardless of quitting motivation. For quitting-unmotivated smokers expecting to smoke, rostral PFC activation was strongly positively correlated with the activation of several areas previously linked to cue-reactivity, including the medial orbitofrontal cortex (OFC) and rostral anterior cingulate cortex (ACC). In contrast, there was a nonsignificant negative relationship between activation of the rostral PFC and activation of the medial OFC/rostral ACC in quitting-motivated smokers expecting to smoke. Results extend previous work examining the effects of smoking expectancy and highlight the utility of examining interregional covariation during cue exposure. Findings also suggest that investigators may need to pay close attention to the motivational contexts associated with their experiments when studying cue-reactivity, as these contexts can modulate not only responses to drug cues, but perhaps also the functional implications of observed activity.

Keywords: drug addiction, quitting, motivation, cue-reactivity, neuroimaging

Several lines of evidence support an association between responses elicited by smoking-related stimuli (i.e., cue-reactivity) and relapse in those attempting to quit smoking (Ferguson & Shiffman, 2009). For instance, Waters and colleagues (2003) found that the magnitude of attentional bias that smokers exhibited for smoking-related stimuli predicted the likelihood that they would relapse early during a quit attempt. Subjective (e.g., self-reported urge or craving; Waters et al., 2004) and physiological (e.g., heart rate; Abrams, Monti, Carey, Pinto, & Jacobus, 1988) responses to smoking cues also have been linked to relapse.

Given the clinical importance of smoking cue-reactivity, it is noteworthy that smokers appear to respond more vigorously to cigarette cues when they believe that smoking soon will be possible, relative to when they believe that they will not have the opportunity to smoke for an extended period of time (Wertz & Sayette, 2001b). Smokers anticipating an opportunity to smoke in the near future report stronger cravings in the presence of cigarette cues (e.g., Carter & Tiffany, 2001; Juliano & Brandon, 1998) and pay greater attention to smoking-related stimuli (Wertz & Sayette, 2001a) than do those who expect a significant delay before smoking is possible. Physiological responses to cigarette cues likewise are modulated by smoking expectancy (referred to interchangeably as *smoking opportunity* and *smoking availability*). For example, bodily responses thought to reflect arousal, such as skin conductance (e.g., Carter & Tiffany, 2001), heart rate (Lazev, Herzog, & Brandon, 1999), and electrocortical activity (Zinser, Fiore, Davidson, & Baker, 1999), are heightened in contexts predictive of smoking availability. More recently, findings from brain imaging research indicate that cue-elicited activation of the orbitofrontal cortex (OFC)—a brain region implicated in monitoring the reward value of stimuli (Kringelbach & Rolls, 2004)—is greater in smokers who expect to smoke soon than in those who do not (McBride, Barrett, Kelly, Aw, & Dagher, 2006; Wilson, Sayette, Delgado, & Fiez, 2005), with similar effects observed in other brain areas supporting affective and motivational processing (e.g., the striatum) in smokers anticipating an intravenous infusion of nicotine (Gloria et al., 2009).

Collectively, these findings suggest that the incentive salience of smoking-related stimuli is enhanced when such cues are encountered in the context of an impending opportunity to smoke—at least for active smokers. To date, most smoking cue-reactivity

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studies, including those examining the effects of smoking expectancy, have included participants with no expressed intention of quitting smoking. It is thus perhaps not surprising that findings point toward the experience of an appetitive anticipatory state associated with the expectation of a chance to smoke. As noted by Sayette (2004, p. 456), "When a smoker expects to satisfy an urge. . .[t]he moments just prior to use, and even the beginning of consumption, may be particularly positive." In accord with this idea, quitting-unmotivated smokers expecting to smoke imminently are more likely to display facial expressions related to positive affect and less likely to display expressions related to negative affect, compared with when they do not expect to smoke in the near future (Sayette & Hufford, 1995; Sayette et al., 2003).

To our knowledge, laboratory studies have not examined smoking cue-reactivity in quitting-motivated smokers presented with an opportunity to smoke. This is an important limitation, as naturalistic research suggests that the presence of cigarette cues coupled with smoking availability (e.g., being offered a cigarette by a friend) significantly increases the risk of relapse for those trying to quit smoking (Ferguson & Shiffman, 2009). Presumably, individuals motivated to quit smoking may endeavor to inhibit their responses to a cigarette cue (Sayette, 2004). It is quite possible that attempts to regulate or suppress cue-reactivity to resist smoking are associated with different patterns of cue-reactivity than the eager anticipation of cigarette consumption. Examining how quitting-unmotivated and quitting-motivated smokers respond differently when faced with a cigarette cue may shed light on the positive anticipatory mechanisms that contribute to the maintenance of smoking and those that are used to cope with these appetitive reactions. Results from such research may have important clinical implications, particularly for treatments with a motivational focus (e.g., motivational interviewing; Hettema & Hendricks, 2010).

In the present study, we examined the effects of smoking opportunity on responses to a cigarette cue in both quitting-unmotivated and quitting-motivated smokers using functional MRI (fMRI). fMRI provided the opportunity to uncover differences in the reactivity of quitting-unmotivated and quitting-motivated smokers that may be difficult to detect using other methods, such as self-reported urge or peripheral physiological measures. Our primary aim was to compare patterns of neural activity during cigarette cue exposure in quitting-unmotivated and quitting-motivated smokers who were told that they would be given a chance to smoke within seconds. Consistent with prior research (Sayette, 2004; Sayette et al., 2003), we predicted that cue exposure would be associated with positive anticipatory responses in quitting-unmotivated smokers presented with the opportunity to smoke. In contrast, we hypothesized that quitting-motivated smokers would be motivated to inhibit their responses to a cigarette cue when faced with the opportunity to smoke.

Research has begun to identify the neural mechanisms involved in the regulation of cue-elicited responses by addicted individuals (Brody et al., 2007; Kober et al., 2010; Volkow et al., 2010). Results from these studies indicate that the modulation of cue-reactivity involves many of the same brain regions that have been implicated in the regulation of affective and motivational states more generally (Davidson, Fox, & Kalin, 2007; Delgado, Gillis, & Phelps, 2008; Ochsner & Gross, 2005). More specifically, they suggest that the inhibition of cue-elicited responses is associated with increases in the activation of areas of the brain that implement domain-general control processes, including medial and lateral prefrontal cortex (PFC), and decreases in the activation of areas supporting more circumscribed affective/motivational processes (e.g., the valuation of an impending reward), including the orbitofrontal cortex, striatum, insula, and amygdala (Brody et al., 2007; Kober et al., 2010; Volkow et al., 2010). These findings provide a framework for generating predictions regarding how motivation to quit smoking might affect cue-elicited neural activation in individuals anticipating an opportunity to smoke, which we hypothesized would involve many of the regions identified in prior research on emotion regulation.

However, in contrast to prior brain imaging studies of emotion regulation, which primarily have compared neural responses during active regulation and passive control conditions, we posited that both quitting-unmotivated and quitting-motivated smokers would be actively engaged in regulatory processing when presented with a cigarette and a chance to smoke. We therefore predicted that both quitting-unmotivated and quitting-motivated smokers would exhibit cigarette-related increases in the activation of areas that previously have been linked to emotion-regulation and decision-making, such as the rostral and dorsolateral prefrontal cortices (Davidson et al., 2007). Critically, though, we hypothesized that quitting-unmotivated and quitting-motivated smokers would utilize the regulatory processing supported by these regions toward different ends (actively savoring vs. actively inhibiting cue-elicited responses, respectively; see Sayette, 2004). Accordingly, we expected that the effects of quitting motivation would be particularly evident when examining the relationship between the activation of control-related regions and the activation of areas involved in affective/motivational processing (i.e., as opposed to through differences in the mean activation level within brain regions in isolation). This notion is consistent with the growing emphasis on the importance of characterizing interregional interactions for understanding the neurobiological processes underlying cognition, more generally (McIntosh, 2000; Tomasi & Volkow, 2011). Indeed, techniques for exploring such interactions are increasingly being applied to investigate the neurobiological processes associated with addiction to cigarettes and other substances (e.g., Cole et al., 2010; Daglish et al., 2003; Janes et al., 2010; Tomasi et al., 2010; Zhang et al., 2011). A primary goal of the current study was to apply similar analytic techniques to investigate the effects of quitting motivation on functional connectivity (i.e., the degree to which the activation of spatially distinct brain regions correlate; Friston, Frith, Liddle, & Frackowiak, 1993), with a particular focus on cognitive control-related brain regions exhibiting significant cue-elicited increases in activation in both quitting-unmotivated and quitting-motivated smokers.

