ORIGINAL INVESTIGATION

Prequit fMRI Responses to Pleasant Cues and Cigarette-Related Cues Predict Smoking Cessation Outcome

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ABSTRACT

Introduction: The reasons that some smokers find it harder to quit than others are unclear. Understanding how individual differences predict smoking cessation outcomes may allow the development of more successful personalized treatments for nicotine dependence. Theoretical models suggest that drug users might be characterized by increased sensitivity to drug cues and by reduced sensitivity to nondrug-related natural rewards. We hypothesized that baseline differences in brain sensitivity to natural rewards and cigarette-related cues would predict the outcome of a smoking cessation attempt.

Methods: Using functional magnetic resonance imaging, we recorded prequit brain responses to neutral, emotional (pleasant and unpleasant), and cigarette-related cues from 55 smokers interested in quitting. We then assessed smoking abstinence, mood, and nicotine withdrawal symptoms during the course of a smoking cessation attempt.

Results: Using cluster analysis, we identified 2 groups of smokers who differed in their baseline responses to pleasant cues and cigarette-related cues in the posterior visual association areas, the dorsal striatum, and the medial and dorsolateral prefrontal cortex. Smokers who showed lower prequit levels of brain reactivity to pleasant stimuli than to cigarette-related cues were less likely to be abstinent 6 months after their quit attempt, and they had higher levels of negative affect during the course of the quit attempt.

Conclusions: Smokers with blunted brain responses to pleasant stimuli, relative to cigarette-related stimuli, had more difficulty quitting smoking. For these individuals, the lack of alternative forms of reinforcement when nicotine deprived might be an important factor underlying relapse. Normalizing these pathological neuroadaptations may help them achieve abstinence.

INTRODUCTION

A major barrier to successful treatment of nicotine dependence is the persistent risk of relapse (Hughes, Keely, & Naud, 2004). Identifying the factors that put certain smokers at a greater risk of relapse than others would allow clinicians to develop and implement personalized interventions that target these specific risk factors. Emotional and motivational processes are important contributors to relapse. For example, smokers may smoke to avoid unpleasant withdrawal states (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004) or to alleviate craving evoked by drug-related cues (Ferguson & Shiffman, 2009). According to the incentive sensitization theory of addiction (Robinson & Berridge, 2003), repeated drug use causes progressive increases in drug-induced neural activation (i.e., sensitization) in the mesolimbic brain reward systems that control approach behavior. This sensitized neural activity becomes conditioned to cues that accompany drug exposure, affording them excessive incentive salience. Thus, drug-related cues capture a user's

attention and might trigger the pursuit of drugs that is associated with the subjective experience of “wanting” or “craving” a drug.

Volkow and colleagues proposed that addiction includes an additional process whereby the incentive salience of nondrug-related (i.e., natural) rewards decreases as dependence develops (Koob & Volkow, 2010; Volkow et al., 2010). Thus, drug-dependent individuals may be more likely to pay attention to and approach drug-related cues than natural rewards, making it difficult to abstain. This phenomenon has been described in terms of “reward sensitivity” (i.e., decreased sensitivity to natural rewards and increased sensitivity to drug rewards). Several studies provide empirical support for the hypothesis that low sensitivity to natural rewards is present in cocaine addicts (Dunning et al., 2011), alcoholics (Heinz et al., 2007), and smokers (Addicott et al., 2012; Diggs, Froeliger, Carlson, & Gilbert, 2013; Rose et al., 2013). We (Versace et al., 2012) recently showed that smokers characterized by prequit blunted brain responses to pleasant stimuli and by enhanced responses to cigarette cues have more

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difficulties in achieving long-term smoking abstinence than smokers characterized by normal responses to pleasant stimuli. In our previous work, we estimated sensitivity to pleasant and cigarette-related cues by measuring the amplitude of the late positive potential (LPP), a sensitive and reliable biomarker of motivational significance (Hajcak, MacNamara, & Olvet, 2010; Lang & Bradley, 2009) thought to originate in the occipital–parietal cortex (Keil et al., 2002; Sabatinelli, Lang, Keil, & Bradley, 2007). However, event-related potential (ERP) measures such as the LPP provide limited information about the neural circuits that might underlie individual differences in sensitivity to natural and drug-related rewards. Identifying the specific neural systems underlying abnormal responses to these stimuli could inform the development of new interventions aimed at enhancing the relative salience of natural rewards and increase abstinence from nicotine as well as other addictive drugs (Volkow & Li, 2005). In the current study, we used functional magnetic resonance imaging (fMRI) to measure baseline brain responses of smokers interested in quitting.

Previous fMRI studies found that responses to drug-related cues and natural rewards are larger than those to neutral cues in several structures associated with reward processing, including the dorsal and ventral striatum, the medial prefrontal cortex, and—importantly—the parietal and occipital regions thought to be the source of the LPP (Chase, Eickhoff, Laird, & Hogarth, 2011; Engemann et al., 2012; Kuhn & Gallinat, 2011; Versace et al., 2011). On the basis of our previous work (Versace et al., 2012), we hypothesized the existence of two subgroups of smokers: one group (the “low reward sensitivity” group) characterized by blunted prequit fMRI responses to pleasant stimuli and by enhanced responses to cigarette cues in the parietal and occipital visual association areas, and the other group (the “high reward sensitivity” group) characterized by higher fMRI responses to pleasant stimuli than cigarette cues. We also hypothesized that the low reward sensitivity group would have a higher risk of relapse following a smoking cessation attempt. Finally, we capitalized on the high spatial resolution of fMRI to determine whether between-group differences in reward sensitivity were present in brain regions other than the extended visual system.

