Neural Substrates of Resisting Craving During Cigarette Cue Exposure

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Background: In cigarette smokers, the most commonly reported areas of brain activation during visual cigarette cue exposure are the prefrontal, anterior cingulate, and visual cortices. We sought to determine changes in brain activity in response to cigarette cues when smokers actively resist craving.

Methods: Forty-two tobacco-dependent smokers underwent functional magnetic resonance imaging, during which they were presented with videotaped cues. Three cue presentation conditions were tested: cigarette cues with subjects allowing themselves to crave (cigarette cue crave), cigarette cues with the instruction to resist craving (cigarette cue resist), and matched neutral cues.

Results: Activation was found in the cigarette cue resist (compared with the cigarette cue crave) condition in the left dorsal anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and precuneus. Lower magnetic resonance signal for the cigarette cue resist condition was found in the cuneus bilaterally, left lateral occipital gyrus, and right postcentral gyrus. These relative activations and deactivations were more robust when the cigarette cue resist condition was compared with the neutral cue condition.

Conclusions: Suppressing craving during cigarette cue exposure involves activation of limbic (and related) brain regions and deactivation of primary sensory and motor cortices.

Key Words: Cingulate cortex, cue-induced cigarette craving, functional magnetic resonance imaging, nicotine dependence, visual cortex

Cigarette craving is associated with relapse in smokers attempting to maintain abstinence (Catley *et al.* 2000; Killen and Fortmann 1997; Niaura *et al.* 1989; Swan *et al.* 1996). In tobacco-dependent smokers, craving increases naturally over the minutes and hours following the last cigarette (Jarvik *et al.* 2000; Schuh and Stitzer 1995) and can be elicited readily in the laboratory using cigarette-related cues (Brody *et al.* 2002; Carter and Tiffany 1999; Due *et al.* 2002; McClernon *et al.* 2005). The neurobiology of both craving (Nestler 2002; Weiss 2005) and the ability to resist craving (Modell and Mountz 1992; Stormark *et al.* 1995) are growing areas of interest, because medications that inhibit craving or enhance the ability to resist craving may prove useful for the treatment of tobacco dependence (a condition with a relatively low long-term treatment response rate) (Fiore *et al.* 2000; Jorenby *et al.* 1999).

Several research groups have examined regional brain activation associated with presentation of cigarette-related cues and correlations between brain activity and cigarette craving. The most commonly reported areas of activation during presentation of visual cigarette-related (compared with neutral) cues are the medial (Lee *et al.* 2005; McClernon *et al.* 2005) and lateral (Due *et al.* 2002; Lee *et al.* 2005) frontal cortex, anterior cingulate cortex (ACC) (Brody *et al.* 2002; Due *et al.* 2002; Lee *et al.* 2005; McClernon *et al.* 2005; Smolka *et al.* 2006; Wilson *et al.* 2005), precuneus (Lee *et al.* 2005), cuneus (Smolka *et al.* 2006; Wilson *et al.* 2005), and occipital cortex (Lee *et al.* 2005; Wilson *et al.* 2005). The most commonly reported regions found to have positive correlations between activity and cigarette craving are the lateral prefrontal cortex (PFC) (Brody *et al.* 2002; McClernon *et al.* 2005) and ACC (McClernon *et al.* 2005; Zubieta *et al.* 2005). Recently, researchers have begun to use cues and functional brain imaging to examine situations that mimic more complex real life smoking situations (e.g., Wilson *et al.* 2005).

In addition to functional imaging studies of cue-induced craving, studies of cognitive reappraisal and cognitive modulation of emotion provide insight into brain mechanisms of resisting the urge to smoke, since these functions may be elicited during exposure to cues with craving resistance. Prior research has demonstrated both activation of the dorsal ACC (Kalisch *et al.* 2006; Ochsner *et al.* 2004; Phillips *et al.* 2003; Ray *et al.* 2005), PFC (Ray *et al.* 2005; Pessoa *et al.* 2002), and other brain regions associated with emotion (Ochsner *et al.* 2004; Pessoa *et al.* 2002; Ray *et al.* 2005) and deactivation of the visual system (Pessoa *et al.* 2002) during active reappraisal and modulation of emotional responses to cues. Mental effort has also been linked to activation of the dorsal ACC (Paus *et al.* 1998). Based on these studies and the imaging studies cited above, we hypothesized that the dorsal ACC, PFC, and related regions would be activated and that the visual system would be deactivated when smokers resist craving during cigarette-related cue exposure.

In the present study, we used functional magnetic resonance imaging (fMRI) to examine brain function in smokers facing a situation that they commonly encounter, especially if they are trying to quit smoking, namely resisting the urge to smoke while being exposed to cigarette-related cues.