Method

Participants

Cigarette smokers (n = 100) ages 18 to 45 were recruited through advertisements in the community and local newspapers. Usable data were collected from 90 participants (three participants were excluded because of data loss resulting from technical error, and seven participants were excluded because of excessive head motion during fMRI scanning). Self-identified ethnicity of the

sample was as follows: 69% Caucasian, 26% African American, 2% Hispanic, 3% other. Both smokers with no expressed intention of quitting and those wishing to quit smoking were sought for enrollment. Regarding the latter, advertisements recruited smokers who were planning on quitting smoking in the near future and who were interested in entering smoking cessation treatment but did not explicitly offer treatment as a component of the study. Quitting-unmotivated smokers ($n = 43$) had to report that they currently were not planning to quit smoking. Quitting-motivated smokers ($n = 47$) had to report that they were planning on quitting smoking within two weeks, were interested in smoking cessation treatment, and were willing to initiate an attempt to quit smoking during the experiment.

The distribution of participants across groups was as follows: quitting-unmotivated/instructed-yes ($n = 21$; 9 female, 12 male), quitting-unmotivated/instructed-no ($n = 22$; 9 female; 13 male), quitting-motivated/instructed-yes ($n = 26$; 12 female, 14 male), quitting-motivated/instructed-no ($n = 21$; 9 female, 12 male). Both quitting-unmotivated and quitting-motivated participants had to report smoking an average of 15 to 40 cigarettes per day for the past 24 months. All participants were right-handed and had to pass an MRI safety screening. Written informed consent was obtained from all participants, and all procedures were approved by the local Institutional Review Board. Individuals were paid US$100 for their participation.

Design and Overview

Participants completed two sessions during the study, which are described in detail below. Those deemed eligible based upon a telephone screening were scheduled for an initial baseline session during which questionnaires and behavioral working memory assessments were administered. Participants then were scheduled for the fMRI-based experimental session (held within two weeks of the baseline session), during which they performed a working memory task and cue exposure procedure while fMRI data were collected. For quitting-motivated smokers, the experimental session was scheduled to coincide with the first day of an attempt to quit smoking. Specifically, quitting-motivated smokers were instructed to initiate a cessation attempt 12 hrs before the onset of the experimental visit. Members of each group (quitting-motivated and quitting-unmotivated) were assigned randomly to one of two smoking opportunity conditions (instructed-yes or instructed-no) for the experimental session. Participants in the instructed-yes condition were informed that they would have the opportunity to smoke during the study, while those in the instructed-no condition were told that they would not be able to smoke until after the 2-hr study had ended.

Materials

Questionnaires. During the baseline assessment, participants completed questionnaires measuring the following: current and past smoking practices (Shiffman, Paty, Kassel, Gnys, & Zettler-Segal, 1994), level of nicotine dependence (Fagerstrom Test for Nicotine Dependence [FTND]; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991; Nicotine Dependence Syndrome Scale [NDSS]; Shiffman, Waters, & Hickcox, 2004), smoking abstinence self-efficacy (Relapse Situation Efficacy Questionnaire [RSEQ]; Gwaltney, et al., 2001), trait self-control (Self Control Scale [SCS]; Tangney, Baumeister, & Boone, 2004), positive and negative affect (Positive and Negative Affect Schedule [PANAS]; Watson, Clark, & Tellegen, 1988), and tendency to respond in a socially desirable manner (Balanced Inventory of Desirable Responding Version 6 [BIDR-6]; Paulhus, 1991). To measure the effects of nicotine withdrawal on cognitive and emotional functioning, participants completed questionnaires measuring the following at the beginning of the experimental session (i.e., after abstaining from smoking for 12 hrs): current levels of positive and negative affect (state version of the PANAS; Watson et al., 1988) and mental energy/fatigue (State Self-Control Capacity Scale [SSCCS]; Ciarocco, Twenge, Muraven, & Tice, 2007). As the focus of the present study is on neural responses during cue exposure, questionnaire data are presented only briefly.

Cue exposure fMRI task. Participants completed a cue exposure procedure adapted from prior research (Wilson et al., 2005). Each run of the task began with a 48-s resting baseline epoch during which participants were asked to relax and remain still. After this initial baseline period, an object was placed in the participant's left hand and prerecorded instructions identifying the object were delivered via intercom. Participants were instructed to passively view the object, which they held for a period of 74 s. To allow participants to see what they were holding, a live video feed from a camera focused on their left hand was projected onto a visual display positioned inside the magnet's bore (viewed using a mirror placed above the participant's eyes). Participants completed three runs of the cue exposure task, during which they held a small notepad, a roll of electrical tape, and a cigarette (one of their preferred brand) in the first, second, and third runs, respectively. The notepad and roll of tape were control objects designed to elicit relatively small changes in affect. The first run served as a practice run that allowed participants to acclimate to the task and was excluded from analyses.

Upon presentation of the cigarette, a prerecorded message was delivered via intercom reminding participants whether or not they would be given the opportunity to smoke soon. Those assigned to the instructed-yes condition were told that they would be removed from the scanner in 40 s and would be permitted to smoke the cigarette they were holding immediately if they chose to do so; those assigned to the instructed-no condition were told that they would be removed from the scanner in 40 s but would not be permitted to smoke the cigarette they were holding (see Wilson et al., 2005). Because there is evidence that exposure to smoking cues affects behavioral and neural responses to subsequently presented items (for review, see Sayette, Griffin, & Sayers, 2010), the order in which objects were presented was fixed in the aforementioned sequence.

Urge to smoke. Participants verbally rated their urge to smoke on a scale from 0 (*absolutely no urge to smoke at all*) to 100 (*strongest urge to smoke I've ever experienced*). This single-item scale has proven sensitive to a wide range of craving experiences (see Juliano & Brandon, 1998; Sayette, Martin, Wertz, Shiffman, & Perrott, 2001) and allows for the rapid and repeated measurement of urge throughout the study. Participants rated their current urge to smoke three times during the experimental session: (1) at the start of the experimental session prior to both the delivery of smoking opportunity instructions and placement in the scanner (urge-baseline), (2) while holding the roll of tape at the conclusion

of the second run of the cue exposure task (urge-control cue), and (3) while holding a cigarette at the conclusion of the third run of the cue exposure task (urge-cigarette cue).

Working memory tasks. Participants also completed behavioral working memory assessments and an fMRI-based working memory task (a verbal n-back task adapted from Ravizza, Delgado, Chein, Becker, & Fiez, 2004) as a part of a larger study examining individual differences in working memory functioning in individuals who smoke. These results will be presented in a separate article.

Procedure

Baseline session. After an initial telephone screening, eligible participants completed a baseline assessment session scheduled to begin between 11:00 a.m. and 4:00 p.m. During this session, participants first provided a baseline carbon monoxide (CO) sample (BreathCo, Vitalograph, Lenexa, Kansas). They then completed the two behavioral working memory tasks. Next, participants completed the following questionnaires: demographic information form, NDSS, RSEQ, SCS, and the trait version of the PANAS. Finally, quitting-motivated smokers were referred for treatment at one of two randomly assigned smoking cessation programs in the community. They telephoned their assigned program to enroll at the conclusion of the baseline session while still in the laboratory. Participants did not receive treatment during the course of the present study, and details regarding their utilization of treatment were not collected.

