

Activation in Mesolimbic and Visuospatial Neural Circuits Elicited by Smoking Cues: Evidence From Functional Magnetic Resonance Imaging

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Objective: The authors sought to increase understanding of the brain mechanisms involved in cigarette addiction by identifying neural substrates modulated by visual smoking cues in nicotine-deprived smokers.

Method: Event-related functional magnetic resonance imaging (fMRI) was used to detect brain activation after exposure to smoking-related images in a group of nicotine-deprived smokers and a nonsmoking comparison group. Subjects viewed a pseudo-random sequence of smoking images, neutral nonsmoking images, and rare targets (photographs of animals). Subjects pressed a button whenever a rare target appeared.

Results: In smokers, the fMRI signal was greater after exposure to smoking-related images than after exposure to neutral images in mesolimbic dopamine reward circuits known to be activated by addictive

drugs (right posterior amygdala, posterior hippocampus, ventral tegmental area, and medial thalamus) as well as in areas related to visuospatial attention (bilateral prefrontal and parietal cortex and right fusiform gyrus). In nonsmokers, no significant differences in fMRI signal following exposure to smoking-related and neutral images were detected. In most regions studied, both subject groups showed greater activation following presentation of rare target images than after exposure to neutral images.

Conclusions: In nicotine-deprived smokers, both reward and attention circuits were activated by exposure to smoking-related images. Smoking cues are processed like rare targets in that they activate attentional regions. These cues are also processed like addictive drugs in that they activate mesolimbic reward regions.

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Cues related to addictive drugs are well known to induce craving and drug use in addicts. The sight of a bare forearm may prompt a heroin user to inject, while the sight and smell of a burning cigarette will elicit a strong urge to smoke in an abstinent smoker (1, 2). However, despite extensive behavioral and physiological work on cue effects, relatively few studies have explored the effects of drug cues on human brain activity.

Several imaging studies have examined the effects of drug-related stimuli on brain activation in substance users. Two positron emission tomography studies used visual stimuli (a cocaine video and a neutral-content video) to detect brain regions in cocaine addicts activated by drug craving (3, 4). One study found significant activation in the amygdala, anterior cingulate, and temporal pole, while the other detected significant activation in the dorsolateral prefrontal, medial orbitofrontal, temporal, retrosplenial, visual, and temporal/parietal cortices. Likewise, functional magnetic resonance imaging (fMRI) studies have detected significant activation of the anterior cingulate (5–7) and activation (5, 6) or deactivation (7) of the prefrontal cortex by cocaine videos. Many brain regions activated by a cocaine video were also activated by a sex

video in both cocaine-using and comparison subjects, suggesting a common neural circuit that responds to emotionally evocative stimuli (5). Similarly, an fMRI study found cue-induced activation of the right amygdala/hippocampus, superior temporal gyrus, and cerebellum in abstinent alcoholics before cognitive therapy for alcohol abuse but no cue-induced activation of the amygdala and cerebellum after therapy (8).

To our knowledge, no previous studies have used event-related fMRI to examine the neural response to smoking cues in nicotine-deprived smokers. Therefore, our research investigated brain areas modulated by brief exposure to smoking-related stimuli. While previous addictive-cue studies have primarily focused on limbic brain regions, we hypothesized that two distinct neural circuits might be activated by smoking cues: a reward circuit identified by animal studies of drug reinforcement and a visuospatial attention circuit identified by human functional imaging studies. The reward circuit consists of mesocorticolimbic regions that include the ventral tegmental area, nucleus accumbens, amygdala, hippocampus, medial dorsal thalamus, ventral pallidum, and prefrontal cortex (9, 10). This circuit, although clearly activated by ingestion

of addictive substances, may also be activated by cues predicting their availability. Key substrates in this circuit, including the amygdala, nucleus accumbens, and ventral tegmental area, are activated by environmental stimuli associated with reward (11–14). The visuospatial-attention circuit includes the dorsolateral and ventrolateral prefrontal cortex (inferior frontal gyrus and middle frontal gyrus), anterior cingulate, parietal cortex (intraparietal sulcus), and extrastriate visual cortex (fusiform gyrus). Human functional imaging studies have identified these areas as being activated by rare targets during detection tasks (15–18). We therefore postulated that visual smoking cues would activate these areas preferentially in nicotine-deprived smokers.