Methods and Materials

Subjects

Forty-two otherwise healthy smokers (≥15 cigarettes/day), who met DSM-IV criteria for nicotine dependence, were recruited through local newspaper and internet advertisements. Subjects

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underwent telephone and in-person screening. For the telephone screening, medical, psychiatric, and substance abuse histories were obtained without personal identifiers. In-person screening was performed by a primary study investigator (A.L.B. or R.E.O.) and included screening questions from the Structured Clinical Interview for DSM-IV (SCID) (First *et al.* 1995) and administration of the Smoker's Profile, Fagerström Test for Nicotine Dependence (FTND) (Fagerström 1978; Heatherton *et al.* 1991), Urge to Smoke (UTS) Scale (Brody *et al.* 2002; Jarvik *et al.* 2000), and Hamilton Depression (HAM-D) (Hamilton 1967) and Anxiety (HAM-A) (Hamilton 1969) rating scales. Exhaled carbon monoxide (CO) levels were measured at the time of initial screening to verify recent smoking (an exhaled CO of ≥8 ppm) using a MicroSmokerlyzer (Bedfont Scientific Ltd, Kent, United Kingdom). Smokers in this study were treatment seeking, and received standardized treatment following this fMRI protocol with practical group counseling, bupropion hydrochloride (HCl), or placebo.

Exclusion criteria included: 1) history of any Axis I psychiatric diagnosis other than nicotine dependence as determined by screening questions from the SCID, 2) medical conditions that might affect brain function, 3) current use of medications that could alter brain function, and 4) pregnancy (because of the medication trial following this fMRI study). Subjects with recreational alcohol (≤1 drink per day), drug (<1 use per week), or caffeine (≤2 cups of coffee per day or the equivalent) use not meeting criteria for abuse/dependence were allowed to participate but were instructed to abstain for 24 hours prior to scanning (72 hours for marijuana, verified by urine toxicology screen, if subjects reported illicit drug use within the past year).

fMRI Procedure

Within 1 week of the in-person screening, subjects underwent fMRI scanning. They were instructed to smoke their usual morning cigarette(s) prior to testing, which began at 7:00 AM. At that time, subjects were interviewed to ensure that they had smoked that morning, and smoking was verified with an exhaled CO measurement in the same manner as described above. Scanning began at 7:15 AM and the data of interest were obtained about 10 min later, so that these tobacco-dependent participants would be abstinent for 25 min and would be expected to have some craving (Schuh and Stitzer 1995) but would still be responsive to cigarette-related cues.

Functional scanning was performed with a 1.5 T Magnetom Sonata scanner (Siemens AG, Erlangen, Germany) with echo-planar imaging capability, using a gradient-echo, echo-planar acquisition sequence in which the repetition time was 2.5 sec, echo time was 45 msec, flip angle was 80°, matrix image was 128 by 64, field of view was 40 by 20 cm, and in-plane resolution was 3 mm. Sixteen slices, each 4 mm thick, with a 1-mm gap between slices were obtained every 2.5 sec for 45 sec while the subjects were exposed to each cigarette-related and neutral cue and during control (resting state with a blank screen) periods. High-resolution spin-echo echo-planar scans (128 by 256 matrix; in-plane resolution, 1.5 mm; repetition time, 4000 msec; echo time, 54 msec; four excitations), acquired in the same plane as the functional scans, were acquired with bandwidth matched to that of the functional studies. The spatial distortions of the functional and high-resolution spin-echo echo-planar imaging scans were held in common to facilitate the subsequent spatial normalization procedure.

Cue Presentation and Craving Monitoring

Videotaped cues were developed based on work by our group (Brody *et al.* 2002; Conklin and Tiffany 2001) and others. Twenty-seven video cues with different scenarios (18 cigarette and 9 neutral) were used for this study. These cues were filmed from the first person point of view and were 45 sec in length. They were intended to present generic situations and were filmed with a professional actor and actress. Cigarette cue videos presented smoking in a variety of situations (e.g., writing a letter, standing outside of a building, driving), with the first 10 to 15 sec of each video being preparation to smoke (taking out a cigarette and lighter and preparing to light the cigarette) and the remainder of the video being actual cigarette smoking (with the burn of the cigarette upon being lit and exhaled cigarette smoke being visible). Neutral cue videos were filmed in similar settings but did not include smoking or cigarette paraphernalia.

For presentation of videos, magnetic resonance imaging (MRI)-compatible goggles were fitted to the subject's head using a headphone/microphone headset (MRVision 2000 Ultra, Resonance Technology, Northridge, California). These goggles provide a 1024 × 768 digital image with a 30° field of view. The headphones provided stereo sound with noise cancellation and 30 db attenuation, while the microphone utilized active noise cancellation. Each participant was positioned on the scanner bed and his/her head fixed in place using adjustable tabs in the coil to minimize movement.

Prior to scanning, participants were shown how to provide ratings of their craving using an optically isolated universal serial bus (USB) interface, which consisted of a five-button (1 = low to 5 = high) response box (Rowland Institute at Harvard, Cambridge, Massachusetts). Subjects provided ratings of their craving immediately following each cue presentation. Cabling for the response box and videos was passed though a radio frequency (RF) and magnetically shielded panel (MRA Inc., Washington, Pennsylvania) into a control room where Pentium notebook computers (IBM Corporation, Armonk, New York) were used to play the video cues and record button presses.