METHODS

Participants

Participants were recruited from the Houston, TX, metropolitan area using newspaper and radio advertisements seeking volunteers who were interested in participating in a smoking cessation study that involved medication (varenicline, bupropion, or placebo) and counseling (for details about the clinical trial, see Cinciripini et al., 2013). A subset ($n = 59$; 25 women) of those randomized to treatment in the clinical trial ($n = 294$) completed the fMRI scan prior to starting the study medication while they were still smoking at their regular rate. Inclusion criteria were: 18–65 years old, smoked ≥ 5 cigarettes/day for at least the past 6 months, baseline expired carbon monoxide (CO) level > 6 ppm, no current diagnosis of a psychiatric or substance use disorder (other than nicotine dependence), no contraindications for the study medications, fluency in English, and having a working telephone. fMRI participants were required to meet the additional inclusion criteria of having no contraindications for fMRI, being right handed

(to avoid lateralization effects in the fMRI data), and having self-reported European ancestry (to maintain a homogeneous sample for future genetic analyses). All participants provided written informed consent, and the research was approved by the University of Texas MD Anderson Cancer Center’s Institutional Review Board. Participants were paid \$50 for completing the fMRI scan.

Results from a subsample ($n = 35$) have been previously published (Versace et al., 2011); however, the goals and methods of the analysis presented in that publication (i.e., comparing brain responses to emotional and cigarette-related cues in smokers) are different from those for the current manuscript and did not influence the analyses presented below. Because of equipment failures, the final cohort size for this analysis is 55 (25 women).

Stimuli

Participants viewed one of three sets of 64 pictures selected from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2005) and from other smoking-related picture collections (Carter et al., 2006; Gilbert & Rabinovich, 1999). In each set, pictures belonged to four categories: pleasant (eight high-arousal erotic pictures and eight low-arousal romantic pictures), unpleasant (eight high-arousal mutilation pictures and eight low-arousal sad pictures), neutral (16 neutral people), and cigarette related (16 pictures of people smoking). The pictures were displayed for 3 s each, separated by a 15-s interval. Pictures were presented in a pseudorandom order using an fMRI compatible stimulus presentation system (IFIS/SA; Invivo) and subtended a horizontal viewing angle of approximately 15° . Both the valence and arousal normative means for the IAPS pictures used in the three picture sets were statistically comparable (picture set $\times$ picture category interactions were not significant for valence or arousal; $F_s < 0.6$, $p_s > .8$). The mean (SD) normative valence ratings were 6.6 (0.4) for erotica, 7.4 (0.5) for romance, 5.3 (0.7) for neutral, 2.9 (0.8) for sad, and 1.8 (0.3) for mutilations. The mean (SD) arousal ratings were 6.3 (0.4) for erotica, 4.9 (0.7) for romance, 3.6 (0.5) for neutral, 4.8 (0.8) for sad, and 6.4 (0.7) for mutilations. For a list of the specific pictures used in this study, see [Supplementary Methods](#) and [Results](#).

Questionnaires and Smoking Assessment

Before the fMRI session, participants completed questionnaires to assess their demographic characteristics, smoking behavior, nicotine dependence, and trait affective disposition: the Fagerström Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991), the Wisconsin Inventory of Smoking Dependence Motives (Smith et al., 2010), the Depression Proneness Inventory (DPI; Strong, Brown, Kahler, Lloyd-Richardson, & Niaura, 2004), the Fawcett–Clark Pleasure Scale (Fawcett, Clark, Scheftner, & Gibbons, 1983), and the Behavioral Inhibition System and Behavioral Approach System scales (Carver & White, 1994).

To evaluate changes in abstinence, mood, and nicotine withdrawal symptoms during the clinical trial, we used a battery of self-report measures, including the Center for Epidemiological Studies Depression Scale (Radloff, 1977), the Positive and Negative Affect Scale (Watson, Clark, & Tellegen, 1988), the brief form of the Questionnaire on Smoking Urges (QSU-Brief; Cox, Tiffany, & Christen, 2001), and the Wisconsin Smoking

Withdrawal Scale (WSWS; Welsch et al., 1999). This battery was administered on the day of the fMRI scan and 24 hr, 1, 4, 7, 12, and 24 weeks after the scheduled quit date.

Procedure

Participants were asked to smoke normally before the fMRI session so that they would be in a nondeprived state. After providing an expired CO sample and completing the questionnaire battery (~30 min), they completed the fMRI procedure, which has been previously used in our laboratory (Versace et al., 2011). After a short acclimation period during which instructions were given (i.e., to watch the pictures as they appear on the screen), participants viewed the pictures while the blood-oxygenation-level-dependent (BOLD) fMRI signal was measured using a T2*-weighted, gradient echo, echoplanar imaging protocol with the following parameters: repetition time = 3,000 ms, echo time = 25 ms, flip angle = 90°, image matrix = 64 × 64, in-plane resolution = 2.5 × 2.5 mm, slice thickness = 2.5 mm, slice gap = 0.5 mm. This provided a voxel size of 2.5 × 2.5 × 3 mm. fMRI images were collected as 50 coronal slices and covered all but the most anterior and most posterior edges of the brain. After discarding the first two fMRI images acquired in the time series to allow the signal to reach steady-state levels, image acquisition was time locked to stimulus presentation such that 335 images were obtained over the course of the run. The fMRI run lasted approximately 17 min.

After the picture-viewing run, a high-resolution (1-mm³ voxels) structural MRI was obtained using an inversion-recovery prepared, fast-spoiled gradient echo pulse sequence (repetition time = 6.4 ms, echo time = 2.1 ms, inversion time = 400 ms, flip angle = 20°).