Method

Subjects

Twelve subjects who smoked at least 15 cigarettes/day participated in this study (four women and eight men; mean age=22.7 years, SD=3.6, mean cigarettes/day=23.5, SD=7.7). Subjects agreed to abstain from smoking after midnight of the evening before the scanning session. Data from one male smoker were excluded from all analyses because of intermittent sleeping during the session; subsequent analyses are reported on the remaining 11 smokers. Six subjects who had never smoked cigarettes on a regular basis were recruited to serve as a comparison group (two women and four men; mean age=25.0 years, SD=5.4). Subjects completed a brief medical screening form and did not report any intercurrent neurologic disorders or current use of psychoactive medications. All female subjects tested negative on a serum β human chorionic gonadotropin pregnancy test. Alcohol use was limited to two or fewer drinks in the preceding 24 hours and none in the preceding 10 hours. All subjects were right-handed. All research was conducted under the guidelines of the institutional review board of Duke University Medical Center.

Subject Preparation

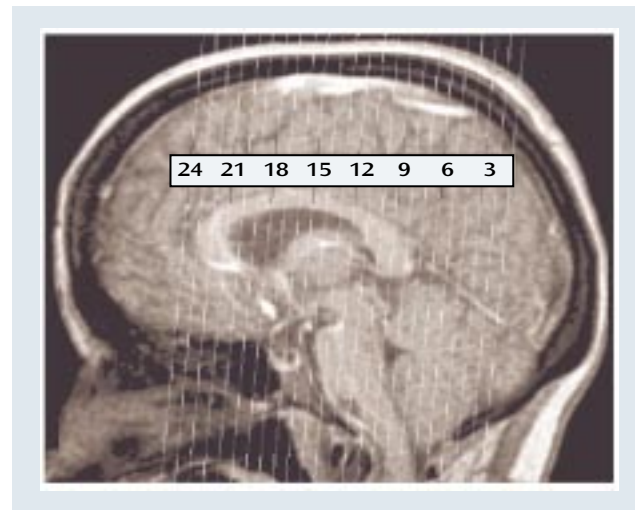
For subjects in the smoking group, all sessions took place in mid-morning, after approximately 10 hours of smoking deprivation. A BreathCO carbon monoxide monitor (Vitalograph Inc., Lenexa, Kan.) was used to measure carbon monoxide in the exhaled breath in order to verify smoking abstinence. The mean carbon monoxide reading for the group was 13.2 ppm before scanning, a value similar to that reported in other studies requiring overnight smoking abstinence (19).

During the imaging session, each subject laid on the scanner gurney, with his or her head resting on a foam cushion inside the head coil. Head motion was restricted by a vacuum pack system around the sides of the head and tape stretched across the forehead. Only minimal head motion (2 mm or less in the x, y, or z direction) was measured in any run, and therefore motion correction of the data was not performed. However, the presence of significant motion-related variability cannot be ruled out as a source of noise in the functional imaging data. Experimental stimuli were projected behind the subject's head onto a screen, which was viewed using goggles with attached mirrors.

Imaging Parameters

All subjects were scanned on a 1.5 T GE Signa scanner with 41 mT/m gradients for fast echo-planar imaging. Following initial sagittal structural scanning (two-dimensional spoiled gradient recall acquisition; nine slices around midline; 5 mm thick), 24 oblique coronal slices were selected perpendicular to the line con-

FIGURE 1. Placement of Coronal Slices for a Functional Magnetic Resonance Imaging Analysis of Brain Activation in 11 Nicotine-Deprived Smokers and Six Nonsmokers After Exposure to Smoking, Neutral, and Target Stimuli^a



^a Each slice is 5 mm thick, with no spaces between slices; the 17th slice is centered on the anterior commissure.

necting the anterior and posterior commissures. The 17th slice (posterior to anterior) was centered on the anterior commissure (Figure 1). For definition of regions of interest, high-resolution T1-weighted structural images were obtained (TE=14 msec, flip angle=90°, TR=500 msec, in-plane resolution=0.94 mm²). For functional imaging, an echo-planar pulse sequence obtained T2*-weighted images sensitive to blood-oxygenation-level-dependent contrast (slices coplanar to structural images: TR=2000 msec, TE=40 msec, flip angle=90°, in-plane resolution=3.75 mm²).