After completing baseline assessment, participants were scheduled for the experimental session. They were instructed to abstain from smoking and from using any nicotine-containing products for at least 12 hrs before the experiment and that a CO sample would be obtained to verify compliance with these instructions. Participants also were instructed to refrain from consuming drugs or alcohol for the 24 hrs preceding the experiment and were instructed to bring a pack of their cigarettes to the experimental session.

Experimental session. Experimental sessions began between 11:00 a.m. and 2:00 p.m. on a subsequent day. Upon arrival, participants reported the last time they smoked a cigarette and a second CO sample was obtained to check compliance with deprivation instructions. Participants had to have a CO level that was at least 50% lower than the initial sample provided during the baseline assessment session. This cutoff was established based upon prior experience with similar samples and procedures (e.g., Sayette, Loewenstein, Griffin, & Black, 2008). Those who did not meet the CO requirements were withdrawn from the experiment. Participants next presented their pack of cigarettes and lighter to the experimenter. To assess the effects of nicotine deprivation on mood and mental state, participants subsequently completed the state version of the PANAS and the SSCCS. They then completed a pre-cue–exposure urge rating (urge–baseline).

Participants then were told whether or not they would be given the opportunity to choose to smoke during the experimental session. Those in the instructed-yes condition were informed that they would be removed from the scanner for a brief break during the study, at which point they would be able to smoke. As in our previous study (see Wilson et al., 2005), these instructions were delivered by an experimenter standing in front of a sign designating the room as a "smoking area for research purposes only." This room was located in close proximity to that housing the MRI scanner, thus enhancing the likelihood that participants would anticipate having the opportunity to smoke almost immediately after cigarette cue exposure. Participants in the instructed-no condition also were told that they would be removed from the scanner for a break but were instructed that they would not be able to smoke during the study and therefore would have to wait about 2 hrs before having the chance to smoke. This time frame has been used in prior research to create an expectancy of not being able to smoke (see also Juliano & Brandon, 1998; Wilson et al., 2005).

Participants subsequently were placed inside the scanner. After collection of anatomical images, participants completed the verbal n-back and cue exposure tasks while fMRI data were collected. Additional urge ratings were collected immediately after the second (urge-control cue) and third (urge-cigarette cue) runs of the cue exposure task while participants were still holding the roll of tape and cigarette cues, respectively.

All participants were removed from the scanner immediately after rating their urge to smoke at the conclusion of the third run of the cue exposure task. Those assigned to the instructed-yes condition were subsequently presented with an opportunity to smoke. Individuals who chose to smoke were escorted outside where they were permitted to smoke one of their cigarettes at their own pace, which took approximately 5 min on average. Those who chose not to smoke were given a 5-min break. Participants in the instructed-no group were not presented with an opportunity to smoke but were permitted to take a 5-min break. After taking a break or smoking a cigarette, all participants completed the smoking history questionnaire, the BIDR-6, and a posttask questionnaire. Next, participants were given an opportunity to participate in additional research examining the relationship between certain genetic polymorphisms and neural responses to cigarette cues, which is not the focus of the present article. Finally, participants were debriefed and paid for their participation.

FMRI data acquisition. Scanning was conducted using a 3-Tesla head-only Siemens Allegra magnet (Siemens Corporation, New York) equipped with a standard transmit/receive head coil. Before functional scanning, a 40-slice oblique-axial anatomical series ($3.125 \times 3.125 \times 3.0$ mm voxels) was acquired parallel to the anterior commissure-posterior commissure plane using a standard T2-weighted pulse sequence. Additionally, a high-resolution ($1 \times 1 \times 1$ mm voxels) three-dimensional structural volume was collected using a magnetization-prepared rapid gradient-echo sequence. Next, functional images were acquired in the same plane as the 40-slice anatomical series with coverage limited to the 38 center slices using a one-shot echo-planar imaging pulse sequence (TR = 2000 ms, TE = 25 ms, FOV = 20 cm, flip angle = 79°). Heart rate was recorded during the acquisition of fMRI data using pulse oximetry from the right middle finger (In vivo 4500 Pulse Oximeter, In vivo Research Inc, Orlando, FL).

FMRI data analysis. Analysis of fMRI data was conducted using utilities from the following software pages: Analysis of Functional NeuroImages (AFNI, Version 2.6; Cox, 1996), Automated Image Registration (AIR, Version 3.08; Woods, Cherry, & Mazziotta, 1992), FMRIB's Software Library (FSL, Release 4.1; Smith et al., 2004), and the NeuroImaging Software Package (NIS 3.5; Laboratory for Clinical Cognitive Neuroscience, University of Pittsburgh, and the Neuroscience of Cognitive Control Laboratory,

Princeton University). Software integration and image format conversion was implemented using the Functional Imaging Software Widgets graphical computing environment (Fissell et al., 2003).

A series of preprocessing steps was used to correct for artifacts and to account for individual differences in anatomy before analyzing fMRI data. Functional images were corrected for head motion and adjusted for drift within and between runs. Participants exhibiting movement that exceeded 3 mm or 3° were excluded from subsequent analysis (seven participants were excluded on this basis, as previously noted). Anatomical images from each participant were coregistered to a common reference anatomy using a six-parameter rigid-body automated registration algorithm, and the transformation matrix generated during this step then was applied to the participant's functional images. Subsequently, functional images were globally mean-normalized and smoothed using a three-dimensional Gaussian filter (4 mm full width at half maximum). Group-based statistical maps were transformed into MNI stereotaxic space (FSL's MNI 152; T1, 1 × 1 × 1 mm) for anatomical localization.

Two steps were used to analyze fMRI data from the cue exposure task. First, data were analyzed using a standard two-level random-effects general linear model approach implemented on a voxel-wise (i.e., whole brain) basis using the AFNI program 3dDeconvolve. Predictors for each cue type (i.e., control and cigarette) were entered into a GLM to obtain parameter estimates (i.e., beta coefficients) for each participant. As in our prior work (see Wilson et al., 2005), data collected during the final 48 s of the control and cigarette cue exposure epochs were included in analyses; data collected during the initial 26 s of exposure to cues were excluded from the model entirely to allow for stabilization of responses associated with the instructions identifying the object and, for the run in which the cigarette was presented, reminding participants whether or not they would be given the choice to smoke soon. These beta weight estimates were divided by the estimated baseline to convert them to units of percent change to facilitate interpretation (an approach that has been used in several published studies; e.g., see Campbell-Sills et al., 2011; Pagnoni, Zink, Montague, & Berns, 2002) and were entered into a second-level mixed model analysis of variance (ANOVA) with quitting motivation (quitting-unmotivated vs. quitting-motivated) and smoking opportunity (instructed-yes, instructed-no) as between-participants factors and cue (control cue, cigarette cue) as a within-participants factors. The ANOVA was conducted using the AFNI GroupAna program, which supports the analysis of unbalanced models.

As noted above, we were particularly interested in examining the effects of quitting motivation on functional connectivity in individuals anticipating an opportunity to smoke, especially between brain areas supporting regulatory processing (putative sources of modulation) and those supporting affective/motivational processing (putative targets of modulation). To test this prediction, we identified brain areas of a priori interest that exhibited a smoking opportunity × cue interaction and used these as seed regions in follow-up functional connectivity analyses. Specifically, voxel-wise hierarchical multiple regression was used to evaluate the extent to which quitting motivation modulated the relationship between activation of the seed region(s) and the activation of other areas of the brain during cigarette cue exposure across participants assigned to the instructed-yes condition. This approach, which provides a reasonable approximation of temporal connectivity (Horwitz, Rumsey, & Donohue, 1998; Schafer et al., 2009), was chosen over methods in which the time course of distinct regions are correlated within participants because of the temporal structure of the cue exposure paradigm (i.e., while the paradigm is effective for estimating response magnitude, it is less suitable for precisely estimating the time course of activation because the cigarette cue was presented a single time). The fit of a model including two first-order terms (activation of the seed region and quitting motivation) and one second-order term (the interaction between activation of the seed region and quitting motivation) was compared with that of a model containing only the first-order terms, with the goal of assessing the extent to which the addition of the interaction term significantly improved the fit of the regression model (i.e., for which the functional connectivity of the seed was modulated by quitting motivation).