The smoking cessation clinical trial began the day after completing the fMRI session. The quit date was scheduled approximately 2 weeks later.

Data Analysis

fMRI data were analyzed using BrainVoyager QX (version 2.4.2, Brain Innovation). Images were preprocessed using a standard set of procedures that included slice-timing correction, motion correction, spatial smoothing with a 5-mm Gaussian kernel, and removal of low frequency drifts from the fMRI time course by filtering out a Fourier basis set with 20 cycles in the time course, which corresponds to a high-pass filter with a cutoff frequency of 0.02 Hz (Goebel, Esposito, & Formisano, 2006; Versace et al., 2011). The preprocessed fMRI images were aligned to the participant's anatomical image and transformed into standard Talairach–Tournoux space.

After preprocessing, we followed a two-step analytic procedure. First, we divided smokers into two groups using BOLD responses evoked in the visual system by the experimental stimuli. We validated the clinical relevance of this classification by examining between-groups differences in treatment outcome measures. Second, we used the classification obtained in the first step to identify other brain regions showing different patterns of response in the two groups of smokers.

Classification of Smokers Based on Brain Responses to Cigarette-Related and Emotional Pictures

The first analytic step aimed at replicating the results obtained by Versace et al. (2012) using ERPs and determine whether

individual differences in brain responses to cigarette-related and emotional pictures in the visual system could be used to divide smokers into two groups. We used a general linear model (GLM) to localize a region of interest (ROI) where BOLD responses to emotional and cigarette-related pictures were larger than those to neutral pictures. We expected this ROI to be located in posterior regions of the brain because these regions are the most likely generator of the LPP (Keil et al., 2002; Sabatinelli et al., 2007), the ERP component that we previously used to uncover differences in reward sensitivity (Versace et al., 2012).

This ROI was located using a whole-brain, voxelwise, random-effects GLM (Mumford & Nichols, 2009) to identify voxels showing significantly stronger BOLD responses to cigarette-related, pleasant, and unpleasant pictures than to neutral pictures. The first level of this hierarchical model included a fixed-effects term for each stimulus category that was obtained by convolving a canonical hemodynamic response function with the time course of picture presentation. Head motion parameters were included as additional first-level, fixed-effects, confound predictors. Subject was included as a random effect in the second level of the model. A statistical parametric map of the contrast of cigarette-related, pleasant, and unpleasant versus neutral pictures was computed and thresholded for statistical significance using a false discovery rate (FDR) of $q < .01$ and a minimum cluster size of 1,000 mm³, which corresponded to a single-voxel threshold of $t(54) = 3.57$, $p < .0008$. From this ROI, we extracted each subject's BOLD signal and transformed it to percent change from the session's mean. Next, for each trial, the data during a window lasting from 6 to 12 s after picture onset were baseline corrected by subtracting the data point immediately preceding the onset of the picture. The baseline-corrected data from the 6- to 12-s time window were then averaged across picture category to create a percent change score for each participant for pleasant, unpleasant, neutral, and cigarette-related pictures (Versace et al., 2011). Using regression parameters (β estimates) from the GLM for each picture category instead of percent change scores produced similar results, but percent change scores are more easily interpreted.

To classify smokers based on their brain responses to emotional and cigarette stimuli, we used the strategy of Versace et al. (2012). We standardized (z -transformed) the percent change scores from the 6- to 12-s post-picture-onset window for pleasant, unpleasant, neutral, and cigarette-related pictures within subjects (to prevent the classification algorithm from being biased by individual differences in absolute BOLD responses). The standardized scores were entered into a k -means cluster analysis (Statistica version 10, StatSoft). Cluster analysis is a multivariate technique that groups objects (i.e., participants) based on their characteristics (i.e., patterns of brain activity) (Hair & Black, 2000). The k -means method divides participants into a number of clusters, k , which is specified a priori. Based on our previous research, we hypothesized the presence of $k = 2$ subgroups of smokers (Versace et al., 2012). Initial cluster centers were computed by first sorting distances between all participants and then choosing participants at constant intervals. The clustering algorithm divided the smokers into two distinct groups based on their BOLD responses to the pictures such that variability was minimized within groups and maximized between them.

To examine how BOLD responses in this brain region differed between the two groups, we used mixed model analysis

(SAS PROC MIXED version 9.2, SAS Institute Inc.) in which group, picture category, and their interaction were modeled as fixed effects and subject as a random effect. Significant main effects and interactions were followed up with pairwise comparisons of means using a least squares mean procedure. It should be noted that the intent of this follow-up analysis was not to make statistical inferences about which brain regions showed greater response to emotional and cigarette pictures than neutral pictures, but instead to explore how brain responses in the ROI previously identified by the GLM differed between the two groups formed by the cluster analysis (Poldrack & Mumford, 2009).

Statistical Analysis of Abstinence and Questionnaire Data

This analysis aimed at validating the clinical relevance of group assignment from the cluster analysis by examining between-groups differences in treatment outcome measures. We assessed biochemically confirmed (expired CO level < 10 ppm and cotinine < 15 ng/ml), self-reported smoking abstinence during each follow-up visit. At the 24-hr postquit visit, self-reported 24-hr abstinence and expired CO were used. At subsequent time points, 7-day point prevalence (no smoking during the past 7 days) was used (Hughes et al., 2003). For each time point, logistic regression (SAS PROC LOGISTIC version 9.2) was used to test the effect of group assignment from the cluster analysis on abstinence, controlling for the effect of medication type (placebo, bupropion, or varenicline), age, and DPI score (these two variables differed between groups at the pre-fMRI baseline visit; see Results section).