Behavioral Task Procedures

Three stimulus types were employed: smoking-related images, neutral images, and target images (20). All images were color photographs, subtending approximately 20° by 16° of visual angle. Smoking-related images included pictures of people smoking, hands holding cigarettes, and pictures of cigarettes alone. Neutral images were matched by the experimenters to approximate the general content (objects, hands, and faces), complexity, and affective content of the smoking images, but they did not contain any smoking cues. Pictures of animals were designated as target images, at which point subjects were required to press a button on a response box.

Sixty smoking-related images, 60 neutral images, and 15 target images were presented to each subject. Each image was presented for 4 seconds with a fixation cross appearing for 14 seconds between images. Fifteen trials were presented in each of nine runs. Each run contained six to seven neutral images, six to seven smoking-related images, and one to two target images. Stimuli were presented in a random order, with the constraint that no more than two stimuli of the same type appeared consecutively.

Subjective Measures Questionnaire

Subjects answered three questions related to mood and craving immediately before scanning, after the fourth run, and after scanning was completed: "How much do you want to smoke a cigarette right now?" "How stressed or anxious do you feel right now?" "How would you describe your mood right now?" Answers were given as ratings on a 7-point scale, which ranged from "not at all"

to "extremely" for questions 1 and 2 and from "very sad" to "elated" on question 3.

fMRI Data Analysis

Peristimulus epochs (18 seconds total: 2 TRs before and 7 TRs after) were extracted from the raw MR time course to be averaged for each of the stimulus types. Therefore, for each voxel in each subject's data, three epochs were identified: a smoking image epoch with nine time points (-4, -2, 0, 2, 4, 6, 8, 10, and 12), a neutral image epoch with nine time points, and a target epoch with nine time points. The smoking and neutral epochs contained the data from the average of 60 trials each, while the target epoch contained data from the average of 15 trials.

The fMRI signal change was examined in predefined regions of interest. The designated areas included those implicated in mesocorticolimbic reward circuits (ventral tegmental area, nucleus accumbens, amygdala, hippocampus, medial thalamus, and prefrontal cortex [defined as middle frontal gyrus, inferior frontal gyrus, and lateral orbitofrontal gyrus]) and in visuospatial-attention circuits (intraparietal sulcus, fusiform gyrus, anterior cingulate, inferior frontal gyrus, and middle frontal gyrus). From these hypotheses, 11 unique brain areas were predefined. After subdividing the amygdala, hippocampus, and fusiform gyrus into anterior and posterior sections and adding a white matter comparison region, a total of 14 regions of interest per subject were identified. Although the ventral pallidum was implicated as a key substrate in mesocorticolimbic circuits, it could not be included in the analysis because of susceptibility-associated fMRI signal loss. The orbitofrontal gyrus (lateral) and nucleus accumbens were included, but they border on areas prone to susceptibility artifact. Therefore, these regions of interest may have included some voxels that were subject to signal loss. The ventral tegmental area was not distinguishable from medial substantia nigra, and the region defined as the ventral tegmental area included the medial substantia nigra. Regions of interest were drawn by the authors on the high-resolution structural images of each subject and were identified by comparison to a MR-specific brain atlas (21). Reliability of region-of-interest drawing was assessed by selecting a random sample of 50 regions of interest from the total set, which were drawn by two individuals. The agreement (voxel overlap percentage) between these regions of interest was greater than 85%.

For each subject, percent signal change from baseline in each epoch was calculated for each time bin and averaged according to stimulus type. The average signal from the time bins at -4, -2, and 0 seconds was considered to be the prestimulus baseline signal. Sobel edge-detection algorithms were used to identify boundaries in the functional images, which were then manually coregistered with the anatomical images by using custom scripts written in MATLAB (Mathworks, Natick, Mass.).

Our initial exploratory analysis consisted of a three-way repeated-measures analysis of variance (ANOVA) performed within the group of smokers with stimulus type (smoking cue, neutral image), hemisphere (right, left), and time (4, 6, 8, and 10 seconds poststimulus) as factors. We then restricted our within- and between-group planned comparisons to those regions of interest in which the main effect of stimulus type within smokers was significant at an alpha level of 0.10. To evaluate differences between groups, we first calculated the percent signal-change difference between smoking-related and neutral images for each group and used this relative difference as the basis for our statistical comparisons, which used an alpha level of 0.05.