Prior to fMRI scanning, subjects were instructed to allow themselves to crave cigarettes during the cue exposure unless instructed to resist such craving. During scanning, subjects were presented with three runs of three cue videos each (three conditions). Each run consisted of two cigarette cue videos and one neutral cue video. For the pair of videotaped cigarette cues, subjects were either given no instructions and allowed themselves to crave (cigarette cue crave) or were instructed to resist craving (cigarette cue resist). The resist instruction was stated as "during the next video clip, try to resist any feelings of craving for cigarettes." The brief instruction to resist craving was intended to mimic real life situations in which a smoker sees cigarette cues and attempts to resist craving. For the neutral cue videos, subjects were given no instruction. The order of cue conditions was a randomized Latin square design, so that each condition (cigarette cue crave, cigarette cue resist, and neutral cue) appeared in a balanced serial order, with six separate orders of cue presentation. Subjects underwent a brief semi-structured interview after the fMRI scan and were asked 1) if the cigarette cues induced craving, and 2) what strategy they employed to resist craving.

fMRI/Statistical Analysis

For the MRI scans, brain extraction was performed manually using MEDx 3.3 (Sensor Systems Inc., Sterling, Virginia) by removing structures outside of the brain. These extractions were then used to form an "average brain" template that was used later for co-registration (Woods *et al.* 1999).

Functional magnetic resonance imaging analysis was performed using the functional magnetic imaging of the brain

(FMRIB) Software Library (FSL) (www.fmrib.ox.ac.uk/fsl) (Smith *et al.* 2004). Because this was a multisession (multiple repetitions of stimuli presentation during a single fMRI session) multisubject experiment, we used three levels of analysis hierarchically within the FMRI Expert Analysis Tool, version 5.1 (FEAT, University of Oxford, Oxford, United Kingdom, www.fmrib.ox.ac.uk/fsl) part of FMRIB, with the first level analyzing the data from each session (each series of cue presentations) within each subject, the second analyzing across sessions within each subject, and the third analyzing across the group of subjects.

First-level analysis used three primary explanatory variables (cigarette cue crave, cigarette cue resist, and neutral cue conditions). Magnetic resonance (MR) signal from the time spent on instructions and craving ratings was excluded from study analyses. Six contrasts were tested: cigarette cue crave minus neutral cue, neutral cue minus cigarette cue crave, cigarette cue resist minus neutral cue, neutral cue minus cigarette cue resist, cigarette cue crave minus cigarette cue resist, and cigarette cue resist minus cigarette cue crave. Prior to cluster analysis, the voxels were thresholded at $Z > 2.3$, with final cluster thresholding performed at $p = .01$. This cluster thresholding provides correction for multiple comparisons (Forman *et al.* 1995).

Second- and third-level analyses were performed using the FEAT FMRIB's Local Analysis of Mixed Effects (FLAME) tool to estimate the intersession and intersubject random-effects component of the mixed effects variance, with the third-level analysis carried out six times (once for each contrast), using the same statistical thresholds as for the first-level analysis. These statistical thresholds are similar or identical to those of other published activation studies using FSL (Gobel *et al.* 2004; Iannetti *et al.* 2005; Osterbauer *et al.* 2005; Parry *et al.* 2003; Smith *et al.* 2002).

Correlation analysis also was performed to examine the relationship between self-reported craving ratings and brain activity across the three conditions. First-level analysis was done using each session's scan as input data. Two explanatory variables were used, with the first one consisting of the rating scale data and the second consisting of mean data (showing no variability for craving scores). A double-gamma hemodynamic response function (HRF) convolution and temporal filtering were used for both explanatory variables. Two contrasts were performed (rating scale minus mean data and mean minus rating scale), with a Z threshold of 2.3 and a cluster threshold of $p = .01$. Higher-level analyses were then performed in the same manner as described above.

Results

Participants were adults (mean age 38.0 years ± SD 12.4 years; 12 female subjects, 30 male subjects), who smoked an average of 23.3 (± 8.2) cigarettes per day and had a mean 24.1 (± 24.5) pack-year smoking history. The FTND scores were moderately high (5.7 ± 1.7), and HAM-D and HAM-A scores were low (1.9 ± 2.4 and 2.3 ± 2.7, respectively). Exhaled CO levels were 21.1 ± 10.6 ppm at the time of screening and 15.2 ± 7.6 ppm at the time of scanning, consistent with the study protocol.

Subjects rated their craving as mild to moderate (2.4 ± 1.3, on the 1 to 5 scale) during the neutral condition and significantly higher during the cigarette cue crave (2.9 ± 1.4) and cigarette cue resist (3.0 ± 1.3) conditions (paired Student t tests, $p < .0001$ for both contrasts). Differences in craving severity between the cigarette cue crave and cigarette cue resist conditions were not significant (paired Student t tests, $p = .45$). In the semistructured interview following the scans, seven subjects reported that the videos did not affect their craving levels, while the remaining subjects reported mild to moderate changes in craving in response to the cigarette-related cues. In describing strategies used to resist craving, 74% of subjects reported that they tried to distract themselves with thoughts unrelated to smoking or to ignore thoughts about smoking. The remaining 26% were unable to verbalize the strategy that they used. Eight subjects spontaneously reported that the distraction strategy was similar to the one they used when trying to resist the urge to smoke in natural settings.