Mixed model regression was used to assess the effect of group assignment, assessment time point (days from the quit attempt), and their interaction term on each measure of smoking behavior, mood, and withdrawal. All analyses were performed covarying for the corresponding baseline measurement value of each dependent variable, medication type, 7-day point prevalence abstinence (CO and cotinine confirmed), medication status (i.e., whether the participant was taking the treatment medication at any given time point), age, and DPI score. Subjects were modeled as a random effect. To evaluate the interaction of group assignment and assessment time point, we calculated intercepts and slopes for average change over time, which are reported as point estimates and SEs (Brown & Prescott, 1999).

Brain Regions With Different Patterns of Response Among 2 Subgroups of Smokers

The second step of the fMRI analysis aimed at identifying brain regions outside the extended visual system where BOLD responses differed between smokers assigned to the two groups. To prevent voxels used in Step 1 from having an influence on the results of Step 2, all the voxels that formed the ROI used in the cluster analysis in Step 1 were excluded from this analysis. On the remaining voxels, we conducted a GLM that included first-level fixed-effects terms identical to those used in the GLM used in Step 1 (i.e., stimulus category and head motion parameters). At the second level of the model, we included fixed-effects terms for group (Group 1, Group 2), picture category (pleasant, cigarette) and their interaction, and a random-effects term for subject. We limited the picture category factor to pleasant and cigarette cues because, in Step 1, the two groups differed only in their BOLD responses to pleasant

and cigarette-related pictures. We identified brain regions that showed a significant group $\times$ picture category interaction using a FDR of $q < .01$ and a minimum cluster size of 1,000 mm³, which corresponded to a single-voxel threshold of $F(1,53) > 13.24, p < .0007$. Percent change scores were obtained for these regions and analyzed using the procedures described above (see Classification of Smokers Based on Brain Responses to Cigarette-Related and Emotional Pictures section).

RESULTS

Classification of Smokers Based on Brain Responses to Cigarette-Related and Emotional Pictures

The contrast of BOLD responses of the study participants to cigarette-related, pleasant, and unpleasant pictures versus neutral pictures produced a large volume (95,867 mm³) of statistically significant voxels located primarily within gray matter regions of the left and right occipital, posterior parietal, and inferior temporal lobes (Figure 1A). Specific regions located within this ROI included the cuneus, middle occipital gyrus, and inferior occipital gyrus in the occipital lobe; the precuneus and superior parietal lobule in the parietal lobe; and the middle temporal gyrus and fusiform gyrus in the temporal lobe.

Cluster analysis conducted on data extracted from these regions resulted in assignment of 31 smokers (13 women) to Group 1 and 24 smokers (12 women) to Group 2. To evaluate if the two-cluster solution was appropriate, we used Euclidean distances and the Hartigan–Wong algorithm (Hartigan & Wong, 1979) for solutions ranging from 2 to 15 clusters. Convergence of the Cubic Clustering Criterion (Sarle, 1983) and the Duda Index (i.e., $Je(2)/Je(1)$) (Duda & Hart, 1973) indicated the two-class solution as optimal. The two groups did not significantly differ on any baseline measure other than age (the smokers in Group 1 were older; $p < .05$) and scores on the DPI (the smokers in Group 1 scored higher; $p < .05$). Medication assignment during the subsequent clinical trial did not differ between the two groups (Table 1).

To describe the between-groups differences uncovered by the classification algorithm, we ran group $\times$ picture category analyses on BOLD responses from the ROI used in the cluster analysis. Replicating our previous findings (Versace et al., 2012), the group $\times$ picture category interaction [$F(3,159) = 15.79, p < .0001$] was driven by a large difference between BOLD responses to pleasant and cigarette-related pictures in the two groups. In the occipital, posterior parietal, and inferior temporal ROI that was used for the cluster analysis, Group 1 had larger responses to pleasant pictures than to cigarette-related pictures [$F(1,159) = 60.96, p < .0001$] while Group 2 showed the opposite pattern, with larger BOLD responses to cigarette-related pictures than to pleasant pictures [$F(1,159) = 4.17, p = .04$] (Figure 1B). The largest between-group difference in this ROI was for pleasant pictures, with Group 1 showing more activation than Group 2 [$F(1,159) = 11.29, p = .001$]. The between-group difference for cigarette-related pictures was also significant, with Group 2 showing larger BOLD responses in this ROI than Group 1 [$F(1,159) = 5.02, p = .03$]. BOLD responses to neutral [$F(1,159) = 2.82, p = .09$] and unpleasant [$F(1,159) = 0.38, p = .53$] pictures did not differ between groups. These findings are consistent with those from our previous ERP study (Versace et al., 2012): The two groups

Figure 1. (A) Brain areas in the posterior parietal and occipital lobes that showed significantly more blood-oxygenation-level-dependent (BOLD) activation to cigarette-related, pleasant, and unpleasant pictures than to neutral pictures. The t -statistics for voxels exceeding the statistical threshold (false discovery rate of $q < .01$ and minimum cluster size of $1,000 \text{ mm}^3$) are mapped in shades of orange. y refers to Talairach coordinate of the coronal slice. (B) Mean percent change in BOLD activity for each picture category as a function of group assignment, averaged across the brain regions with significant activation shown in (A). (C) Mean percent change in BOLD activity as shown in (B) after dividing responses to pleasant and unpleasant pictures into high-arousal and low-arousal subcategories. $^*(p < .05)$ and $^{**}(p < .01)$ indicate significant differences between BOLD responses to pleasant and cigarette-related pictures. CIG = cigarette; ERO = erotica (high-arousal pleasant); MUT = mutilations (high-arousal unpleasant); NEU = neutral; PLE = pleasant; ROM = romance (low-arousal pleasant); SAD = sad (low-arousal unpleasant); UNP = unpleasant.

respond differently to pleasant and cigarette-related pictures but not to neutral or unpleasant pictures. This pattern of results suggests that differences in relative sensitivity to drug-related and nondrug-related rewards can explain the between-groups differences.