To evaluate whether self-report measures were associated with fMRI activation, we performed a correlation analysis in which the mean craving, stress, and mood scores for each subject were correlated with the maximal difference in response between smoking-related and neutral images during the 4–10-second poststimulus period for each region of interest.

Results

Subjective Measures

All smokers were craving cigarettes at baseline, with mean craving scores (rated on a scale of 0 to 6) increasing over the course of the session (baseline: mean=3.71 [SD=1.49]; mid-scan: mean=4.50 [SD=0.76]; postscan: mean=5.02 [SD=0.74]). Nonsmokers, as expected, were not craving cigarettes at any time point (score=0).

Stress scores (rated on a scale of 0 to 6) were higher in the smoking group and increased over time (baseline: mean=2.85 [SD=1.45]; mid-scan: mean=3.63 [SD=1.41]; postscan: mean=3.82 [SD=1.6]). Nonsmokers showed a decrease in stress over time (baseline: mean=1.55 [SD=0.84]; mid-scan: mean=1.48 [SD=0.53]; postscan: mean=0.50 [SD=0.84]). A two-factor ANOVA detected a main effect of group ($F=18.62$, $df=1, 45$, $p=0.0006$), no main effect of time, and an interaction between group and time ($F=6.24$, $df=2, 45$, $p=0.005$).

Smokers reported lower mood states (rated on a scale of -3 to 3; 0=neutral) than did nonsmokers (main effect of group: $F=6.25$, $df=1, 45$, $p=0.02$). Mean mood scores over time for smokers and nonsmokers were 0.00 (SD=0.77) and 0.98 (SD=1.47), respectively, at baseline; 0.06 (SD=0.94) and 1.10 (SD=0.74) at mid-scan; and 0.10 (SD=1.24) and 1.40 (SD=0.84) at postscan. No significant main effects of time or interactions between group and time were seen for mood scores.

Since there was little overlap between smokers and nonsmokers in stress and mood scores, and no overlap in craving scores, it was not possible to distinguish whether craving, stress, or mood affected activation independently of smoking status. Within the group of smokers considered alone, there were no significant correlations between behavioral measures and fMRI data.

fMRI Analyses

For smokers, the main effects of stimulus type (neutral versus smoking images, both hemispheres combined) were significant for the posterior fusiform gyrus, intraparietal sulcus, posterior hippocampus, medial thalamus, ventral tegmental area, posterior amygdala, inferior frontal gyrus, middle frontal gyrus, and nucleus accumbens (Table 1). Planned comparisons of right- and left-hemisphere activation for neutral versus smoking-related images detected significant activation in the right hemisphere for all of these same regions of interest, with the exception of the nucleus accumbens. Significant left-sided activation was detected in the intraparietal sulcus, medial thalamus, ventral tegmental area, and middle frontal gyrus. Nonsmokers showed no significant differences in response to stimulus type (neutral versus smoking-related images) in either the lateralized or combined analyses.

In the between-group comparisons (Table 1), smokers demonstrated significantly greater relative activation to smoking-related images (versus neutral images) than

TABLE 1. Brain Areas of Greater Activation After Exposure to Smoking Cues Than After Neutral Image Exposure in Nicotine-Deprived Smokers (N=11) and Areas of Greater Relative Activation (Smoking Cues Minus Neutral Images) in Smokers Than in Nonsmokers (N=6)