In comparing the cigarette cue crave with neutral cue exposure, higher MR signal was found during the cigarette cue crave condition in secondary visual processing centers on the left (cuneus, lingual gyrus, and lateral occipital gyrus), the supramarginal gyrus bilaterally (extending to the lateral occipital gyrus on the right), and left angular gyrus (Table 1 and Figure 1). There were no voxels with significantly lower MR signal for the cigarette cue crave (compared with the neutral) condition.

For the comparison of the cigarette cue resist with the neutral cue exposure, higher MR signal was found in the cigarette cue resist condition in the posterior cingulate cortex (PCC) extending to the precuneus and retrosplenial area bilaterally, medial aspect of the superior frontal gyrus and dorsal anterior cingulate cortex (ACC) spanning the midline, left angular gyrus, and supramarginal gyri bilaterally (Table 2 and Figure 2). Lower MR signal was found in the cigarette cue resist condition in the cuneus and postcentral gyri bilaterally and right precentral gyrus.

In directly contrasting the cigarette cue resist with the cigarette cue crave condition, higher MR signal was found in the cigarette cue resist condition in the left ACC, medial superior frontal gyrus, precuneus, and PCC (Table 3 and Figure 3). Lower MR signal for the cigarette cue resist condition was found in the cuneus and lateral occipital gyri bilaterally, left middle temporal gyrus, and right postcentral gyrus. Analysis of the subgroup of subjects that used distraction as a strategy to resist cue-induced craving revealed almost identical areas of activation and deactivation to the overall group, except that the size of the lower MR signal in the cuneus was considerably larger (5031 voxels).

Examination of associations between Urge to Smoke Scale ratings and MR signal revealed positive correlations for the medial aspect of the superior frontal gyrus, supramarginal gyrus, precuneus, inferior frontal gyrus/anterior insula, and corpus callosum bilaterally, along with the left precentral gyrus, putamen, and middle frontal gyrus and right lingual gyrus extending to the fusiform gyrus. Negative correlations were found for the cuneus bilaterally; left occipital gyrus, anterior temporal lobe, postcentral gyrus, and insula; and right angular gyrus (Table 4 and Figure 4).

Discussion

Treatment-seeking cigarette smokers have heightened craving when exposed to cigarette-related cues in a laboratory setting, regardless of whether or not they attempt to resist the urge to smoke. The extent of this heightened craving was consistent with prior functional brain imaging research demonstrating cigarette cue-induced craving (Brody *et al.* 2002; McBride *et al.* 2006; Wilson *et al.* 2005). However, patterns of regional brain activation (and deactivation) were clearly different depending on whether or not subjects attempted to resist craving.

Consistent with prior research (Lee *et al.* 2005; Smolka *et al.* 2006; Wilson *et al.* 2005), exposure to visual cigarette cues when

Table 1. Cigarette Cue Crave Versus Neutral Cues

Regions		Number of Voxels in Cluster	x, y, z Talairach Coordinates	Cluster *Z* Score	*p*
Cigarette > Neutral					
Retrosplenial Area	L	537	−12, −60, 4	4.53	2.26e-08
Cuneus	L		−14, −70, 12	4.29	
			−4, −70, 6	4.08	
Precuneus	L		−14, −74, 26	3.89	
			−10, −86, 34	3.36	
Lingual Gyrus	L		−6, −72, −16	3.57	
Supramarginal Gyrus	R	183	54, −62, 20	4.29	.002
			54, −66, 20	3.99	
Lateral Occipital Gyrus	R		36, −82, −10	4.16	
			28, −82, −10	3.62	
			44, −84, 12	3.30	
Supramarginal Gyrus	L	171	−50, −48, 20	4.39	.003
			−46, −62, 28	3.57	
			−54, −52, 28	3.38	
Angular Gyrus	L		−46, −74, 12	4.10	
			−40, −70, 14	3.65	
			−52, −70, 14	2.97	
Cigarette < Neutral					
No Activations					

L, left; R, right.

subjects allowed themselves to crave (compared with the neutral cue condition) activated primary (left lateral occipital gyrus) and secondary (left cuneus, precuneus, and lingual and angular gyri, and bilateral supramarginal gyri) visual processing centers that also are activated during heightened visual attention (Makino *et al.* 2004; Roland and Gulyas 1995; Servos *et al.* 2002) and recognition of familiar objects (Sugiura *et al.* 2005) and memories (Yonelinas *et al.* 2005). The retrosplenial cortex also showed activation in this analysis, possibly related to its role in memory formation (Ranganath *et al.* 2005), including recall of autobiographical (Steinvorth *et al.* 2006) and emotionally salient events (Maddock 1999). While these results do overlap with regions found to activate in previous studies, we did not find activation in the prefrontal cortex or ACC, as has been reported previously when comparing cigarette-related with neutral cue states, possibly because subjects in this study may have experienced greater arousal when asked to resist craving with corresponding lower levels of arousal when not asked to resist.