Based upon Monte Carlo simulations conducted using the AFNI AlphaSim utility, it was determined that a combined per-voxel threshold of $p < .005$ and cluster-extent threshold of 11 or more contiguous voxels would yield a corrected cluster-wise false positive rate of $p < .05$. These threshold parameters were applied to all group-based statistical maps except for the one corresponding to a main effect of cue, which proved to be particularly robust (i.e., a very large region consisting of 1532 voxels that encompassed several functionally distinct brain areas surpassed this combined threshold). Accordingly, a per-voxel threshold of $p < .0001$ and minimum cluster extent of 11 contiguous voxels was applied to the cue main effect map (this combination yields a corrected cluster-wise false positive rate of $p < .002$, as determined using the AlphaSim utility).

Results

Comparisons of Sample Characteristics

Select sample characteristics are summarized in Table 1. We performed univariate ANOVAs (continuous variables) and chi-square tests (categorical variables) to evaluate the similarity of smoking practices, demographic variables, and psychosocial characteristics across conditions. There were significant differences between quitting motivation groups in age and trait self-control, with quitting-unmotivated participants being younger [quitting-unmotivated: $M = 27.6$, $SD = 6.1$; quitting-motivated: $M = 31.7$ years old, $SD = 8.2$; $F(1, 86) = 7.44$, $p < .01$, $\eta^2 = .08$] and reporting lower levels of trait self-control [quitting-unmotivated: $M = 108.3$, $SD = 20.2$; quitting-motivated: $M = 118.1$, $SD = 17.3$; $F(1, 86) = 5.96$, $p < .02$, $\eta^2 = .07$; possible scores on the SCS range from 36 to 180, with higher scores indicating greater trait self-control] than quitting-motivated participants. There also were significant differences between smoking opportunity conditions in trait positive affect and educational level, with the instructed-no group reporting greater levels of trait positive affect [instructed-no: $M = 36.7$, $SD = 7.3$; instructed-yes: $M = 31.7$, $SD = 7.6$; $F(1, 86) = 4.23$, $p < .05$, $\eta^2 = .05$; possible scores on the PANAS positive affect subscale range from 10 to 50, with higher scores indicating greater levels of trait positive affect] and fewer years of formal education completed [instructed-no: $M = 12.6$ years of education, $SD = 2.0$; instructed-yes: $M = 13.5$, $SD = 2.2$; $F(1, 86) = 4.25$, $p < .05$, $\eta^2 = .05$] than the instructed-yes group. Ethnicity distribution, income level, number of cigarettes

Table 1
Mean (SD) for Select Participant Characteristics

		Instructed-yes		Instructed-no	
	Full sample (n = 90)	Quitting-unmotivated (n = 21)	Quitting-motivated (n = 26)	Quitting-unmotivated (n = 22)	Quitting-motivated (n = 21)
Age in years	29.9 (7.5)	26.1 (6.0)	31.5 (7.5)	29.1 (5.9)	32.0 (9.2)
Years of formal education	13.0 (2.2)	13.8 (2.5)	13.2 (1.9)	12.8 (1.9)	12.3 (2.1)
Cigarettes per day	20.3 (5.5)	19.6 (6.0)	20.4 (5.4)	19.6 (4.6)	21.7 (6.1)
Number of quit attempts	1.9 (2.4)	2.2 (2.3)	2.2 (2.2)	2.0 (3.2)	1.2 (1.3)
FTND	5.0 (1.6)	4.8 (1.7)	5.3 (1.6)	5.5 (1.6)	4.6 (1.5)

Note. FTND = Fagerstrom Test for Nicotine Dependence.

smoked per day, number of quit attempts, level of nicotine dependence, confidence in ability to abstain from smoking, trait negative affect, and tendency to give honest but positively biased self-reports were similar across groups (p values $> .05$).

Smoking Behavior and Quit Interest

The majority (22 of 26) of quitting-motivated participants in the instructed-yes group chose to smoke when given the opportunity. All but two of the quitting-unmotivated participants in the instructed-yes group chose to smoke during the study; as may be expected given such small numbers, results do not change by removing data from these two participants. Participants rated their current interest in quitting at the conclusion of the experiment from 1 (*not at all interested*) to 10 (*extremely interested*). We conducted a 2 (quitting motivation) $\times$ 2 (smoking opportunity) ANOVA with self-reported interest in quitting as the dependent variable (ratings from six participants were missing; results include data from the remaining 84). Results revealed a main effect of quitting motivation, with quitting-motivated participants reporting a greater interest in quitting (M = 7.99, SD = 2.02) than quitting-unmotivated participants (M = 6.02, SD = 2.69), $F(1, 80) = 13.88$, $p < .001$, $\eta^2 = .15$.

Post-Deprivation Subjective State

We conducted separate 2 (quitting motivation) $\times$ 2 (smoking opportunity) ANOVAs to compare postdeprivation levels of self-reported affect and mental fatigue across groups. There were no main effects of quitting motivation or smoking opportunity and no quitting motivation $\times$ smoking opportunity interactions (all ps $> .05$) for these variables.

Effects of Cue Exposure on Self-Reported Urge and Heart Rate

Urge ratings were recorded at three points. Table 2 presents urge ratings throughout the study. A 2 (quitting motivation) $\times$ 2 (smoking opportunity) $\times$ 3 (time) mixed model ANOVA with the three urge ratings as a repeated variable revealed a main effect of Time, $F(2, 172) = 24.87$, $p < .001$, $\eta^2 = .22$. As shown in Table 2, mean urge ratings rose over time, with the largest increase occurring after the presentation of the cigarette cue. The statistical significance of this pattern was confirmed by Bonferroni-corrected pairwise comparisons, which indicated that urge-control cue ratings were significantly greater than were urge-baseline ratings ($p = .03$) and that urge-cigarette cue ratings were significantly greater than both urge-control cue ($p < .001$) and urge-baseline ($p < .001$) ratings. None of the remaining effects were significant.

Heart rate was recorded during the fMRI-based cue exposure task (see Table 2). Because of technical error, data were not collected from 19 participants (five quitting-unmotivated/instructed-yes, nine quitting-unmotivated/instructed-no, three quitting/instructed-yes, and two quitting/instructed-no participants). Using data from the remaining 71 participants, we conducted a 2 (quitting motivation) $\times$ 2 (smoking opportunity) $\times$ 2 (cue) ANOVA, with heart rate (beats/min) averaged across the time period during which the control and cigarette cues were held as the dependent variable. We observed a significant main effect of

Table 2
Mean (SD) Self-Reported Urge Ratings and Heart Rate

		Instructed-yes		Instructed-no	
	Full sample (n = 90)	Quitting-unmotivated (n = 21)	Quitting-motivated (n = 26)	Quitting-unmotivated (n = 22)	Quitting-motivated (n = 21)
Urge–baseline	59.6 (27.1)	58.7 (26.2)	61.7 (29.4)	52.7 (26.4)	65.3 (25.9)
Urge–control cue	66.0 (27.2)	64.8 (27.3)	68.7 (25.1)	64.6 (23.7)	65.2 (34.0)
Urge–cigarette cue	73.9 (27.0)	74.5 (28.3)	77.2 (24.6)	73.1 (24.0)	70.1 (32.3)
Heart rate–control cue	61.4 (8.1)	62.8 (8.3)	62.2 (6.7)	59.7 (10.8)	60.4 (7.7)
Heart rate–cigarette cue	62.2 (8.5)	64.9 (8.2)	62.7 (7.4)	60.7 (11.3)	60.5 (7.8)