Region of Interest	Slice Number(s)	Slice Location (mm from anterior commissure)	Analyses ^a			
			Differences Between Smoking-Related Images and Neutral Images in Smokers ^b		Differences Between Smokers and Nonsmokers in Relative Activation ^c	
			F (df=1, 10)	p	F (df=1, 15)	p
Posterior fusiform gyrus	2–5	–75 to –60	4.90	0.05		
Left			4.40	0.06	2.27	0.15
Right			5.08	0.05	3.77	0.07
Anterior fusiform gyrus	6–9	–55 to –40	3.24	0.10		
Intraparietal sulcus	2–6	–75 to –55	7.47	0.02		
Left			5.50	0.04	0.65	0.43
Right			8.41	0.02	4.49	0.05
Posterior hippocampus	11–12	–30 to –25	7.61	0.02		
Left			3.83	0.08	6.63	0.02
Right			9.69	0.01	13.02	0.003
Anterior hippocampus	13–14	–20 to –15	4.64	0.06		
Left			3.65	0.09	3.86	0.07
Right			3.97	0.07	1.99	0.18
Medial thalamus ^d	13–14	–20 to –15	9.92	0.01		
Left			10.29	0.01	9.16	0.01
Right			8.92	0.02	8.42	0.01
Ventral tegmental area ^d	13	–20	9.87	0.01		
Left			5.79	0.04	0.08	0.78
Right			6.84	0.03	8.21	0.01
Posterior amygdala	15	–10	5.05	0.05		
Left			2.77	0.13	1.36	0.26
Right			6.58	0.03	4.98	0.04
Anterior amygdala	16	–5	1.99	0.19		
Anterior cingulate ^e	17–20	0 to 15	3.66	0.08	2.94	0.11
Inferior frontal gyrus	17–21	0 to 20	4.72	0.05		
Left			3.31	0.10	2.80	0.12
Right			4.86	0.05	7.02	0.02
Middle frontal gyrus	17–21	0 to 20	12.98	0.004		
Left			11.61	0.007	4.67	0.05
Right			12.69	0.005	4.94	0.04
White matter	18–19	5 to 10	2.14	0.18		
Nucleus accumbens	19	10	5.27	0.04		
Left			0.61	0.45	0.01	0.92
Right			4.64	0.06	0.14	0.71
Orbitofrontal gyrus	22–24	25 to 35	0.00	0.99		

^a Initial exploratory analysis performed within the group of smokers consisted of a repeated-measures analysis of variance with stimulus type (smoking cues, neutral images), hemisphere (right, left), and time (4, 6, 8, and 10 seconds poststimulus) as factors. Within- and between-group planned comparisons of hemispheric activation were restricted to those regions of interest in which the main effect of stimulus type within smokers for the combined hemispheres was significant at an alpha level of 0.10.

^b Significant results represent regions in which activation in the smokers was greater after exposure to smoking-related images than after neutral images, with the exception of the nucleus accumbens, in which activation was greater after exposure to neutral images than after smoking cues.

^c Significant results represent regions in which relative activation (smoking-related images minus neutral images) was greater in the smokers than in the nonsmokers.

^d For within-group analyses: df=1, 9; for between-group analyses: df=1, 14.

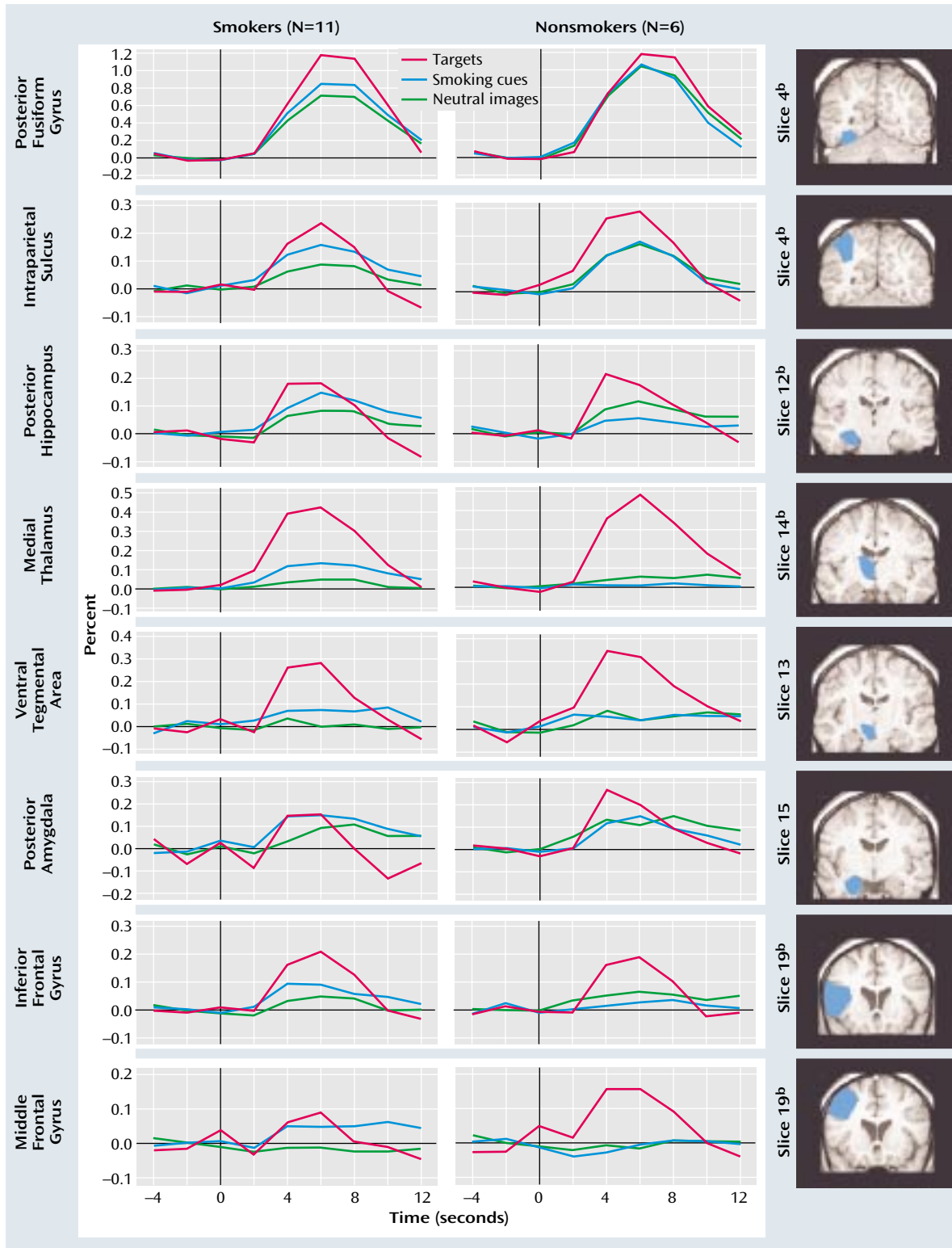
^e Defined as one central (combined) region of interest.