Reward sensitivity differences were present irrespective of the arousal level of the pleasant pictures. [Figure 1C](#) shows that, in Group 1, both high-arousal (i.e., erotica) and low-arousal (i.e., romantic) pleasant pictures evoked larger BOLD responses than cigarette pictures in the occipital, posterior

Table 1. Age, Smoking History, and Questionnaire Scores

Variable	High reward sensitivity group (<i>n</i> = 31)	Low reward sensitivity group (<i>n</i> = 24)	Total (<i>n</i> = 55)
	% (<i>n</i>)	% (<i>n</i>)	% (<i>n</i>)
Gender			
Female	41.9 (13)	50.0 (12)	45.5 (25)
	Mean (<i>SD</i>)	Mean (<i>SD</i>)	Mean (<i>SD</i>)
Age (years)	46.84 (10.73)	39.46 (10.21)*	43.62 (11.04)
Years smoking	26.77 (11.50)	21.00 (10.49)	24.25 (11.35)
Current smoking rate (cigarettes/day)	21.70 (9.18)	21.25 (10.67)	21.50 (9.77)
Expired CO (ppm)	22.06 (6.96)	26.52 (14.20)	23.96 (10.77)
FTND score	4.83 (1.93)	4.71 (2.33)	4.78 (2.10)
WISDM-Brief (total score)	48.74 (10.45)	48.59 (13.19)	48.67 (11.63)
CES-D (total score)	7.87 (6.49)	5.00 (3.99)	6.62 (5.68)
DPI	2.85 (0.90)	2.28 (0.88)*	2.60 (0.93)
FCPS	3.77 (0.40)	3.85 (0.36)	3.81 (0.38)
BAS (total score)	27.17 (5.97)	28.67 (5.03)	27.83 (5.57)
BIS (punishment sensitivity score)	14.63 (2.99)	15.58 (4.04)	15.06 (3.49)
QSU-Brief (total score)	4.88 (2.02)	4.49 (2.71)	4.71 (2.33)
PANAS negative affect	17.07 (5.03)	15.57 (4.77)	16.42 (4.93)
PANAS positive affect	35.33 (5.96)	36.78 (8.06)	35.96 (6.91)
Medication group	<i>n</i> (Female)	<i>n</i> (Female)	<i>n</i> (Female)
Placebo	11 (5)	8 (4)	19 (9)
Bupropion	9 (4)	8 (4)	17 (8)
Varenicline	11 (4)	8 (4)	19 (8)

Note. BAS = Behavioral Approach System; BIS = Behavioral Inhibition System; CES-D = Center for Epidemiological Studies Depression Scale; CO = carbon monoxide; DPI = Depression Proneness Inventory; FCPS = Fawcett–Clark Pleasure Scale; FTND = Fagerström Test for Nicotine Dependence; PANAS = Positive and Negative Affect Scale; QSU = Questionnaire on Smoking Urges; WISDM = Wisconsin Inventory of Smoking Dependence Motives. An asterisk indicates that the low reward sensitivity group significantly differed from the high reward sensitivity group, measured using a two-sample *t* test ($p < .05$). Medication and gender were equally distributed across the two reward sensitivity groups.

parietal, and inferior temporal ROI that was used for the cluster analysis [$F_s(1,265) > 13.32$, $ps < .0003$]. In Group 2 (in the same ROI), cigarette pictures evoked BOLD responses comparable with those evoked by erotic [$F(1,265) = 0.21$, $p = .64$] and larger than those evoked by romantic [$F(1,265) = 10.82$, $p = .0011$] pictures (Figure 1C).

Abstinence, Smoking Behavior, and Withdrawal Symptoms

The clinical significance of cluster identification was confirmed by the between-groups differences observed in the treatment outcome measures. During the quit attempt, Group 1 had higher abstinence rates than Group 2, with the exception of the 4-week follow-up visit (Figure 2). Replicating our previous findings (Versace et al., 2012), logistic regression indicated that (after controlling for medication, age, and DPI), the smokers in Group 1 had higher long-term abstinence rates than the smokers in Group 2 (7-week postquit time point [Wald $\chi^2(1) = 3.52$, $p = .06$]; 3 months [Wald $\chi^2(1) = 2.11$, $p = .15$], 6 months [Wald $\chi^2(1) = 4.02$, $p = .045$]).

Consistent with their higher long-term abstinence rate, smokers in Group 1 showed smaller rates of increase in the number of cigarettes smoked per day and in CO levels over the course of the abstinence period than those in Group 2 (Table 2). Furthermore, Group 2 showed increasing negative

affect (depression, sadness, anxiety, and anger), decreasing positive affect, and greater sleep disturbance over the course of the quit attempt. The two groups did not significantly differ on measures of craving (QSU-Brief or WSWs craving scale).

