ORIGINAL ARTICLE

Brain Metabolic Changes During Cigarette Craving

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Background: In functional brain imaging studies, exposure to cues related to cocaine, opiates, and alcohol in dependent individuals is associated with activation of the anterior cingulate gyrus, amygdala, orbitofrontal cortex, and dorsolateral prefrontal cortex. Craving for these substances positively correlates with activity in the orbitofrontal cortex, dorsolateral prefrontal cortex, and anterior insula. The objective of this study was to determine changes in regional cerebral glucose metabolism and correlations between craving and regional metabolism in heavy cigarette smokers exposed to cigarette-related cues.

Methods: Twenty heavy smokers (who smoked ≥20 cigarettes per day) and 20 nonsmoking control subjects underwent 2 fluorine 18–fluorodeoxyglucose positron emission tomography scans 10 days apart in randomized order: one while watching a videotape that presented cigarette-related cues and handling a cigarette, and the other while watching an educational (nature) videotape and handling a neutral object (pen).

Results: From the neutral to the cigarette cue scan, heavy smokers had greater increases than nonsmoking controls in relative glucose metabolism in the perigenual anterior cingulate gyrus spanning the midline. Significant positive correlations were found between intensity of craving and metabolism in the orbitofrontal cortex, dorsolateral prefrontal cortex, and anterior insula bilaterally. An unexpected positive association was found between craving and metabolism in the right sensorimotor cortex.

Conclusions: Brain regions associated with arousal, compulsive repetitive behaviors, sensory integration, and episodic memory are activated during exposure to cigarette-related cues and cigarette craving. These regional brain activations and associations with craving are similar to findings with other addictive substances.

Arch Gen Psychiatry. 2002;59:1162-1172

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DESPITE NEW medication options for nicotine dependence, abstinence rates after 6 months or more of treatment remain relatively low at 14% to 35.5%.[1-5] A possible route to the development of more effective treatments is through a better understanding of the neurobiological substrates of cigarette craving, because the severity of craving has repeatedly been linked with relapse in smokers attempting to quit.[6-9]

In heavy smokers, craving for cigarettes begins within minutes after smoking a cigarette and increases steadily, reaching peak levels at around 3 to 6 hours of abstinence.[10,11] In addition to abstinence-associated craving, an increased urge to smoke can be induced reliably in the laboratory by exposure to conditioned cues related to smoking behavior. These include videotapes,[12] audiotapes,[13] mental imagery,[14,15] visual imagery,[16] and exposure to cigarettes or cigarette-related items.[17,18] A meta-analysis[19] of the effectiveness of eliciting cigarette craving with cigarette-related vs neutral cues reveals clear reactivity to cigarette cues in heavy smokers.

To our knowledge, there are no published reports of functional brain imaging studies examining cigarette craving. However, 2 types of analyses have been performed to examine brain mediation of craving for addictive substances other than cigarettes (primarily cocaine, but also opiates and alcohol). First, brain activity has been studied when subjects are exposed to substance-related cues compared with neutral cues. In these studies, replicated findings include activation of the anterior cingulate gyrus (AC),[20-26] amygdala/temporal pole,[20,25,27,28] orbitofrontal cortex (OFC),[20,27-30] and lateral prefrontal cortex (primarily the dorsolateral prefrontal cortex [DLPFC]).[21,22,28,30,31] No regional deactivations have been consistently found. Second, craving has been

examined more directly by determining relationships between subjective self-ratings of craving and regional brain function. In these studies, replicated findings include positive correlations between craving and activity in the OFC,[24,26,28,32,33] DLPFC,[21,28,30,32] and anterior insula.[29,33] No negative correlations have been consistently found.

The aims of the present study were to determine changes in regional brain metabolism when nicotine-dependent subjects were exposed to cigarette-related (compared with neutral) cues and to determine regional cerebral metabolic correlates of cigarette craving. For this study, the term craving was defined using synonyms such as urge, want, or desire to smoke, along with anticipation of the pleasant effects of smoking at the time that rating scales were administered. This definition was chosen because it has been strongly linked with actual tobacco use[34] and has been used in other research into neurobiological aspects of cigarette craving,[11,35-37] while acknowledging the complexity of the meaning of drug craving.[38-41] We hypothesized that exposure to cigarette-related (compared with neutral) cues in heavy smokers would result in increased craving, along with the same regional brain activations and associations between craving and regional brain activity as those seen with other addictive substances.