Note. Urge was assessed using a single-item 0–100 scale, with higher numbers indicating greater urge to smoke. Heart rate is presented in beats per minute.

cue, $F(1, 67) = 11.40$, $p < .01$, $\eta^2 = .15$; this was subsumed, however, under a significant quitting motivation × cue interaction, $F(1, 67) = 5.88$, $p < .02$, $\eta^2 = .08$. To test the nature of this interaction, the effect of cue was tested separately for the quitting-unmotivated and quitting groups, with data collapsed across Smoking Opportunity conditions. For quitting-unmotivated participants, heart rate was significantly faster during exposure to the cigarette cue than during exposure to the control cue, $F(1, 28) = 13.57$, $p < .01$, $\eta^2 = .33$. In contrast, heart rate during the cigarette cue did not differ significantly from heart rate during the control cue for quitting-motivated participants, $F(1, 41) = .71$, $p > .40$, $\eta^2 = .02$. None of the remaining effects were significant.

fMRI Results

Main effect of cue. Brain regions exhibiting a main effect of cue are summarized in Table 3 and depicted in Figure 1. Activation was greater during the presentation of the cigarette cue than the control cue in several areas, including multiple sites in the prefrontal, parietal, and occipital cortices; the anterior cingulate cortex (ACC); the posterior cingulate cortex; the cerebellum; thalamus; and basal ganglia. Greater activation during the control cue relative to the cigarette cue was observed in a region of the left superior temporal gyrus.

Smoking opportunity × cue interaction. A significant smoking opportunity × cue interaction was observed in a region of the rostral PFC extending from the middle to the superior frontal gyrus (see Table 4 and Figure 1). The effect of cue was examined separately for the instructed-yes and instructed-no conditions (collapsed across quitting motivation groups) to characterize the interaction. For participants in the instructed-yes condition, activation in the rostral PFC was significantly greater during the cigarette cue than during the control cue, $F(1, 46) = 33.43$, $p < .001$, $\eta^2 = .42$. In contrast, for participants in the instructed-no condition, activation in this area was significantly greater during the control cue than during the cigarette cue, $F(1, 42) = 6.19$, $p < .02$, $\eta^2 = .13$.

Quitting motivation × cue interaction. A significant quitting motivation × cue interaction was observed in the left precentral gyrus and left lingual gyrus (see Table 4 and Figure 1). To determine the nature of these interactions, each region of interest (ROI) was probed to examine the effect of cue separately for the quitting-unmotivated and quitting-motivated groups, with data collapsed across smoking opportunity conditions. For quitting-unmotivated participants, activation was significantly greater during the control cue than during the cigarette cue for both regions [left precentral gyrus: $F(1, 42) = 9.11$, $p < .01$, $\eta^2 = .18$; left lingual gyrus: $F(1, 46) = 5.46$, $p < .03$, $\eta^2 = .12$]. In contrast, for quitting-motivated participants, activation was significantly greater during the cigarette cue than during the control cue for both ROIs [left precentral gyrus: $F(1, 46) = 6.43$, $p < .02$, $\eta^2 = .13$; left lingual gyrus: $F(1, 46) = 10.39$, $p < .01$, $\eta^2 = .18$].

Quitting motivation × smoking opportunity × cue interaction. There was a significant quitting motivation × smoking opportunity × cue interaction in the dorsal ACC extending to medial frontal gyrus, a portion of the cuneus extending to the precuneus, the lingual gyrus, and the brainstem (see Table 4 and Figure 1). To decompose these interactions, we stratified the data by smoking opportunity condition and tested the interaction between quitting motivation and cue separately for each ROI. For participants assigned to the instructed-yes condition, this two-way interaction was significant in the dorsal ACC ($p < .05$), cuneus/precuneus ($p < .01$), and brainstem ($p < .01$) and marginally significant in the lingual gyrus ($p = .05$). As summarized in Table 5, follow-up contrasts revealed that activation during the cigarette cue was greater than that during the control cue for quitting-unmotivated participants in the instructed-yes condition in each of these brain areas, while there was no significant effect of cue for quitting-motivated participants in the instructed-yes condition in any of the regions.

For participants in the instructed-no group, the two-way interaction of quitting motivation and cue was significant in the dorsal ACC ($p < .05$), lingual gyrus ($p < .01$), and brainstem ($p < .01$)

Table 3
Brain Regions Exhibiting a Significant Main Effect of Cue

Region	BA	Size (mm^3)	MNI coordinates			Average *F* ratio
			x	*y*	*z*	
Cigarette > control						
Posterior cingulate g	31	405	3	−20	36	20.52
Posterior cingulate g	31	513	1	−49	33	19.82
L angular g	39	1512	−55	−61	31	20.74
Precuneus/cuneus	18/7	351	−2	−75	29	18.21
Rostral ACC/medial frontal g	32/9/10	5535	6	49	0	22.59
L inferior frontal g	47/45	729	−47	24	−4	20.39
R inferior frontal g	47	675	48	28	−5	21.7
Cerebellum		513	1	−68	−18	21.48
L caudate nucleus		297	−14	7	12	21.25
B thalamus		5589	8	−14	7	21.95
R putamen		378	24	9	1	19.22
L putamen		648	−25	10	−9	20.71
Control > cigarette						
L superior temporal g	22	513	−53	−20	2	21.06

Note. Coordinates are given for local maxima of activation cluster in MNI atlas space. ACC = anterior cingulate cortex; B = bilateral; BA = Brodmann's area; g = gyrus; L = left hemisphere; R = right hemisphere.

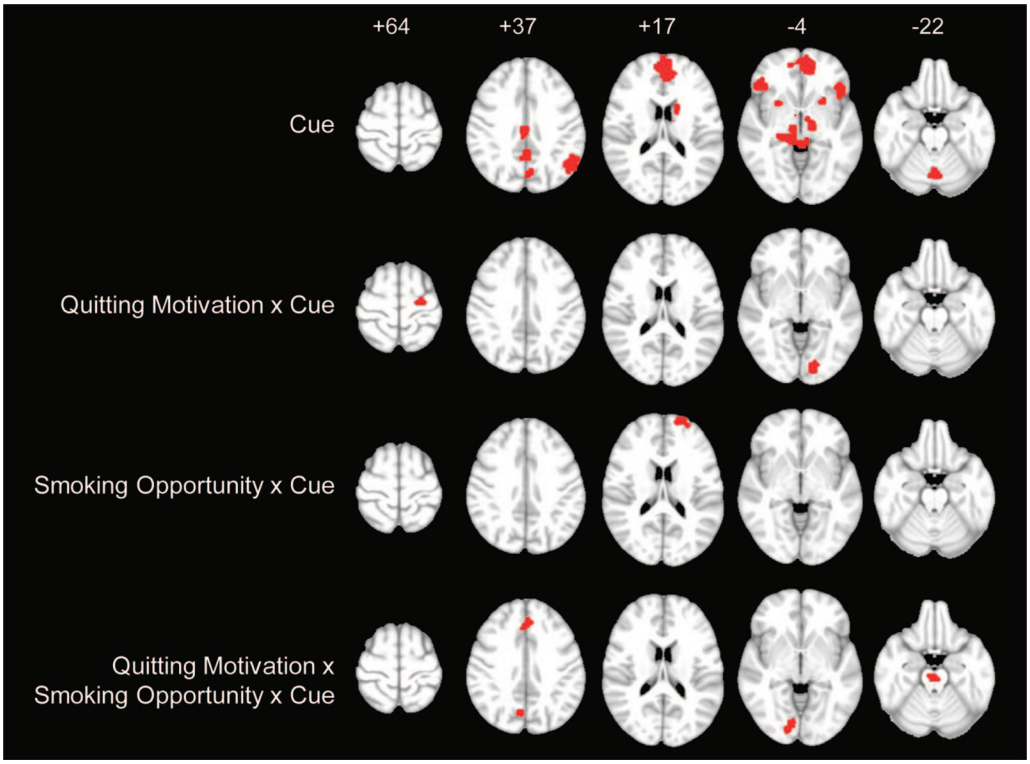

Figure 1. Row 1: Regions exhibiting a significant main effect of cue. Row 2: Regions exhibiting a significant quitting motivation × cue interaction. Row 3: Regions exhibiting a significant smoking opportunity × cue interaction. Row 4: Regions exhibiting a significant quitting motivation × smoking opportunity × cue interaction. The numbers above each column denote the distance (millimeters) from the anterior commissure–posterior commissure plane in MNI atlas space. Brain slices are right-left reversed.