Brain Regions With Different Patterns of Response Among 2 Subgroups of Smokers

The next step in the fMRI analyses aimed at identifying brain regions outside the extended visual system in which the two groups of smokers differed in BOLD responses to pleasant and cigarette-related stimuli. We conducted a voxelwise GLM on BOLD responses measured in all voxels that were not part of the ROI used in Step 1. This GLM included group (high reward sensitivity, low reward sensitivity) as a between-subjects factor and picture category (pleasant, cigarette related) as a within-subjects factor. Areas that showed a significant group $\times$ picture category interaction are shown in Table 3 and Figure 3A. For illustrative purposes, we show the percent change in BOLD signal for each picture category in Figures 3B and 3C from one representative region, the dorsal striatum. In this region, Group 1 had larger BOLD responses to pleasant pictures than cigarette-related pictures, whereas Group 2 showed the opposite effect. BOLD responses to neutral or unpleasant pictures did not differ between the groups. These results were not driven by the arousal level of the pleasant pictures (Figure 3C). In

Group 1, in the dorsal striatum, both high-arousal and low-arousal pleasant pictures evoked larger BOLD responses than cigarette pictures. In Group 2, cigarette-related pictures evoked BOLD responses comparable with those evoked by

high-arousal pleasant pictures and larger than BOLD responses evoked by low-arousal pleasant pictures. All other regions listed in Table 3 showed a similar pattern of activation.

Figure 2. Percentage of smokers in each group who were abstinent at each postquit time point. * indicates a significant difference between groups, $p < .05$. At each time point, the odds ratio (OR) and 95% CI that smokers in Group 1 were abstinent, relative to those in Group 2, were as follows. 24 h: OR = 1.40, 95% CI = 0.40–4.91; 1 w: OR = 1.74, 95% CI = 0.49–6.15; 4 w: OR = 1.37, 95% CI = 0.37–5.07; 7 w: OR = 3.98, 95% CI = 0.94–16.84; 12 w: 2.83, 95% CI = 0.70–11.47; 24 w: OR = 6.34, 95% CI = 1.04–38.64. h = hours, w = weeks.

DISCUSSION

By using fMRI to measure prequit brain responses to pleasant and cigarette-related stimuli, we demonstrated that smokers can be divided into two groups. Group 2 exhibited enhanced responses to cigarette-related cues, relative to pleasant stimuli (i.e., natural rewards). We labeled this group of smokers the “low reward sensitivity” group. On the other hand, we labeled Group 1 as the “high reward sensitivity” group to highlight their larger responses to pleasant stimuli than to cigarette-related cues.

Volkow and colleagues proposed that addicted individuals are characterized by increased sensitivity to drug-related cues and reduced sensitivity to natural rewards (Koob & Volkow, 2010; Volkow et al., 2010). Our findings indicated that although smokers showed increased reactivity to cigarette-related cues relative to neutral stimuli, the low reward sensitivity group was characterized by blunted responses to natural rewards relative to cigarette-related cues. This explains why we found no differences between pleasant and cigarette-related cues in our previous analysis of a subsample of these participants (Versace et al., 2011). If the high reward sensitivity group shows larger responses to pleasant pictures than cigarette-related pictures, whereas the low reward sensitivity group shows the opposite pattern, the average activity across all smokers reveals no difference between responses to drug-related versus natural rewards. This illustrates the importance of considering individual differences, both when studying reward sensitivity and when designing smoking cessation interventions.

Table 2. Smoking Behavior, Affect, and Withdrawal Symptoms

Measure	Den DF	Main effect of time (F)	Group $\times$ time interaction (F)	Slope (SE)	
				High reward sensitivity group	Low reward sensitivity group
No. of cigarettes smoked (past 12 hr)	341	16.31**	4.35*	0.0281 (0.0118)*	0.0517 (0.0110)**
Expired CO (ppm)	200	13.55**	5.73*	0.0278 (0.0133)*	0.0601 (0.0141)**
CES-D (total score)	218	1.59	4.70*	–0.0004 (0.0108)	0.0243 (0.0116)*
PANAS positive affect	216	1.48	5.21*	0.0006 (0.0104)	–0.0234 (0.0111)*
PANAS negative affect	216	0.38	3.41	–0.0128 (0.0086)	0.0033 (0.0091)
QSU-Brief (total score)	202	1.43	2.76	–0.0057 (0.0030)	–0.0007 (0.0031)
WSWS anger	217	0.32	10.18**	–0.0094 (0.0044)*	0.0050 (0.0047)
WSWS anxiety	217	0.02	4.93*	–0.0052 (0.0052)	0.0065 (0.0055)
WSWS concentration	217	0.03	1.08	–0.0013 (0.0035)	0.0024 (0.0037)
WSWS craving	217	0.13	3.60	–0.0083 (0.0064)	0.0040 (0.0068)
WSWS hunger	217	0.03	2.65	–0.0040 (0.0059)	0.0058 (0.0063)
WSWS sadness	217	2.26	6.93**	0.0000 (0.0051)	0.0136 (0.0054)*
WSWS sleep disturbance	217	0.03	8.79**	–0.0096 (0.0071)	0.0117 (0.0075)

Note. CES-D = Center for Epidemiological Studies Depression Scale; CO = carbon monoxide; PANAS = Positive and Negative Affect Scale; QSU = Questionnaire on Smoking Urges; WISDM = Wisconsin Inventory of Smoking Dependence Motives. Results of mixed model regression testing the effect of group on the change in scores on several measures as a function of time since the quit-smoking date. Den DF refers to the number of denominator degrees of freedom for the F -statistics for the main effect of time and the group $\times$ time interaction (all tests had 1 numerator degree of freedom). Slope refers to the slope of the regression lines for each group. Slopes are presented as point estimates, with SE s in parentheses. Asterisks following the F -statistics indicate a statistically significant main effect of time or group $\times$ time interaction. Significant group $\times$ time interactions indicate that the slopes significantly differed between the high reward sensitivity and low reward sensitivity groups. Asterisks following the slopes indicate that the individual slope is significantly different from zero: * $p < .05$, ** $p < .01$.