METHODS

GENERAL

Forty subjects (20 heavy smokers and 20 nonsmoking control subjects) underwent 2 fluorine 18–fluorodeoxyglucose (FDG) positron emission tomography (PET) scans: one while watching a videotape containing cigarette-related cues and handling a cigarette in their dominant hand, and the other while watching an educational (nature) videotape and handling a neutral object (pen) in their dominant hand. Magnetic resonance imaging (MRI) scans of the brain were also obtained to enhance accurate localization of structures on FDG PET scans. The study was described to subjects before scanning, and written informed consent was obtained using a form approved by the Greater Los Angeles Veterans Affairs Healthcare System Institutional Review Board.

SUBJECTS

Twenty heavy smokers (who smoked ≥20 cigarettes per day) and 20 nonsmoking controls, aged 21 to 65 years, were recruited through advertisements in local newspapers. Subjects were screened initially during a telephone interview in which medical, psychiatric, and substance abuse histories were obtained. Heavy smokers met the *DSM-IV* criteria for nicotine dependence, while nonsmoking control subjects had done nothing more than experiment with cigarettes (smoking <5 cigarettes during their lifetime). To examine groups that would differ most from each other in response to cigarette-related cues, light smokers (who smoked <20 cigarettes per day) and former regular smokers were excluded from the study.

Other exclusion criteria were any history of or current Axis I psychiatric diagnosis, including mood, anxiety, or psychotic disorders or history of substance abuse or dependence other than nicotine dependence (as assessed with screening questions from the Structured Clinical Interview for *DSM-IV*).[42] Subjects were also excluded if they were taking medication or had any history of or current medical condition that might affect the central nervous system at the time of scanning (eg, current treatment with a β-blocker or an analgesic medication or a history of head trauma or epilepsy). Pregnancy was an exclusion criterion because of the potential risk of radiation exposure to a fetus. Subjects with recreational alcohol, other drug, or caffeine use not meeting the criteria for dependence were allowed to participate in the study, but were instructed to abstain from these substances for 24 hours before scanning (for 72 hours for marijuana; verified by a urine toxicology screen, if indicated). Caffeine intake near the time of scanning was prohibited based on a report[43] linking caffeine with protection from anxiety and psychophysiological changes related to cigarette cues in ex-smokers. Subjects with more than the equivalent of 2 cups of coffee per day (200-300 mg/d of caffeine) were excluded, as were subjects who experienced caffeine withdrawal (irritability, flushing, or headache). Two additional subjects started but were withdrawn from the study because it was determined that their substance use was greater than they had initially described (one with alcohol and one with marijuana use). Subjects were compensated $20 per hour for study participation.

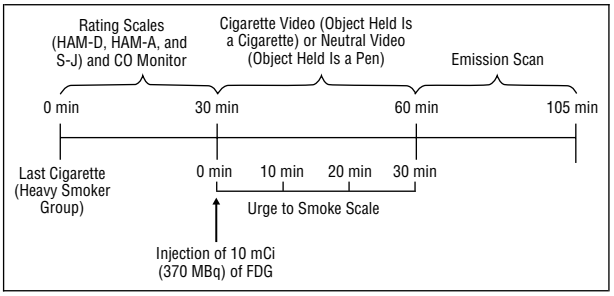

Figure 1. Positron emission tomography session timeline (see the "Rating Scales, Craving Induction, and PET Image Acquisition" subsection of the "Methods" section for details). HAM-D indicates Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale; S-J, Shiffman-Jarvik Scale; CO, carbon monoxide; and FDG, fluorine 18–fluorodeoxyglucose.

RATING SCALES, CRAVING INDUCTION, AND PET IMAGE ACQUISITION

Heavy smokers and controls underwent 2 PET scanning sessions, roughly 10 days apart, in randomized order—one when presented with cigarette-related cues, and the other when presented with neutral cues (**Figure 1**). The PET sessions commenced between 1 and 4 PM. Heavy smokers were instructed to smoke as per their usual habit until the time of each scan and smoked a cigarette immediately before each PET session. The Hamilton Depression Rating Scale[44] and the Hamilton Anxiety Rating Scale[45] (HAM-D and HAM-A, respectively) were then administered to all subjects, along with the Shiffman-Jarvik Scale,[46] to measure cigarette withdrawal symptoms. Immediately before injection of FDG, exhaled carbon monoxide (CO) levels were measured (EC-50 Micro Smokerlyzer II; Bedfont Scientific Ltd, Kent, England) to approximately quantify recent cigarette use. This rating scale period (including CO monitoring) lasted 30 minutes so that cue exposure began when heavy smokers would be expected to have mild craving that could be either stimulated by cigarette-related cues or unaffected by neutral cues, and that would not be confounded by the effects of nicotine intake immediately preceding scanning.