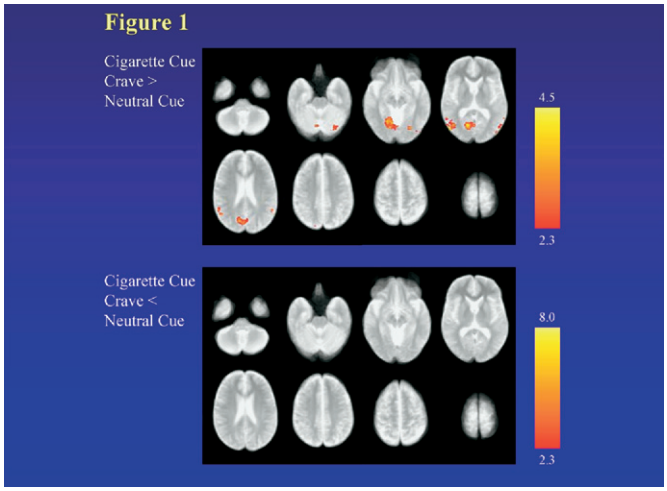

Figure 1. Functional MRI findings when cigarette smokers (n = 42) were exposed to cigarette-related cues and allowed themselves to crave (cigarette cue crave condition) compared with the neutral cue condition. The top panel shows higher MR signal for the cigarette cue crave condition in the left cuneus, lingual gyrus, and lateral occipital gyrus, the supramarginal gyrus bilaterally, and the left angular gyrus. The bottom panel shows no voxels with significantly lower MR signal for the cigarette cue crave condition. Scaling for *Z* scores is presented on the right. MRI, magnetic resonance imaging; MR, magnetic resonance.

For the cigarette cue resist compared with the neutral cue condition, activation was also found in secondary visual processing centers (bilateral precuneus, left angular gyrus, and bilateral supramarginal gyri) and retrosplenial cortex (bilaterally), but these clusters were larger than those found in the preceding analysis. This analysis also revealed activation of the dorsal ACC, a region associated with response conflict (Liu *et al.* 2004), decision making (Paulus *et al.* 2005; Rushworth *et al.* 2004; Turk *et al.* 2004), regulation of anxiety-related behavior (Kalin *et al.* 2005), and planning (Lazeron *et al.* 2000), and the PCC, a region associated with responses to anxiety-provoking video (Fredrikson *et al.* 1997) and recognition of words in an emotionally negative context (Maratos *et al.* 2001). Deactivations were found with resisting craving in the sensorimotor cortices (bilateral postcentral and right precentral gyri) and cuneus bilaterally.

For the central analysis of this study comparing responses to the cigarette cues with versus without resisting cigarette craving, greater MR signal was found with resisting craving in regions involved in decision making/planning (left dorsal and perigenual ACC) and attentional motivation (left PCC), along with a secondary visual processing center (left precuneus). Lower MR signal was found in a visual processing center (left cuneus) and in motor cortex (right postcentral gyrus). The dorsal ACC activation and visual cortical deactivation found here are consistent with examinations of brain function during cognitive reappraisal and cognitive modulation of emotion (Kalisch *et al.* 2006; Ochsner *et al.* 2004; Pessoa *et al.* 2002; Ray *et al.* 2005). Engagement of the ACC, which is implicated in conflict avoidance and attentional control (Barch *et al.* 2001; Braver *et al.* 2001; Liu *et al.* 2004), may

Table 2. Cigarette Cue Resist Versus Neutral Cues

Regions		Number of Voxels in Cluster	x, y, z Talairach Coordinates	Cluster *Z* Score	*p*
Cigarette Resist > Neutral					
Posterior Cingulate Cortex	L	1780	−6, −56, 34	5.43	1.07e-22
			−18, −68, 20	4.86	
Precuneus	B		16, −70, 20	5.26	
			−8, −70, 28	4.83	
Retrosplenial Area	B		−14, −58, 6	4.99	
			10, −56, 6	4.64	
Superior Frontal Gyrus	B	395	0, 28, 26	3.85	1.79e-07
			−6, 50, 34	3.76	
			0, 44, 8	3.73	
			−2, 34, 28	3.68	
			−4, 36, 28	3.65	
Dorsal Anterior Cingulate Cortex	L		−4, 10, 34	3.64	
Angular Gyrus	L	348	−46, −76, 26	4.89	7.75e-07
			−48, −64, 26	4.09	
			−36, −78, 26	3.98	
			−38, −86, 26	3.74	
Supramarginal Gyrus	L		−56, −52, 28	4.35	
			−52, −62, 26	4.00	
Supramarginal Gyrus	R	274	42, −62, 26	3.71	1.23e-05
			48, −72, 26	3.50	
			54, −62, 20	3.49	
			48, −64, 28	3.41	
			42, −78, 28	3.28	
			50, −58, 34	3.26	
Cigarette Resist < Neutral					
Postcentral Gyrus	R	705	36, −48, 50	5.07	1.14e-11
			46, −32, 42	5.07	
			50, −32, 42	5.05	
			32, −54, 56	4.25	
			40, −42, 48	4.14	
			44, −36, 20	3.81	
Cuneus	B	676	10, −94, 12	4.95	2.58e-11
			−12, −º92, 12	4.87	
			6, −96, 20	4.60	
			0, −86, 6	4.46	
			−2, −90, 12	4.26	
			−18, −90, 28	3.62	
Postcentral Gyrus	L	642	−36, −48, 50	5.03	6.87e-11
			−38, −38, 42	4.96	
			−24, −58, 56	4.55	
			−52, −30, 34	4.47	
			−26, −54, 50	4.17	
			−52, −26, 28	4.04	
Precentral Gyrus	R	126	22, −20, 56	3.90	.007
			18, −22, 64	3.65	
			36, −18, 56	2.54	