Table 3. Brain Regions With Significant Group $\times$ Picture Category Interaction

Brain area	Hem	BA	Location			Size (mm ³)	$F_{\max}$
			x	y	z		
Precuneus	B	7	0	-46	49	11,893	41.14
	L	7	-17	-69	29	1,773	27.85
Paracentral lobule	L	31	0	-22	44	1,745	23.82
Middle temporal gyrus	R	39	43	-64	23	1,498	24.25
	R	21	50	-4	-17	1,057	36.88
Postcentral gyrus	R	2	48	-26	38	11,277	39.60
Inferior precentral gyrus	L	44	-55	11	9	1,117	18.96
	R	44	53	11	7	1,609	25.57
Superior precentral gyrus	L	6	-53	-4	32	2,194	23.93
Posterior thalamus	L	—	-16	-24	4	1,038	21.22
	R	—	12	-18	4	1,255	23.72
Putamen	R	—	20	3	5	1,180	24.75
Caudate head	R	—	22	18	3	1,278	23.09
Caudate body	R	—	6	4	15	878	28.44
Middle frontal gyrus	R	9	45	7	38	4,835	31.07
	R	8	31	29	38	3,788	33.70
Medial frontal gyrus	L	8	-1	22	42	4,615	38.35
	R	10	6	47	13	1,758	26.34

Note. B = bilateral; BA = Brodmann area, FDR = false discovery rate; Hem = hemisphere, L = left, R = right. These brain areas were identified using a group (high reward sensitivity, low reward sensitivity) $\times$ picture category (cigarette-related, pleasant) voxelwise generalized linear model on all voxels that were not used to divide the smokers into groups. Location is expressed in Talairach coordinates (mm) and is presented for the center of gravity of each activation cluster. $F_{\max} = F(3,159)$ statistic for the group $\times$ picture category interaction from the peak voxel in each cluster (all voxelwise $ps < .0001$, $p[\text{FDR}] < .01$).

The results reported here replicate and extend the findings that we previously obtained from an independent sample using ERPs (Versace et al., 2012). In both studies, the low reward sensitivity group had more difficulty in achieving long-term smoking abstinence than did the high reward sensitivity group. fMRI allowed us to extend our results beyond the previous study and identify specific brain systems, notably the dorsal striatum and medial prefrontal cortex, which differed between groups. These structures are involved in reward processing and receive projections from ascending dopamine systems that are considered a “common pathway” of activation shared by all rewarding stimuli, including drugs of abuse (Kelley & Berridge, 2002; Nestler, 2005). In fact, a recent fMRI study found that smokers had larger brain responses to cigarette cues than to other pleasant cues in the middle frontal gyrus, whereas nonsmokers had larger responses to pleasant cues than cigarette cues (Diggs et al., 2013). Thus, the smokers in the low reward sensitivity group in our study may have had a difficult time quitting smoking because their brain reward systems were biased such that (a) cigarette-related cues were highly salient, serving as an antecedent to smoking and (b) alternative rewarding behaviors were not sufficiently attractive or reinforcing to be maintained. Our experimental paradigm could contribute to efforts to tailor smoking cessation treatments by providing a means of identifying individuals who may be less likely to achieve long-term abstinence. For example, smokers with blunted brain responses to pleasant stimuli may benefit from interventions designed to enhance their ability to extract pleasure from everyday activities (MacPherson et al., 2010; Xu, Floyd, Westmaas, & Aron, 2010; Xu et al., 2012). Given the common functional effects exerted by drugs of abuse on brain reward systems (Nestler, 2005), this approach could also be used to predict relapse vulnerability for other addictions. For example, there is evidence that alcoholics with stronger brain

responses to pleasant stimuli have better treatment outcomes (Heinz et al., 2007). ERPs, an approach that is cost-effective and well tolerated by patients, could be used for pretreatment screening, whereas fMRI could be used in a preclinical setting to refine our understanding of individual differences in brain reward sensitivity and their relationship to the success of quit attempts.

This fMRI paradigm could also facilitate the development of new smoking cessation medications aimed at normalizing brain activity in areas showing abnormal reactivity to pleasant and drug-associated stimuli. Animal models have shown that individual differences in the attribution of incentive salience to reward-related stimuli may be related to addictive behavior (Flagel, Watson, Akil, & Robinson, 2008; Tomie, Grimes, & Pohorecky, 2008). For example, rats showing Pavlovian “sign-tracking” (i.e., approaching and engaging the conditioned stimulus instead of the intrinsically rewarding unconditioned stimulus) are more vulnerable to cocaine dependence than those that show “goal-tracking” (i.e., approaching the unconditioned stimulus; Flagel et al., 2008, 2010; Meyer, Ma, & Robinson, 2012). Brain systems such as the striatum and medial prefrontal cortex are involved in the expression of sign-tracking (Flagel et al., 2011; Flagel, Watson, Robinson, & Akil, 2007; Tomie, Aguado, Pohorecky, & Benjamin, 2000; Tomie et al., 2008). The fact that the low reward sensitivity group showed excessive incentive salience to cigarette cues and that this was reflected in differential activation in the same brain regions that distinguish sign-trackers from goal-trackers, suggests that the individual differences found here might map onto those observed in the animal model. This hypothesis provides an opportunity to link findings from animal models and human fMRI studies and perhaps to help develop interventions aimed at shifting incentive salience from drug-related cues to alternative sources of reward.