Subjects then received an injection of 10 mCi (370 MBq) of FDG during a 30-second period into the right antecubital vein, while seated 100 cm in front of a videotape monitor in a room adjacent to the PET camera. During the subsequent 30-minute uptake period of FDG, subjects watched either the cigarette cue videotape and held one of their own cigarettes in their

dominant hand or the neutral (nature) videotape and held a neutral object (pen) in their dominant hand. The videotapes used for this study consisted primarily of material that elicited differing intensities of cigarette craving in heavy smokers in earlier work.[12] The cigarette cue videotape depicts a man and a woman smoking in various situations (during breakfast, while waiting for a bus, and sitting at a desk) on a day when the man is going on a job interview. The neutral videotape presented educational material about birds. Because these videotapes did not last for the full 30-minute uptake period, additional videotaped material from our laboratory was added to the original videotapes. For the cigarette cue videotape, the remaining videotape depicted writing a letter while smoking a cigarette, with the camera positioned to provide the first-person point of view. In this portion of the videotape, a cigarette is lit on camera and a lighter and ashtray are seen. For the neutral videotape, additional educational material about nature was shown.

During this uptake period, the Urge to Smoke (UTS) Scale[11] was administered every 10 minutes, taking approximately 1 minute to complete each time. This scale consists of 10 items with analog ratings (from 0 [definitely not] to 6 [definitely]). Items on this scale included a desire to smoke freely, an urge and a craving for a cigarette, a desire to smoke as soon as possible, the degree to which a cigarette would be pleasant, and the extent to which the subject misses a cigarette. On this scale, increased urges are associated with higher values on all items, in accordance with a recent study[47] demonstrating the advantage of this design.

After the 30-minute uptake period, emission scanning was performed. A 1-minute transmission scan was obtained for positioning using a germanium Ge 68 external source, followed by a 40-minute emission scan. The PET images were acquired with a scanner (ECAT 953; CTI-Siemens, Knoxville, Tenn), with 31 slices in the 2-dimensional mode. The average transaxial resolution was 5 to 6 mm full width at half maximum; plane spacing, 3.12 mm; and axial field of view, 10.8 cm. Reconstruction was performed using filtered back projection with an automatically computed attenuation correction.

After completion of both PET sessions, subjects were interviewed informally to assess reactions and interest level for each cue presentation session.

MRI SCANNING AND PET-TO-MRI REALIGNMENT

An MRI scan of the brain was obtained for each subject during the 10-day period between the 2 PET scans. This MRI scan had the following specifications: 3-dimensional Fourier analysis spoiled-gradient–recalled acquisition (repetition time, 30 milleseconds; echo time, 7 milleseconds; 30° angle; 2 acquisitions; and 256×192 view matrix). The acquired volume was reconstructed as roughly 90 contiguous 1.5-mm-thick transaxial slices.

The PET and MRI scans were coregistered for precise localization of hand-drawn regions of interest (ROIs). The MRI and PET scans were retrieved onto a workstation (SUN Ultra 1 Workstation; SUN Microsystems, Mountain View, Calif). The PET-to-MRI coregistration was performed using a UNIX-based medical image visualization and analysis program (MEDx 3.3; Sensor Systems Inc, Sterling, Va), and the Automated Image Registration method was used for PET-to-MRI coregistration.[48]

Six ROIs were drawn bilaterally on MRI scans and transferred onto coregistered PET scans (**Figure 2**). Five subjects (2 smokers and 3 controls) did not have usable MRI scans, and so ROIs were drawn on their PET images. Based on a priori hypotheses derived from the literature review, these ROIs were the dorsal and ventral AC, the amygdala, the OFC, the DLPFC, and the anterior insula. The dorsal and ventral halves of the AC were drawn in approximately 11 planes each, while the entire amygdala was drawn in roughly 9 planes. The OFC was drawn in about 14 planes, consisting of the medial and lateral orbital gyri and excluding the gyrus rectus. The DLPFC consisted of the dorsal portion of the middle frontal gyrus and was drawn in approximately 11 planes. The anterior insular region was drawn as the anterior half of the insular cortex in about 17 planes. Whole brain was also drawn so that ratios of ROI–global metabolism could be calculated for statistical analysis.

STATISTICAL ANALYSES

Mean (±SD) scores for all clinical rating scales were determined for the neutral and cigarette cue scans within the heavy smoker and nonsmoking control groups. To examine group differences in clinical data scores and change from the neutral to the cigarette cue scans, repeated-measures analyses of variance were performed for the 5 clinical measures obtained (exhaled CO level, UTS Scale score, HAM-D score, HAM-A score, and Shiffman-Jarvik Scale score), with the clinical measure as the repeated measure and group (heavy smoker vs nonsmoking control) as the between-subject factor.