B, bilateral; L, left; R, right.

reflect the active direction of attention away from the hypersalient smoking stimuli as an effortful process that is contrary to automatic patterns of attention. Taken together, these findings suggest that actively suppressing the urge to smoke involves a redistribution of resources from sensory and motor areas to limbic (and related) brain areas.

While results here are in agreement with prior work, two aspects of the central study comparison were surprising, namely that subjects reported slightly (and nonsignificantly) more craving and that brain activation (particularly in the ACC and PCC) was greater when subjects were actively trying to resist the urge to smoke than when they allowed themselves to crave. These findings may be partly accounted for by the "white bear" effect, where subjects paradoxically think more strongly about a topic that they are instructed to suppress (Enticott and Gold 2002; Wegner *et al.* 1987). While control instructions, such as asking subjects to actively try to crave during the cigarette cue crave presentation or to resist craving during the neutral cue presentation, would control for the intention aspects of the results, the present study sought to simulate real-life situations. And indeed, subjects did report that study conditions mimicked naturally occurring situations.

Craving levels positively correlated with MR signal in the same decision-making (dorsal ACC), attentional-processing (PCC),

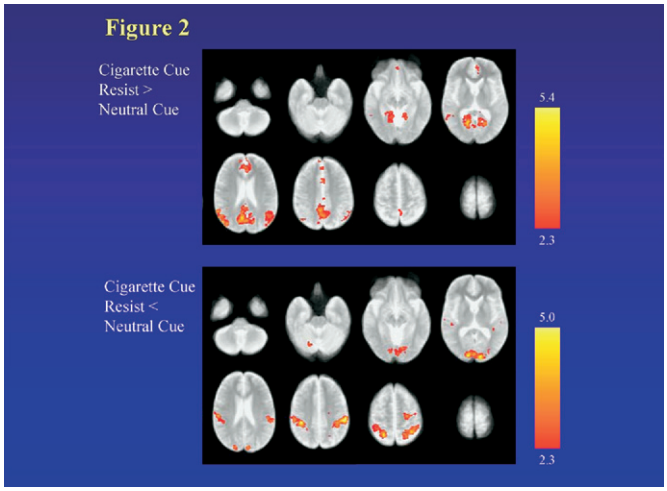

Figure 2. Functional MRI findings when smokers were exposed to cigarette-related cues and resisted craving (cigarette cue resist condition) compared with the neutral cue condition. The top panel shows higher MR signal for the cigarette cue resist condition in the posterior cingulate cortex extending to the precuneus and retrosplenial area bilaterally, the medial aspect of the superior frontal gyrus and anterior cingulate cortex spanning the midline, the left angular gyrus, and the supramarginal gyrus bilaterally. The bottom panel shows lower MR signal for the cigarette cue resist condition in the cuneus and postcentral gyri bilaterally and the right precentral gyrus. MRI, magnetic resonance imaging; MR, magnetic resonance.

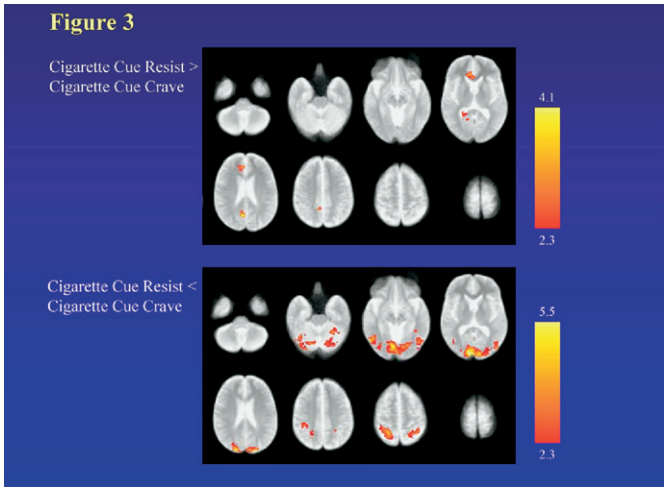

Figure 3. Functional MRI findings when smokers were exposed to cigarette-related cues and resisted craving (cigarette cue resist condition) compared with cigarette-related cues and allowing craving (cigarette cue crave condition). The top panel shows higher MR signal for the cigarette cue resist condition in the left anterior cingulate cortex, precuneus, and posterior cingulate cortex. The bottom panel shows lower MR signal for the cigarette cue resist condition in the cuneus and lateral occipital gyri bilaterally, left middle temporal gyrus, and right postcentral gyrus. MRI, magnetic resonance imaging; MR, magnetic resonance.