Figure 3. (A) Brain areas showing a significant group (Group 1, Group 2) × picture category (pleasant, cigarette-related) interaction in a voxelwise generalized linear model conducted across all voxels that were not used to divide the smokers into groups. Orange overlays map the value of the F -statistic for the group × picture category interaction term that exceeded the statistical threshold (false discovery rate of $q < .01$ and minimum cluster size of $1,000 \text{ mm}^3$). x and y refer to Talairach coordinates of the sagittal and coronal slice, respectively. The white circle highlights the dorsal striatal (DS) region. (B) Mean percent change in blood-oxygenation-level-dependent (BOLD) signal for cigarette-related (CIG), pleasant (PLE), neutral (NEU), and unpleasant (UNP) pictures obtained from the dorsal striatum as a function of cluster group assignment. (C) Mean percent change in BOLD activity as shown in (B) after dividing responses to pleasant and unpleasant pictures into high-arousal and low-arousal subcategories. ERO = erotica (high-arousal pleasant); MUT = mutilations (high-arousal unpleasant); ROM = romance (low-arousal pleasant); SAD = sad (low-arousal unpleasant).

Recently, another fMRI study (Janes et al., 2010) found that female smokers with larger responses to cigarette-related cues were most likely to slip after a quit attempt. This result is consistent with the increased reactivity to cigarette cues shown in

our study by the low reward sensitivity group. However, when we compared brain responses with cigarette-related cues as a function of abstinence status (rather than cluster group assignment), the results, although in the same direction reported by

Janes et al. (2010), were far from significant. Furthermore, Janes and coworkers limited their follow-up smoking assessment to 8 weeks and did not measure brain responses to pleasant stimuli, the category where our two groups showed the largest prequit differences. Thus, we hypothesize that increased cigarette cue reactivity might play a pivotal role in the initial phases of the quit attempt (Sayette & Tiffany, 2012) but that intact hedonic capacity may be necessary to sustain long-term abstinence. This hypothesis fits well with self-reports obtained during the quit attempt. When nicotine deprived, smokers characterized by low reward sensitivity might have experienced a steeper increase in negative affect because of their reduced ability to extract pleasure from alternative sources of reward. Previous studies using self-report measures indicated that higher levels of anhedonia are associated with shorter abstinence duration (Leventhal, Waters, Kahler, Ray, & Sussman, 2009). Lack of between-group differences in craving scores over the course of the quit attempt seems to confirm that our methodology is primarily sensitive to differences in affective processing.

Future research is needed to clarify whether the differences we observed between the two groups preceded smoking initiation. Among human adolescents, smokers exhibit decreased brain responses to pictures of pleasurable food compared with nonsmokers of the same age (Rubinstein, Luks, Dryden, Rait, & Simpson, 2011) and low hedonic capacity predicts smoking onset and escalation (Audrain-McGovern et al., 2012). Thus, aberrant responses to pleasant stimuli and cigarette-related cues observed here may develop prior to long-term smoking, but the exact causes and developmental time course of this phenomenon need to be determined.

Our study is limited in that we did not have sufficient power to examine medication $\times$ group interactions in the abstinence or self-report data (i.e., after stratifying the sample into the three medication groups, there were empty cells at some postquit time points). Also, the pleasant stimuli used here are somewhat limited in scope because they were pictorial representation of rewarding stimuli. Future research is needed to examine whether the difference in reactivity to primary and secondary rewards (e.g., food, money) predicts smoking cessation outcomes.

A priori considerations (Keil et al., 2002; Sabatinelli et al., 2007; Versace et al., 2012) prompted us to use prequit activation in posterior brain regions to classify smokers. Given that activity in subcortical regions modulates activation in visual processing systems in the presence of motivationally salient stimuli (Pessoa, 2008), future studies need to evaluate whether using prequit activation from subcortical regions improves the ability to predict future outcomes. It is important to note that analyzing prequit brain activity as a function of postquit abstinence status (at any time point) did not lead to any significant between-group fMRI differences. Such an outcome is not surprising: smokers relapse for different reasons; it is unlikely that these heterogeneous factors will have a common effect on prequit brain activity. Our analytic strategy aimed at isolating one factor (i.e., relative sensitivity to pleasant and cigarette-related cues) to evaluate its influence on the ability to sustain prolonged smoking abstinence.

In summary, we demonstrated that the prospect of long-term abstinence is reduced when the level of brain reactivity to cigarette-related cues equals or exceeds that to pleasant stimuli. Thus, smokers who find natural rewards less emotionally arousing than smoking may have a difficult time experiencing

pleasure during abstinence. For these individuals, the lack of alternative forms of reinforcement combined with the attractiveness of cigarettes may be putting them at high risk for relapse. Normalizing these pathological neuroadaptations may be key to improving abstinence rates in this particular group of addicted individuals.

SUPPLEMENTARY MATERIAL

Supplementary Methods and Results can be found online at <http://www.ntr.oxfordjournals.org>

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DECLARATION OF INTERESTS

PMC served on the scientific advisory board of Pfizer Pharmaceuticals, conducted educational talks sponsored by Pfizer on smoking cessation (2006–2008) and has received grant support from Pfizer. MAK-H has conducted educational talks sponsored by Pfizer Pharmaceuticals and has participated as study physician and coinvestigator in two studies funded by Pfizer Pharmaceuticals. The other authors declare no conflict of interest. In 2011, FV received an independently reviewed competitive grant supported by Pfizer (Global Research Award for Nicotine Dependence).

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FV and JME contributed equally to this work.

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