To examine regional brain metabolic differences between the neutral and cigarette cue scans and correlations between subjective craving and regional brain metabolism, separate statistical analyses were performed using the computer software program Statistical Parametric Mapping, version 99 (SPM; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, England) and drawn ROI values. Results from both methods were used and compared, given the limitations of each.[49-52] Thus, 4 analyses were performed—SPM and ROI for differences between neutral and cigarette cue scan sessions and SPM and ROI for correlations between change in subjective craving and change in normalized metabolism from the neutral to the cigarette cue scan sessions.

For the SPM analysis of differences in regional brain metabolism between the neutral and cigarette cue scans, each subject's pair of images was coregistered, spatially normalized into the standardized brain atlas template within the SPM software package, and smoothed to 10 mm. To determine regions that had significantly different metabolic differences between conditions (neutral vs smoking cues) in our 2 groups (heavy smokers vs healthy controls), we mapped the Z statistic for the group-by-condition interaction. Analyses were also performed to identify the within-group effects of condition (for the 2 study groups separately), to clarify which group had significant increases and decreases in regional metabolism that accounted for significant interactions identified in the previously described analysis. A threshold for significance of $P<.005$ ($Z>2.71$) was used for regions hypothesized to be activated with exposure to cigarette-related cues (AC, amygdala, OFC, and DLPFC) in the heavy smoker group. This threshold is similar to those in other published studies[25,28,33] using PET and SPM to examine drug craving. To scan the brain for significant effects in regions outside of our a priori regions, clusters of voxels passing a threshold of $P<.05$ are also reported, after correction for multiple comparisons performed by the SPM program. The locations of significant voxels were determined by mapping coordinates onto mean images of study PET and MRI scans, the PET template accompanying the SPM program, and a standard atlas.[53] The mapping of coordinates onto the mean PET scan of actual study subjects was reported herein if discrepancies were found between these localization methods. Results are presented using the voxel of peak significance.

For the ROI analysis of differences between the neutral and cigarette cue scans, 1-way analyses of variance were performed using change in normalized metabolic rate (ROI/global) for the a priori ROIs (dorsal and ventral AC, amygdala, OFC, and DLPFC), with hemisphere (left vs right) as a