nonsmokers in the following regions: right intraparietal sulcus, posterior hippocampus (bilateral), medial thalamus (bilateral), right ventral tegmental area, right posterior amygdala, right inferior frontal gyrus, and middle frontal gyrus (bilateral).

Figure 2 illustrates the hemodynamic functions observed in the combined regions of interest. Only those regions of interest showing statistical significance in the ANOVA (smoking cues > neutral cues, within smokers) are depicted. In most regions of interest, the response to target stimuli was greater than the response to either the smoking-related or neutral images. Although there were only 15 target trials per subject, statistical significance

(computed by means of Student's *t* test, two-tailed) was achieved in the following regions of interest for the smoking group (df=10 for all comparisons): bilateral posterior fusiform gyrus (left: *t*=4.15, *p*=0.002; right: *t*=2.28, *p*=0.05), medial thalamus (left: *t*=5.05, *p*=0.0005; right: *t*=4.38, *p*=0.001), ventral tegmental area (left: *t*=2.84, *p*=0.02; right: *t*=3.56, *p*=0.005), right middle frontal gyrus (*t*=2.53, *p*=0.03), right inferior frontal gyrus (*t*=2.32, *p*=0.04), and anterior cingulate (*t*=4.86, *p*=0.001 [combined hemispheres]). Nonsmokers also responded more to targets than to either of the other stimulus types (df=5 for all comparisons). Like smokers, nonsmokers showed significant increases in activation in the bilateral medial thalamus (left: *t*=3.36, *p*=

FIGURE 2. Hemodynamic Function in Nicotine-Deprived Smokers and Nonsmokers After Exposure to Smoking, Neutral, and Target Stimuli^a



^a For each region of interest, mean percent signal change from baseline is depicted for left and right hemispheres combined (only the right region of interest is shaded in blue so that the underlying anatomy can be observed on the left; images follow radiologic convention, i.e., right and left are reversed). Stimulus onset occurred at 0 seconds, stimulus offset at 4 seconds.

^b While only an individual slice of the region of interest is shown, the mean signal from all slices in the region was used in the analysis.

0.02; right: $t=3.23$, $p=0.02$) and ventral tegmental area (left: $t=5.12$, $p=0.004$; right: $t=4.89$, $p=0.005$) and combined anterior cingulate ($t=3.93$, $p=0.01$). In addition, a significant bilateral decrease in activation in the nucleus accumbens was detected (left: $t=2.75$, $p=0.04$; right: $t=2.54$, $p=0.05$).