but not the cuneus/precuneus ($p > .05$; a main effect of cue indicated that activation of this region was greater during the cigarette cue than during the control cue for both quitting-unmotivated and quitting-motivated smokers in the instructed-no condition). Follow-up contrasts were conducted for regions exhibiting a two-way interaction (i.e., for all regions except the cuneus/precuneus). As presented in Table 5, these tests indicated that activation during the cigarette cue was greater than that during the control cue for quitting-motivated participants in the instructed-no condition in the dorsal ACC, lingual gyrus, and brainstem. In contrast, activation during the control cue either did not differ from (dorsal ACC, brainstem) or was significantly greater than (lingual gyrus) activation during the cigarette cue for quitting-unmotivated participants in the instructed-no condition.

Table 4
Brain Regions Exhibiting Significant Interaction Effects

Region	BA	Size (mm^3)	MNI Coordinates			Average *F* ratio
			x	*y*	*z*	
Quitting motivation × Cue interaction						
L precentral g	4	351	−24	−16	64	10.51
L lingual g	18	378	−15	−87	−5	11.10
Smoking opportunity × Cue interaction						
L rostral PFC (superior frontal g/middle frontal g)	10	513	−23	61	16	21.06
Quitting motivation × Smoking opportunity × Cue interaction						
Dorsal ACC	32	297	−2	34	37	9.35
R cuneus/precuneus	18/7	351	9	−74	39	10.22
R lingual g	17/18	918	16	−88	−1	10.60
Brainstem (pons)		297	1	−22	−27	9.94

Note. Coordinates are given for local maxima of activation cluster in MNI atlas space. ACC = anterior cingulate cortex; BA = Brodmann's area; g = gyrus; L = left hemisphere; PFC = prefrontal cortex; R = right hemisphere.

Table 5
Effect of Cue as a Function of Smoking Opportunity and Quitting Motivation in Brain Regions Exhibiting a Significant Quitting Motivation × Smoking Opportunity × Cue Interaction

	Instructed-yes		Instructed-no	
	Quitting-unmotivated	Quitting-motivated	Quitting-unmotivated	Quitting-motivated
Dorsal ACC	Cigarette > Control[b]	ns	ns	Cigarette > Control[c]
Cuneus/precuneus	Cigarette > Control[b]	ns	n/a	n/a
Lingual gyrus	Cigarette > Control[a]	ns	Control > Cigarette[a]	Cigarette > Control[b]
Brainstem	Cigarette > Control[b]	ns	ns	Cigarette > Control[b]

Note. ACC = anterior cingulate cortex; ns = no significant effect of cue; n/a = indicates that follow-up contrasts were not conducted (see *Results*).
[a] $p < .05$. [b] $p < .01$. [c] $p < .06$.

Additional effects. A main effect of quitting motivation was observed in the posterior cingulate gyrus (MNI coordinates $x = -13$, $y = -46$, $z = 12$; size = 967 mm^3; average F ratio = 10.53); signal intensity was lesser for quitting-unmotivated relative to quitting-motivated participants in this region. A significant main effect of smoking opportunity was observed in the precuneus ($x = 0$, $y = -43$, $z = 61$; size = 674 mm^3; average F ratio = 10.01) and left angular gyrus ($x = -58$, $y = -58$, $z = 17$; size = 381 mm^3; average F ratio = 11.37). In both ROIs, responses were more robust for the instructed-yes group than for the instructed-no group. No regions exhibited a significant quitting motivation × smoking opportunity interaction.

Functional Connectivity of Rostral PFC During Smoking Anticipation

To examine our hypothesis that quitting-unmotivated and quitting-motivated smokers anticipating an opportunity to smoke would engage regions of the brain supporting regulatory processing (i.e., regions of the PFC), but toward different ends, we conducted multiple regression analyses aimed at examining the effects of quitting motivation on functional connectivity in these groups. Analyses focused on the rostral PFC region exhibiting a significant Smoking Opportunity × Cue interaction (described above). The rostral PFC served as a particularly suitable region for testing our prediction because, as previously noted, it plays an important role in emotion regulation and, further, it was the sole region exhibiting a cue-elicited increase in activation in both quitting-unmotivated and quitting-motivated smokers who were anticipating an opportunity to smoke within seconds but not those who believed that they would not be able to smoke for hours.

Results are summarized in Table 6.[1] As shown, greater activation of the rostral PFC was associated with greater activation of several regions of the brain in quitting-unmotivated smokers who were anticipating an opportunity to smoke, including the superior frontal gyrus, and the anterior/dorsal and posterior cingulate gyri, and the dorsal (caudate nucleus) and ventral (nucleus accumbens) striatum. Activation of most of these regions exhibited either a nonsignificant (e.g., striatum) or negative (e.g., superior frontal gyrus) association with activation of the rostral PFC for quitting-motivated smokers who were anticipating an opportunity to smoke (see Table 6). The exception to this general pattern was a region of the left postcentral gyrus, which demonstrated a negative and positive correlation with activation of the rostral PFC in quitting-unmotivated and quitting-motivated smokers, respectively.

Of particular interest, quitting-unmotivated smokers who were told that they could smoke soon exhibited a strong positive relationship between the activation of the rostral PFC and a large region of the medial PFC extending to the rostral ACC and OFC [$r(21) = 0.77$, $p < .001$], whereas quitting-motivated smokers exhibited a nonsignificant negative relationship between the activation of these areas [$r(26) = -0.13$, $p = .53$]. As shown in Figure 2, the medial PFC region identified in this contrast overlapped considerably with one demonstrating a significant main effect of cue (cigarette > control). Specifically, 30% of the voxels in the medial PFC that exhibited a main effect of cue also demonstrated a significant effect in the connectivity analysis. As depicted, extensive overlap also was observed in the left caudate nucleus and cerebellum (45% and 42% of the voxels that displayed a main effect of cue in these areas also showed a significant effect in the connectivity analysis, respectively).

To further probe the nature of these patterns, we examined the relationship between brain activation and self-reported urge during cigarette cue exposure, with correlation analysis conducted separately for the quitting-unmotivated and quitting-motivated groups. To be conservative, we only tested correlations for the rostral PFC and medial PFC. Cigarette-related activation of the rostral PFC and medial PFC were not related to self-reported urge during cigarette cue exposure for either group (all ps > .2).

Discussion

The present study examined the effects of motivation to quit smoking and smoking expectancy on cue-elicited neural activity. We found several brain regions that showed significant main effects attributable to cue exposure (i.e., ignoring any effects of smoking opportunity or quitting motivation). Consistent with previous research, cigarette-related increases in activation were observed in the ACC (e.g., Brody et al., 2007; Wagner, Dal Cin, Sargent, Kelley, & Heatherton, 2011), inferior frontal gyrus (e.g., Due, Huettel, Hall, & Rubin, 2002; Okuyemi et al., 2006), poste-

[1] As noted above, quitting motivation groups differed significantly in age and trait self-control, and expectancy conditions differed significantly in trait positive affect. Including these factors as covariates (each included individually in separate models) did not alter connectivity analysis results.