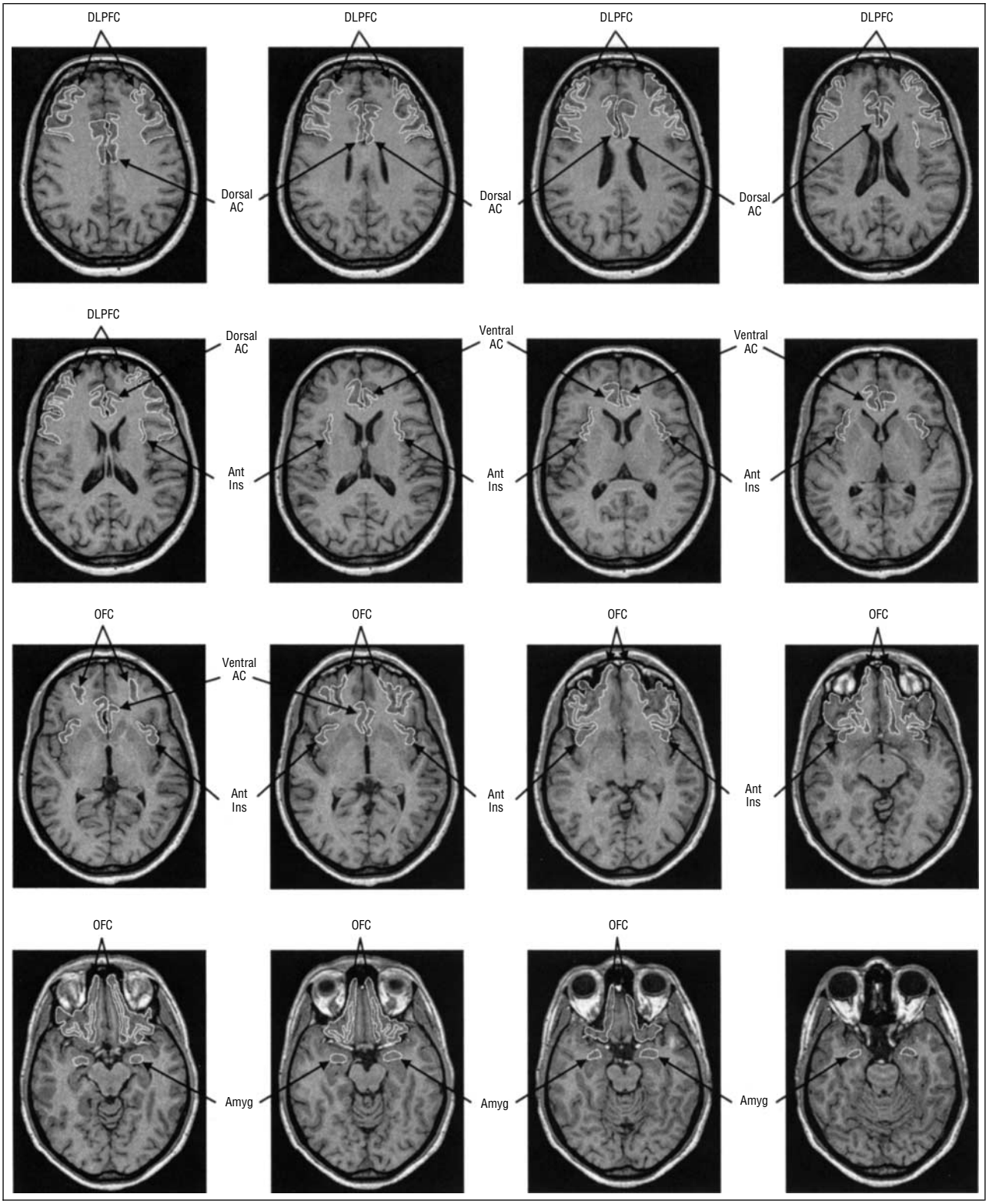

Figure 2. Regions of interest drawn on a magnetic resonance image of a study subject for transfer onto coregistered positron emission tomography scans. Images are presented from dorsal (top) to ventral (bottom). DLPFC indicates dorsolateral prefrontal cortex; AC, anterior cingulate gyrus; Ant Ins, anterior insula; OFC, orbitofrontal cortex; and Amyg, amygdala.

within-subject factor and group (heavy smoker vs nonsmoking control) as a between-subject factor. The statistical criterion for ROI tests of a priori regions was set at $P<.05$ (2-tailed), a threshold similar to other hypothesis-driven PET analyses in this line of research.[20,24,30]

Associations between change in craving (mean UTS Scale scores) and change in regional metabolism were also examined with SPM for the heavy smoker group (nonsmoking controls had no cigarette craving and, therefore, were not studied in this part of the analysis). For this analysis, SPM performed

Table 1. Clinical Variables of the Study Populations*

Variable	Heavy Smokers (n = 20)		Control Subjects (n = 20)	
	Neutral Scan	Cigarette Cue Scan	Neutral Scan	Cigarette Cue Scan
Age, y	42.5 (±10.6)	. . .	36.9 (±11.4)	. . .
Female†	6 (30)	. . .	9 (45)	. . .
Left-handed†	2 (10)	. . .	2 (10)	. . .
Scan interval, d	10.9 (±9.2)	. . .	9.0 (±3.4)	. . .
No. of cigarettes/d	32.6 (±12.4)	. . .	. . .	. . .
Time smoking, y	25.4 (±8.9)	. . .	. . .	. . .
UTS Scale score	2.9 (±1.7)‡§	4.0 (±1.7)	0	0
Exhaled CO, ppm	24.1 (±9.1)‡	23.1 (±8.9)	1.9 (±0.07)	1.9 (±0.08)
HAM-D score	2.0 (±2.6)	2.2 (±2.7)	1.1 (±1.7)	1.0 (±1.5)
HAM-A score	2.2 (±2.0)	2.6 (±2.2)	1.5 (±1.7)	1.7 (±2.3)
S-J Score (per item)	3.4 (±0.7)‡	3.7 (±1.0)	2.0 (±0.3)	2.0 (±0.4)

*Data are given as mean (±SD) unless otherwise indicated. UTS indicates Urge to Smoke; CO, carbon monoxide; HAM-D, Hamilton Depression Rating Scale (17 items); HAM-A, Hamilton Anxiety Rating Scale; S-J, Shiffman-Jarvik Scale; and ellipses, data not applicable.
†Data are given as number (percentage) of subjects.
‡Repeated-measure analysis of variance, between-group effect, $P<.001$.
§Repeated-measure analysis of variance, repeated measures–by–group interaction, $P=.009$.

an analysis of covariance for every voxel for which the conditions were neutral and cigarette-related cue scans, and the condition-dependent covariate was mean UTS Scale score for the 2 scans. This design allowed for the determination of the interaction between condition and covariate. For 20 subjects with 2 scans each, this analysis had 17 *df* ([40 – 19] – 4). When studying the interaction between condition and covariate, voxels were considered significant at $P<.005$ ($Z>2.86$), uncorrected for multiple comparisons if they fell within hypothesized ROIs (OFC, DLPFC, or anterior insula). To scan the brain for unexpected changes, clusters of voxels were also reported as significant if they passed a threshold of $P<.05$, using the SPM threshold for correction for multiple comparisons.