sensorimotor (left precentral gyrus), and secondary visual processing (precuneus, right lingual and fusiform gyri, and bilateral supramarginal gyri) regions as in the preceding analyses, as well as regions that mediate (Goldin *et al.* 2005; Kimbrell *et al.* 1999; Kuchinke *et al.* 2005) and interpret (Drexler *et al.* 2000; Kesler-West *et al.* 2001; Menon *et al.* 2000) emotional stimuli (anterior insula and inferior frontal gyri bilaterally) and a region associated with sustained attention and episodic memory (left middle frontal gyrus) (Cabeza and Nyberg 2000). Negative correlations were found in visual and auditory processing centers, as well as left motor cortex.

Table 3. Cigarette Cue Resist Versus Cigarette Cue Crave

Regions		Number of Voxels in Cluster	x, y, z Talairach Coordinates	Cluster *Z* Score	*p*
Cigarette Cue Resist > Cigarette Cue					
Posterior Cingulate Cortex	L	233	−6, −66, 28	4.15	3.86e-05
			−16, −58, 20	3.84	
			−6, −48, 34	3.75	
Precuneus	L		−6, −62, 34	3.78	
			−10, −52, 42	3.50	
			−18, −68, 20	3.16	
Superior Frontal Gyrus (Medial)	L	119	−6, 34, 28	3.56	.008
			−10, 34, 28	3.49	
Perigenual Anterior Cingulate Cortex	L		−8, 30, 12	3.53	
			−4, 20, 12	3.38	
Anterior Cingulate Cortex (Dorsal)	L		−16, 24, 20	3.16	
Cigarette Cue Resist < Cigarette Cue					
Cuneus	L	3134	−10, −96, 12	5.50	5.93e-35
			−4, −82, 6	5.25	
			−8, −80, 6	5.19	
			−4, −96, 12	5.11	
Middle Temporal Gyrus	L		−50, −68, 0	5.16	
Lateral Occipital Gyrus	L		−42, −76, −8	4.86	
Postcentral Gyrus	R	164	22, −52, 50	4.36	.0008
			32, −54, 56	3.94	
			38, −52, 56	3.92	
			36, −48, 56	3.49	
			26, −52, 64	3.16	
			22, −65, 48	3.16	

L, left; R, right.

Table 4. Correlations Between Cigarette Craving and MR Signal Across All Study Conditions

Regions		Number of Voxels in Cluster	x, y, z Talairach Coordinates	Cluster *Z* Score	*p*
Positive Correlations					
Anterior Cingulate Cortex/Superior Frontal Gyrus	B	778	−4, 12, 42	4.79	1.72e-10
			−2, 4, 50	4.77	
			−4, 30, 28	4.39	
			−10, 26, 28	4.21	
			0, 28, 28	4.10	
			0, 30, 28	3.97	
Supramarginal Gyrus	L	640	−48, −58, 42	5.09	4.5e-09
			−42, −54, 42	4.90	
			−42, −58, 50	4.79	
			−36, −74, 42	4.74	
			−52, −52, 42	4.39	
Precentral Gyrus	L		−44, −28, 56	4.56	
Precuneus	B	619	2, −74, 42	5.27	7.54e-09
			−8, −74, 42	4.90	
			−10, −70, 34	4.71	
			−14, −66, 28	3.98	
			−12, −62, 34	3.26	
Inferior Frontal Gyrus/Anterior Insula	L	581	−46, 14, 6	4.74	1.95e-08
			−30, 20, 6	4.63	
			−38, 10, 6	4.45	
			−48, 12, 6	4.39	
			−34, 6, 12	4.34	
Putamen			−22, 4, 6	4.03	
Middle Frontal Gyrus	L	562	−46, 20, 34	4.69	5.96e-08
			−40, 20, 42	4.43	
			−42, 40, 20	4.02	
			−42, 14, 50	3.97	
			−36, 48, 12	3.95	
			−3, 32, 42	3.75	
Inferior Frontal Gyrus/Anterior Insula	R	522	42, 10, 6	4.71	5.96e-08
			38, 10, 6	4.30	
			32, 10, 4	4.15	
			48, 10, 6	3.96	
			32, 16, 12	3.85	
			28, 16, 12	3.66	
Corpus Callosum	B	351	2, −26, 28	5.05	1.04e-05
			−2, −36, 28	4.86	
Posterior Cingulate Cortex	B		−2, −32, 34	4.83	
			−5, −32, 34	4.80	
			0, −32, 28	4.79	
Supramarginal Gyrus	R	247	34, −58, 42	4.24	.0003
			32, −62, 42	4.23	
			42, −56, 50	4.20	
			46, −56, 42	3.98	
			46, −60, 42	3.91	
			54, −52, 34	3.56	
Lingual Gyrus	R	215	12, −54, −16	3.89	.0008
			10, −46, −8	3.17	
Fusiform Gyrus	R		30, −62, −22	3.65	
			28, −52, −22	3.58	
			30, −56, −22	3.48	
			16, −48, −16	3.41	
Negative Correlation					
Occipital Gyrus	L	1869	−42, −70, −2	4.92	2.95e-20
Cuneus	B		−10, −96, 20	4.79	
			8, −100, 12	4.41	
			−16, −98, 18	4.34	
Angular Gyrus	R		46, −70, 6	4.54	
			48, −64, 6	4.34	
Anterior Temporal Lobe (Heschl's Gyrus)	L	167	−50, −18, 6	4.01	.004
Postcentral Gyrus	L		−58, −22, 12	3.84	
			−58, −32, 12	3.25	