Table 6
Brain Regions Exhibiting a Significant Effect in Functional Connectivity Analysis

Region	BA	Size (mm^3)	MNI coordinates			Quitting-unmotivated	Quitting-motivated
			x	*y*	*z*		
L postcentral g	5	459	−23	−45	75	Neg	Pos
R precentral g	6	648	43	−10	67	Pos	Neg
L superior frontal g	6	513	−12	28	63	Pos	Neg
Posterior cingulate g	31	2025	−6	−42	46	Pos	ns
R superior frontal g	9	351	23	46	43	Pos	Neg
Dorsal ACC	32	486	−1	18	39	Pos	ns
Posterior cingulate g	23	621	0	−10	35	Pos	ns
Medial frontal g/rostral ACC/OFC	9/10/32/11	8100	−6	60	31	Pos	ns
R superior occipital g/middle temporal g	19	567	41	−84	26	Pos	ns
R posterior insula		405	43	−30	23	Pos	ns
R supramarginal g/superior temporal g	40/22	1404	68	−44	18	Pos	ns
R middle temporal g/superior temporal g	21/22	1161	64	−20	−3	Pos	ns
R caudate nucleus		540	6	6	2	Pos	ns
R thalamus		972	4	−31	2	Pos	Neg
B caudate nucleus/ R nucleus accumbens		3159	10	19	0	Pos	ns
L parahippocampal g	36	297	−35	−28	−33	Pos	Neg
Cerebellum		1431	12	−61	−37	Pos	Neg

Note. Coordinates are given for local maxima of activation cluster in MNI atlas space. ACC = anterior cingulate cortex; B = bilateral; BA = Brodmann's area; g = gyrus; L = left hemisphere; Neg = negative correlation with frontopolar seed region; ns = no significant relationship with seed region; OFC = orbitofrontal cortex; Pos = positive correlation with seed region; R = right hemisphere.

rior cingulate gyrus (e.g., McClernon, Kozink, & Rose, 2008; Okuyemi et al., 2006; Wilson et al., 2005), precuneus (e.g., Brody et al., 2007; McBride et al., 2006; McClernon et al., 2008), thalamus (e.g., Due et al., 2002; Franklin et al., 2007; McBride et al., 2006), dorsal striatum (McClernon, Kozink, Lutz, & Rose, 2009; Yalachkov, Kaiser, & Naumer, 2009), and cerebellum (McClernon et al., 2008). In addition, we found that quitting motivation and smoking expectancy modulated cue-related activation of the dorsal ACC and visual cortex (the cuneus/precuneus and lingual gyrus), regions that recently have been implicated in the regulation of cue-elicited responses by treatment-seeking smokers (Brody et al., 2007).

Of primary interest, we found that smoking expectancy, but not quitting motivation, influenced cue-elicited activation of the rostral PFC. The rostral PFC appears to support processes that are critical for decision making, particularly the capacity to maintain information or goals relevant to a task to be completed in the near future while simultaneously performing another task (Badre & D'Esposito, 2009; Braver & Bongiolatti, 2002; Christoff & Gabrieli, 2000; Koechlin & Hyafil, 2007). Cigarette cue exposure was associated with increased activation of the left rostral PFC in both quitting-unmotivated and quitting-motivated smokers who were told that they could smoke soon, suggesting that both groups were engaged in maintenance-related processing while anticipating an opportunity to smoke.

Follow-up analyses revealed, however, that quitting motivation significantly modulated the regions to which the rostral PFC was functionally connected during cue exposure. For quitting-unmotivated smokers who were anticipating an opportunity to smoke, cue-elicited activation of the rostral PFC was positively correlated with the activation of a broad set of brain areas, including a large region of the medial prefrontal cortex encompassing the rostral ACC and medial OFC, as well as the dorsal and ventral striatum. The rostral/ventral portion of the ACC (the so-called "affective division") appears to mediate processes related to affect and motivation, such as evaluating the emotional significance of stimuli (Bush, Luu, & Posner, 2000). Likewise, the medial OFC and striatum play a fundamental role in appraising the value of stimuli and expected outcomes, as well as in the selection of responses aimed at producing desired results (Delgado, 2007; Kringelbach & Rolls, 2004; Peters & Buchel, 2010). Activation of these regions—particularly the medial OFC and striatum—has been found to increase as the value of potential outcomes increase (Delgado, Locke, Stenger, & Fiez, 2003; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). In addition, the OFC, ventral striatum, and, more recently, the dorsal striatum all have been linked to drug craving (Koob & Volkow, 2010). Thus, greater engagement of the rostral PFC was associated with greater activation of areas of the brain implicated in reward-related processing and craving in quitting-unmotivated smokers who were expecting a chance to smoke, perhaps reflecting the use of cognitive control to support positive anticipatory processing. More broadly, our findings indicate that interactions between cognitive control functions and those involved in motivation and reward-processing may be an important component of generating and/or maintaining the appetitive anticipatory state that precedes consumption in active drug users, as has been suggested previously (Goldstein & Volkow, 2002; Grant et al., 1996; Wilson, Sayette, & Fiez, 2004).

A very different pattern of functional connectivity between the rostral PFC and other areas of the brain was observed in quitting-motivated smokers who were faced with a cigarette cue and an opportunity to smoke. Of particular interest, we observed a non-significant negative relationship between activation of the rostral PFC and activation of the large medial prefrontal region comprising the rostral ACC and medial OFC in quitting-motivated smokers anticipating an opportunity to smoke. Thus, in direct contrast to the pattern observed for quitting-unmotivated smokers, greater engagement of the rostral PFC was not associated with the acti-

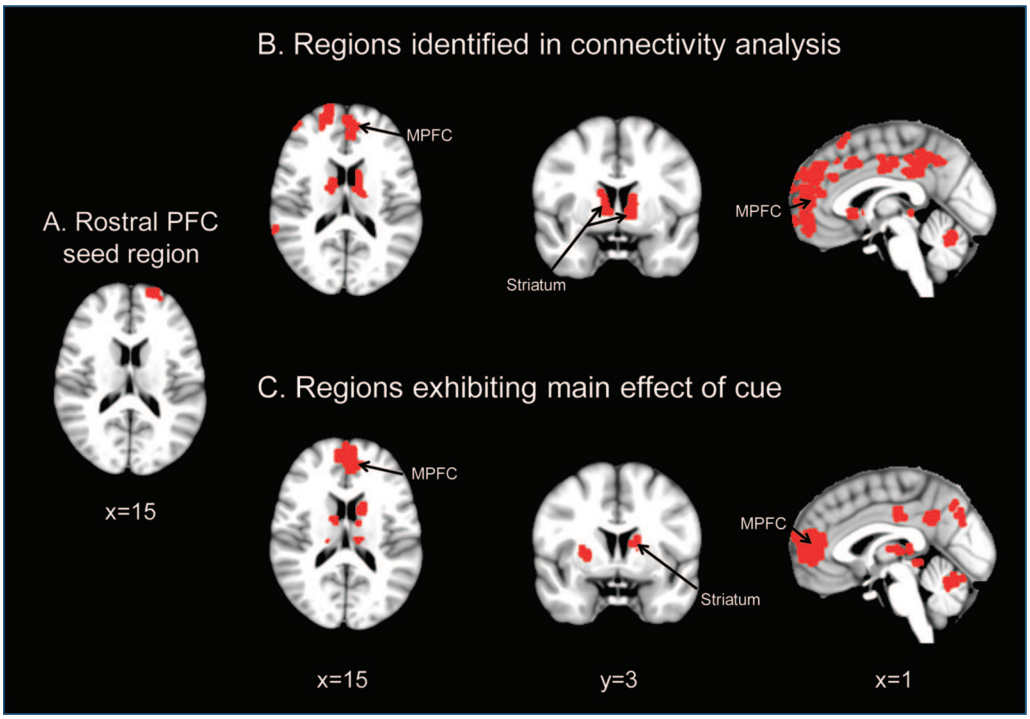

Figure 2. A) Rostral PFC region used as the seed in functional connectivity analysis (see Results). B) Regions exhibiting significant effect in functional connectivity analysis. C) Regions exhibiting a significant main effect of cue (cigarette > control). As shown, overlapping regions of the medial PFC (MPFC) and striatum were identified using these two analysis approaches. The numbers below brain slices denote the distance (millimeters) from the anterior commissure–posterior commissure plane in MNI atlas space along the sagittal (*x*), coronal (*y*), or axial (*z*) plane. Brain slice are right-left reversed.