For the ROI analysis of relationships between craving and regional brain metabolism, Pearson product moment correlation coefficients were calculated between change in mean UTS Scale score and change in normalized ROI value from the neutral to the cigarette cue scans. These calculations were performed for the mean of the right and left OFC, DLPFC, and anterior insula ROIs ($[ROI_{left}+ROI_{right}]/2$). The means of left and right ROIs were used herein because prior literature indicated no laterality for the correlational hypotheses. The threshold for ROI calculations was set at $P<.05$ (2-tailed), without correction for multiple comparisons, given the focused hypotheses.

RESULTS

The heavy smoker and nonsmoking control groups were similar in age, male-female ratio, handedness, and interval between scans (**Table 1**). Each group had 1 occasional marijuana user. There was a significant repeated measures–by–group interaction for UTS Scale score ($F_{1,38}=7.49$, $P=.009$) (Table 1), indicating that heavy smokers had a higher mean UTS Scale score during the cigarette cue scan than the neutral cue scan (compared with the difference between scans for the nonsmoking group). Other repeated measures (exhaled CO levels and scores on the HAM-D, HAM-A, and Shiffman-Jarvik Scale) did not have significant interactions with study group (heavy smoker vs nonsmoking control), indicating that these measures remained similarly stable for the 2 scans within groups. Measures of cigarette use and withdrawal (UTS Scale score, exhaled CO level, and Shiffman-Jarvik Scale score) were significantly higher in the heavy smoker than in the nonsmoking control group ($F_{1,38}=97.9$, $P<.001$; $F_{1,38}=137.1$, $P<.001$; and $F_{1,38}=75.5$, $P<.001$, respectively). The HAM-D and HAM-A scores did not differ significantly between groups ($F_{1,38}=2.4$, $P=.13$; and $F_{1,38}=1.8$, $P=.19$, respectively) or between scans ($F_{1,38}=.43$, $P=.52$; and $F_{1,38}=.18$, $P=.68$, respectively). Of the heavy smokers, 12 (60%) identified the cigarette cue videotape as more interesting than the nature videotape, while only 4 (20%) of the nonsmokers reported that the cigarette cue videotape was more interesting.

REGIONAL METABOLIC DIFFERENCES BETWEEN NEUTRAL AND CIGARETTE CUE SCANS

The SPM program revealed an interaction between metabolic increase (from the neutral to the cigarette cue scans) and group (heavy smoker vs nonsmoking control) in the perigenual AC spanning the midline (183 voxels and roughly corresponding to Brodmann areas 24 and 32) ($P<.001$), along with a smaller activation in the left anterior temporal lobe ($P<.001$) (**Table 2** and **Figure 3**). This analysis, along with the within-group analyses, indicated that heavy smokers had greater increases in metabolism in the AC, temporal lobe, and OFC than nonsmoking controls when presented with cigarette-related (compared with neutral) cues (Table 2). No hypothesized regions had greater decreases in heavy smokers than in nonsmoking controls, and no unhypothesized regions passed correction for multiple comparisons.

In the ROI analysis, only the ventral AC showed a significant between-group difference in change from the neutral to the cigarette cue scans (analysis of variance, $F_{1,38}=5.13$, $P=.03$), with no significant effect of laterality. In the heavy smoker group, normalized ROI values were higher during the cigarette cue than the neutral cue scan in the left (1.12±0.04 vs 1.08±0.06) and right (1.12±0.05 vs 1.09±0.07) ventral AC, while nonsmoking controls had little change in the ventral AC (1.08±0.04

Table 2. Statistical Analysis of Regional Brain Metabolic Increases in Heavy Smokers Compared With Nonsmoking Control Subjects When Exposed to Cigarette-Related (Compared With Neutral) Cues*

	Heavy Smokers (n = 20)							
	Greater Increases Than Nonsmokers (n = 20)				Within-Group Increases			
		Talairach Coordinates				Talairach Coordinates		
Regions	*Z* Score†	*x*	*y*	*z*	*Z* Score†	*x*	*y*	*z*
AC								
Middle/ventral	3.74	6	40	6	4.34	2	48	–12
	3.69	4	38	10	3.47	2	54	–4
	. . .	. . .	. . .	. . .	3.41	8	42	8
	. . .	. . .	. . .	. . .	3.86	–2	46	18
Dorsal	. . .	. . .	. . .	. . .	3.80	4	10	54
OFC	. . .	. . .	. . .	. . .	2.95	–34	22	–20
Ant temp	3.74	–44	–26	0	3.22	–40	–32	2

*Results for the heavy smoker group alone are also shown, while the nonsmoker group did not have statistically significant changes in hypothesized regions. Statistical analysis was performed using a computer software program (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, England). *x* indicates left/right; *y*, anterior/posterior; *z*, superior/inferior; AC, anterior cingulate gyrus; OFC, orbitofrontal cortex; Ant temp, anterior temporal lobe; and ellipses, data not significant.