MR, magnetic resonance; B, bilateral; L, left; R, right.

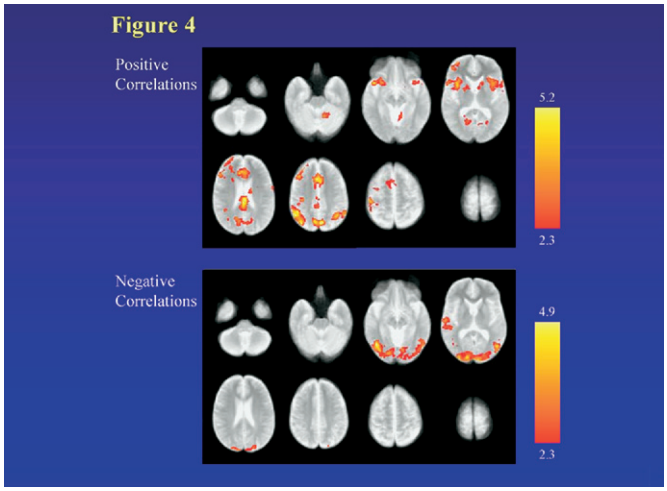

Figure 4. Positive and negative correlations between Urge to Smoke Scale score (craving) and MR signal across all three study conditions. The top panel shows regions with positive correlations, including the anterior cingulate cortex and medial aspect of the superior frontal gyrus, supramarginal gyrus, precuneus, and inferior frontal gyrus/anterior insula bilaterally, along with the left precentral gyrus, putamen, and middle frontal gyrus and right lingual gyrus extending to the fusiform gyrus. Negative correlations were found for the cuneus bilaterally; left occipital gyrus, anterior temporal lobe, postcentral gyrus, and insula; and right angular gyrus. MR, magnetic resonance.

One limitation of this study was the absence of a nonsmoking control group exposed to the same cues as the smokers studied here. However, in our prior work (Brody *et al.* 2002), nonsmokers demonstrated neither cigarette craving nor changes in mood/anxiety associated with presentation of cigarette-related cues. Also, since the primary analysis here was the examination of cigarette cue exposure with and without resisting craving, the use of nonsmoking control subjects would not be expected to help in the central interpretation of this study. The main strengths of this report include a relatively large sample size for a study of this type, the control of cue presentation through specialized MR-compatible equipment, and the fact that cues (e.g., video of chore performance with or without smoking) and states (allowing oneself to crave versus resisting craving while watching similar cues) were matched closely.

In conclusion, we report significant differences in brain function when treatment-seeking smokers are exposed to cigarette-related cues and are actively resisting craving versus allowing themselves to crave. During craving resistance, activation was found in brain regions involved in decision making, regulation of anxiety-related behaviors, and heightened attention, while deactivation was found in primary visual and motor cortices. Similar activations and deactivations were found when comparing the cigarette cue resistance with the neutral cue condition. Additionally, exposure to cigarette cues without craving resistance was found to activate visual processing centers when compared with neutral cue exposure. These results identify regions that may mediate the effects of existing tobacco dependence treatments and that may be targets for medication development. For example, enhanced catecholaminergic (Passerin *et al.* 2000; Schweimer *et al.* 2005), acetylcholinergic (Choi *et al.* 2006; Gozzi *et al.* 2006; Jacobsen *et al.* 2004), and cannabinoid (Mathew *et al.* 1997, 1999; O'Leary *et al.* 2002) neurotransmission activate the ACC, including activation during effortful decision making (Schweimer *et al.* 2005), while enhanced gamma-aminobutyric acid (GABA) (Mintzer *et al.* 2001; Passerin *et al.* 2000) neurotransmission diminishes ACC activation. Currently available medications for tobacco dependence, such as the catecholamine reuptake blocker bupropion HCl (Ascher *et al.* 1995; Horst and Preskorn 1998) and nicotine replacement (acetylcholine agonist) therapy, may exert their therapeutic effects at least partly through enhancement of ACC activation with concomitant improvement in the ability to resist craving, while medications that alter cannabinoid and GABAergic neurotransmission are currently under investigation as potential treatments for tobacco dependence. Thus, the present study may help elucidate the brain mediation of existing tobacco dependence treatments and suggests potential neurotransmitter system targets for medication development.

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