vation of reward-related brain regions in quitting-motivated smokers who were faced with a chance to smoke. In recent work, it has been shown that interventions designed to reduce cue-elicited craving, such as instructing smokers to focus on the long term (presumably negative) consequences associated with smoking (Kober et al., 2010) or providing them with bupropion (a pharmacological agent used as a smoking cessation aid; Brody et al., 2004), are associated with decreases in the activation of the ventral ACC and nearby regions during cigarette cue exposure. In light of such findings, one interpretation of these data is that quitting-motivated smokers who were told that they could smoke soon did not focus on the rewarding aspects of smoking (perhaps even attempting to inhibit reward-related processing of the cue to some extent) because of their implicit motivation to abstain.

These findings extend findings from our previous study, in which cue-elicited increases were observed in a similarly located region of the rostral ACC and adjacent medial PFC in quitting-unmotivated smokers irrespective of smoking expectancy (Wilson et al., 2005). In both our previous study and the current investigation, the level of activation of the rostral ACC/medial PFC associated with cigarette cue exposure did not appear to depend heavily upon whether or not an opportunity to smoke was anticipated or the degree of motivation to quit smoking. The current findings suggest, however, that the coupling between the rostral ACC/medial PFC and other brain areas during cue exposure is sensitive to these contextual factors. Specifically, the rostral ACC/medial PFC region that exhibited cue-elicited increases in activation across quitting motivation and smoking expectancy conditions overlapped significantly with the large region of the medial PFC that was functionally correlated with the rostral PFC in those expecting to smoke (see Figure 2). Taken together, our prior and current results suggest that drug cues reliably activate the rostral ACC and medial PFC but that this activation is not immutable. For example, smokers may deliberately focus their attention on, or shift their attention away from, salient smoking-related stimuli depending upon their motivational state. The present study thus extends our previous findings and highlights the utility of examining interregional covariation during cue exposure. Studies that use similar methods to further characterize such interactions would be valuable.

A limitation of the present study is that most of the quitting-motivated smokers who were presented with an opportunity to smoke during the study chose to do so. It therefore is possible that that their motivational state at enrollment may have shifted by the time of the experiment. Although the intention to quit smoking indeed can be labile (e.g., see Hughes, Keely, Fagerstrom, & Callas, 2005), our categorization of participants' motivational status proved useful for characterizing neural responses meaningfully vis-à-vis the smoking expectancy manipulation. In addition, participants who were identified as quitting-motivated smokers at the time of enrollment endorsed a significantly greater interest in and intent to quit smoking at the conclusion of the study, relative to participants who were identified as quitting-unmotivated smokers at enrollment. While these data are subject to biases in self-report, they are at least consistent with the idea

that quitting-motivated participants were in the intended state during the experiment, and that quitting-unmotivated and quitting-motivated participants differed with respect to smoking intentions. Further, all quitting-motivated participants accepted a referral to a smoking cessation program, supporting the validity of their self-reported intention to quit.

It is possible that unique features of the experimental design contributed to the high proportion of ostensibly quitting smokers who chose to smoke a cigarette during the study. Smokers were presented with a stimulus designed to evoke strong cravings while in the MRI scanner. Then, those assigned to the instructed-yes condition were asked whether or not they wanted to smoke after being removed from the scanner. In some respects, offering participants the opportunity to smoke in this fashion represented a second craving-producing situation (Baker, Morse, & Sherman, 1987). In naturalistic conditions, those who are trying to quit may have more of an opportunity to "escape" situations that provoke craving (e.g., by engaging in a distracting activity or physically distancing themselves from craving-eliciting cues). Perhaps fewer quitting smokers would have chosen to smoke if they had been provided with such opportunities during the experiment or if participants were asked to decide whether or not they wanted to smoke while holding the cigarette cue (i.e., while still in the scanner). Alternatively, while experimenters took care not to influence individuals' decisions after being removed from the scanner, quitting-motivated participants may have seen the opportunity to smoke following cue exposure—one that was offered to them by a researcher in a relatively unique setting—as a legitimate excuse for, or perhaps even tacit approval of, smoking. Further research exploring these possibilities would be useful. Additionally, while our ability to do so was limited by the small number of participants who chose to refrain from smoking in the current study, future work contrasting patterns of cue-elicited neural activation in those who choose to smoke versus those who do not would be informative.

Additional limitations should be mentioned. We identified dissociable patterns of functional connectivity in quitting-unmotivated and quitting-motivated smokers who were expecting an opportunity to smoke. However, we did not find evidence of a differential association between the activation of key brain regions identified in the connectivity analysis and self-reported urge, leaving unclear the motivational significance of the observed patterns. One possibility is that differences in the motivation to quit smoking (and associated use of processes mediated by the rostral PFC) were related to differences in affective valence and/or the amount of ambivalence experienced during cue exposure, more so than overall levels of urge (cf. Sayette & Hufford, 1995; Sayette et al., 2003). Alternatively, differences may have been revealed through the use of a multifactorial measure of craving, which might have allowed for the detection of more nuanced relationships between brain activity and distinct components of urge (e.g., anticipation of pleasure vs. anticipation of relief from negative affect; Tiffany & Drobes, 1991).

It also is worth noting that, whereas our interpretations have focused on the effects that the motivation to quit smoking appears to have on functional connectivity, quitting motivation is undoubtedly associated with other factors (e.g., perceived control over smoking). We cannot rule out the possibility that quitting motivation may have served as a proxy for such variables. Finally, while several studies have demonstrated that smoking cues robustly increase the urge to smoke (Carter & Tiffany, 1999), the design of the current experiment (i.e., the fixed order of cues) leaves open the possibility that observed increases in self-reported craving were attributable in part to the passage of time. We decided against counterbalancing the order of cues because of the concern that nicotine-deprived smokers exposed to smoking cues first would still be experiencing elevated urges during subsequent exposure to control cues (Sayette et al., 2010).

In summary, the present data add to an emerging body of work suggesting that drug use expectancy affects cue-reactivity across multiple response systems. To our knowledge, this is the first fMRI study of its kind to manipulate smoking expectancy among individuals with varying levels of motivation to quit smoking. Results from the current study replicate key findings from our preliminary work with quitting-unmotivated smokers (e.g., cue-elicited increases in the activation of the ACC; Wilson et al., 2005) and, more importantly, extend prior research by providing evidence that quitting-unmotivated and quitting-motivated smokers exhibit divergent patterns of brain activation when anticipating an opportunity to smoke imminently. Our findings suggest that investigators may need to pay close attention to the motivational contexts associated with their experiments when studying cue-reactivity, as these contexts can modulate not only responses to drug-related stimuli but perhaps also the functional implications of observed activity. Further investigation of the nature of these effects would provide important data for understanding the positive anticipatory mechanisms that contribute to the maintenance of smoking and those that are used to cope with these appetitive reactions in those trying to quit.

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