†$Z > 2.71$ was considered significant ($P < .005$).

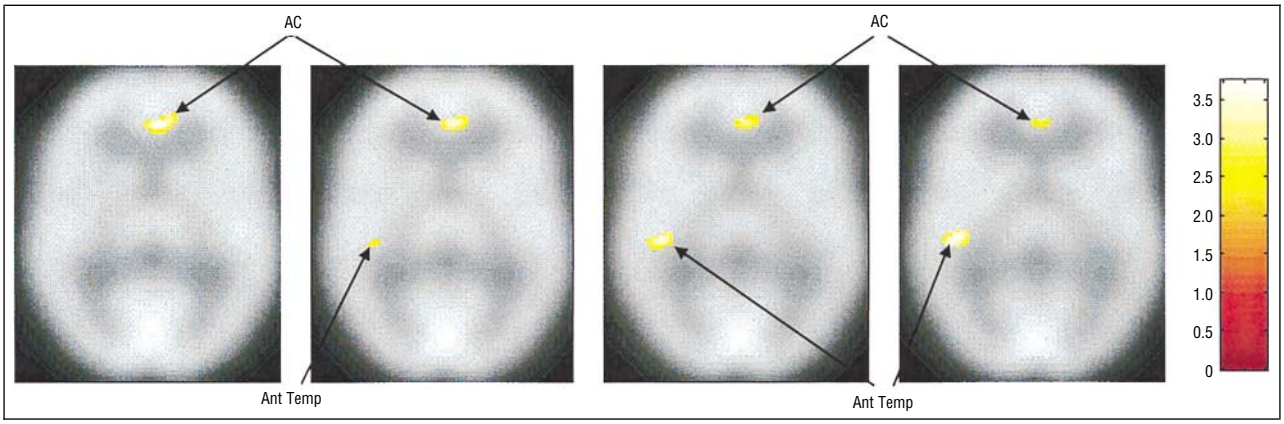

Figure 3. Regions with greater activity in heavy smokers (n=20) than in nonsmoking control subjects (n=20) when exposed to cigarette-related (compared with neutral) cues ($P < .005$, uncorrected) using the computer software program Statistical Parametric Mapping (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, England). Regions shown are the perigenual anterior cingulate gyrus (AC) and the left anterior temporal lobe (Ant Temp) placed on the mean positron emission tomography image from study subjects. Scale represents *Z* score.

vs 1.08±0.05 on the left and 1.11±0.05 vs 1.10±0.06 on the right). Other ROIs did not have significant differences in change scores between the heavy smoker and nonsmoking control groups.

CORRELATIONS BETWEEN CHANGE IN CRAVING AND CHANGE IN REGIONAL BRAIN METABOLISM

Using SPM, all 3 hypothesized regions (OFC, DLPFC, and anterior insula) had significant positive correlations bilaterally with subjective craving (**Table 3** and **Figure 4**). The OFC findings roughly corresponded to the posterior portion of Brodmann areas 11 and 47 ($P < .001$ on the right and $P = .003$ on the left), while the DLPFC findings roughly corresponded to Brodmann areas 9 and 46 ($P = .001$ on the right and $P = .002$ on the left). Anterior insula findings included regions in the anterior half of the insular cortex, but extended further anterior on the right than the left ($P = .002$ on the right and $P < .001$ on the left). A large region including the right superior sensorimotor cortex (*x*, *y*, and *z*=44, –30, and 50, respectively; $P < .001$, corrected) and extending to the right anterior parietal lobe (*x*, *y*, and *z*=44, –46, and 52, respectively; $P < .001$) was the only unhypothesized region to show a significant positive correlation between changes in subjective craving and relative metabolism. No significant negative correlations were found.

In the ROI analysis, a positive correlation was found between change in mean UTS Scale score and change in mean ROI value for the OFC (Pearson product moment $r = 0.52$, $P = .02$), while approaching significance in the DLPFC ($r = 0.39$, $P = .09$). Correlations between change in UTS Scale score and change in normalized regional metabolism in the anterior insula did not approach significance. No significant negative correlations were found.