Discussion

In nicotine-deprived smokers, visual cues related to smoking were associated with greater neural activation both in mesocorticolimbic areas, which have been associated with reward processing, and in areas implicated in visuospatial attention. Within our postulated reward system, we found significant activation in prefrontal regions (inferior frontal gyrus, middle frontal gyrus) and in mesolimbic regions (posterior amygdala, posterior hippocampus, ventral tegmental area, and medial thalamus). Activation within the visuospatial system was found both in posterior extrastriate regions (posterior fusiform gyrus and intraparietal sulcus) and in prefrontal regions that overlap with the reward system (inferior frontal gyrus and middle frontal gyrus). It is important to note that all of these regions showed greater activation to smoking-related than neutral images within the smoking group and greater relative activation (smoking cues minus neutral images) in smokers than in nonsmokers. We discuss here the implications of these results for understanding the neural substrates of responses to drug cues.

Mesocorticolimbic Reward Circuit

Our findings are consistent with relatively recent theories about the role of mesolimbic dopamine substrates in drug reinforcement (11, 13, 22–24). Our subjects did not ingest nicotine, yet we found activation in the ventral tegmental area, posterior amygdala, posterior hippocampus, middle frontal gyrus, inferior frontal gyrus, and the medial thalamus and a suggestion of reduced activity in the nucleus accumbens. These findings indicate that mesocorticolimbic circuits may be activated by salient drug-related stimuli alone, without drug ingestion or its associated reward.

The ventral tegmental area has not been reported as responding to drug cues (nor has it been examined) in previous human cue-only studies and, to our knowledge, has not been identified in any functional imaging study involving rare target images. However, the ventral tegmental area has been identified as participating in drug reinforcement circuits by numerous animal studies. Nicotine, morphine, and alcohol stimulate the ventral tegmental area to release dopamine in the nucleus accumbens (9, 25, 26). Although most frequently associated with reward ingestion, ventral tegmental area activation (or dopamine release into the nucleus accumbens) may also occur in response to stimuli conditioned to predict reward (11–14). In humans, an fMRI study of cocaine users detected ventral tegmental area activation after cocaine ingestion, but its acti-

vation correlated more strongly with measures of feeling “high” than with measures of craving (27). Although we cannot rule out the possibility that smokers experienced conditioned pleasure upon viewing the smoking-related images, the lack of significant mood change and the greater stress reported over the course of the session argue against this explanation.

In the nucleus accumbens, there was less response to smoking cues than to neutral images (within smokers, combined region-of-interest analysis) and less response to target images than to neutral images (within nonsmokers, in left and right hemispheres). However, these findings should be interpreted with caution. Difficulty in identifying nucleus accumbens regions of interest because of susceptibility-related signal loss in ventral regions will increase the effects of motion-related artifacts within this region. Therefore, future work employing pulse sequences designed to minimize susceptibility artifacts could further illuminate nucleus accumbens function in cue-induced craving.

In summary, we have confirmed the participation of mesocorticolimbic regions in response to visual drug-related cues in abstinent users. Given the brief 4-second duration of cue exposure, this response does not necessarily reflect subjective craving. However, regions similar to those identified in our study (including the amygdala and prefrontal cortex) have been identified in previous functional imaging studies in which stimulus duration was adequate for induction of craving (3–7).

Visuospatial Attention Circuit

We found that smoking cues elicit a pattern of active brain regions that has been associated with visuospatial attention. In experiments that require subjects to respond to rare target images within a stochastic sequence, activation has been reported in the anterior cingulate, prefrontal, and extrastriate visual cortices during target detection (15–18). These areas were also activated by the targets within our study. Kirino and colleagues (15) suggested that the dorsolateral prefrontal cortex (similar to our middle frontal gyrus) mediates goal-directed responses that are based on remembered rules, whereas the cingulate gyrus may be associated with competing response alternatives (28). Our results are consistent with this formulation, although our design did not allow distinction between different cognitive processes given the co-occurrence of activation. It is interesting that we found consistent target-related increases in activation in the ventral tegmental area and in the medial thalamus, which have been infrequently studied in target-detection tasks given the emphasis on the prefrontal cortex. Further work will be necessary to elucidate the interconnection between systems responsible for coordinating response strategies and systems associated with reward. Mesocorticolimbic and visuospatial-attention circuits may work in concert in order to increase attention to stimuli of potential importance,

whether they are “targets” as defined by researchers conducting a cognitive study or “targets” such as the sight of a burning cigarette to a nicotine-deprived smoker.

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