COMMENT

Exposure to cigarette-related (compared with neutral) cues was associated with increased normalized bilateral AC metabolism in heavy smokers (in the SPM and ROI

Table 3. Statistical Analysis of Regional Brain Metabolic Changes Having Positive Associations With Subjective Mean Urge to Smoke Scale Scores in the Heavy Smoker Group*

Regions	*Z* Score†	Talairach Coordinates *x*	*y*	*z*
OFC‡				
R	3.93	26	20	−24
	3.02	16	22	−24
L	3.10	−28	36	−16
DLPFC‡				
R	3.53	38	28	34
L	3.30	−28	64	6
	3.26	−38	12	58
	3.00	−28	42	40
	2.99	−26	58	−2
Ant ins‡				
R	3.22	34	20	4
	3.13	36	6	4
L	4.09	−36	4	−2
	3.11	−28	10	−6
Sensorimotor cortex/ant parietal§				
R	5.04	44	−30	50
	4.67	62	−26	48
	4.54	44	−46	52

*Statistical analysis was performed using a computer software program (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, England). *x* indicates left/right; *y*, anterior/posterior; *z*, superior/inferior; OFC, orbitofrontal cortex; R, right, L, left; DLPFC, dorsolateral prefrontal cortex; Ant ins, anterior insula cortex; and Ant parietal, anterior parietal lobe.

†$Z > 2.86$ was considered significant ($P < .005$).

‡Hypothesized.

§Unhypothesized.

analyses), along with increased left anterior temporal lobe and OFC metabolism (in the SPM analysis). Subjective cigarette craving positively correlated with bilateral OFC, DLPFC, and anterior insula metabolism (in the SPM analysis for all regions and in the ROI analysis for the OFC). These findings support our hypotheses based on previous studies of brain mediation of craving for other addictive substances. Taken together, these studies suggest that drug craving involves the activation of a network that includes several elements of the anterior paralimbic system—the AC, the posterior OFC, and the anterior insula—that are heavily interconnected, along with associative areas, such as the DLPFC.

Elevated AC activity has been implicated in various functions that may explain its activation during exposure to cigarette-related (and other drug) cues. Anxiety,[54,55] alertness,[56,57] arousal,[58-60] focused attention,[61-65] and awareness of emotional state[66] have all been associated with the activation of the AC in functional imaging studies of healthy populations. There is considerable overlap between our AC finding (a large area of bilateral activation [in the SPM and ROI analyses]) and the results of other studies[54-59,62-64,66] of AC function. Previous studies with large regional AC activations similar to the one seen herein include a study of alertness[57] and another of arousal.[60] Heavy smokers may experience an increase in these functions during exposure to cigarette cue stimuli, leading to greater relative AC activity (a hypothesis supported by smokers' reports of greater interest in the cigarette cue videotape).

The OFC, which was activated by exposure to cigarette-related cues (on the left) and showed correlations between changes in metabolism and intensity of provoked cigarette craving (bilaterally), has been hypothesized to mediate drug craving through its roles in compulsive repetitive behaviors[67] and in establishing a motivational value of a stimulus based on its potential reward.[68] Activation of the OFC has been demonstrated when subjects with obsessive-compulsive disorder are exposed to obsession-related stimuli[69-71] and when healthy controls are exposed to stimuli requiring decision making that may lead to reward or punishment.[72-74] In addition, gustatory[75,76] and olfactory[77-80] stimuli increase OFC activity, and studies[81,82] in nonhuman primates indicate that taste and smell may be synthesized in the OFC as a secondary processing center. Heavy smokers exposed to cigarette-related cues (including handling a cigarette) may have heightened gustatory and olfactory processing in the OFC, along with thoughts related to compulsive reward-seeking behavior—all of which would lead to OFC activation and the correlations between OFC function and craving seen herein. As has been suggested for other drug addictions, medications that attenuate activation along the OFC–basal ganglia–thalamic pathways may prove successful in the treatment of cigarette craving and addiction.[67]

The anterior insula and the DLPFC (2 other regions whose activity correlated with cigarette craving) have reported functions that may be components of cigarette craving as well. For example, the anterior insula has sensory and motor integration functions and reciprocal connections with the OFC and amygdala (a structure thought to play an important role in the assignment of emotional significance to stimuli).[83-85] The DLPFC is associated with encoding and retrieval of episodic memory, sustained attention, and working memory,[86] leading to the hypothesis that stronger memories and greater sustained attention during cigarette-related cues are associated with greater craving.

The most significant unexpected finding in this study was a strong positive association between the intensity of craving in the heavy smoker group and the relative metabolism in the superior right sensorimotor cortex (including the precentral and postcentral gyrus). In the present study, a tactile stimulus (cigarette) was held in the dominant right hand (for 18 of the 20 smokers) in the cigarette cue session. It is well documented with PET scanning that simple tactile stimulation[87,88] and movement[89-91] of the right hand activate the contralateral sensorimotor cortex. However, tactile stimuli and movement of the right hand invoking greater attention can activate the ipsilateral[57,92,93] or bilateral[94,95] sensorimotor cortex. Thus, the strong unexpected correlation found herein may represent an association between handling the emotionally laden stimulus (cigarette) and regional metabolism in an area that has heightened function during complex attention-demanding tactile stimuli.

The limitations of this study were as follows: (1) the spatial resolution of the PET scanner, which may have limited ability to detect small foci of activation or

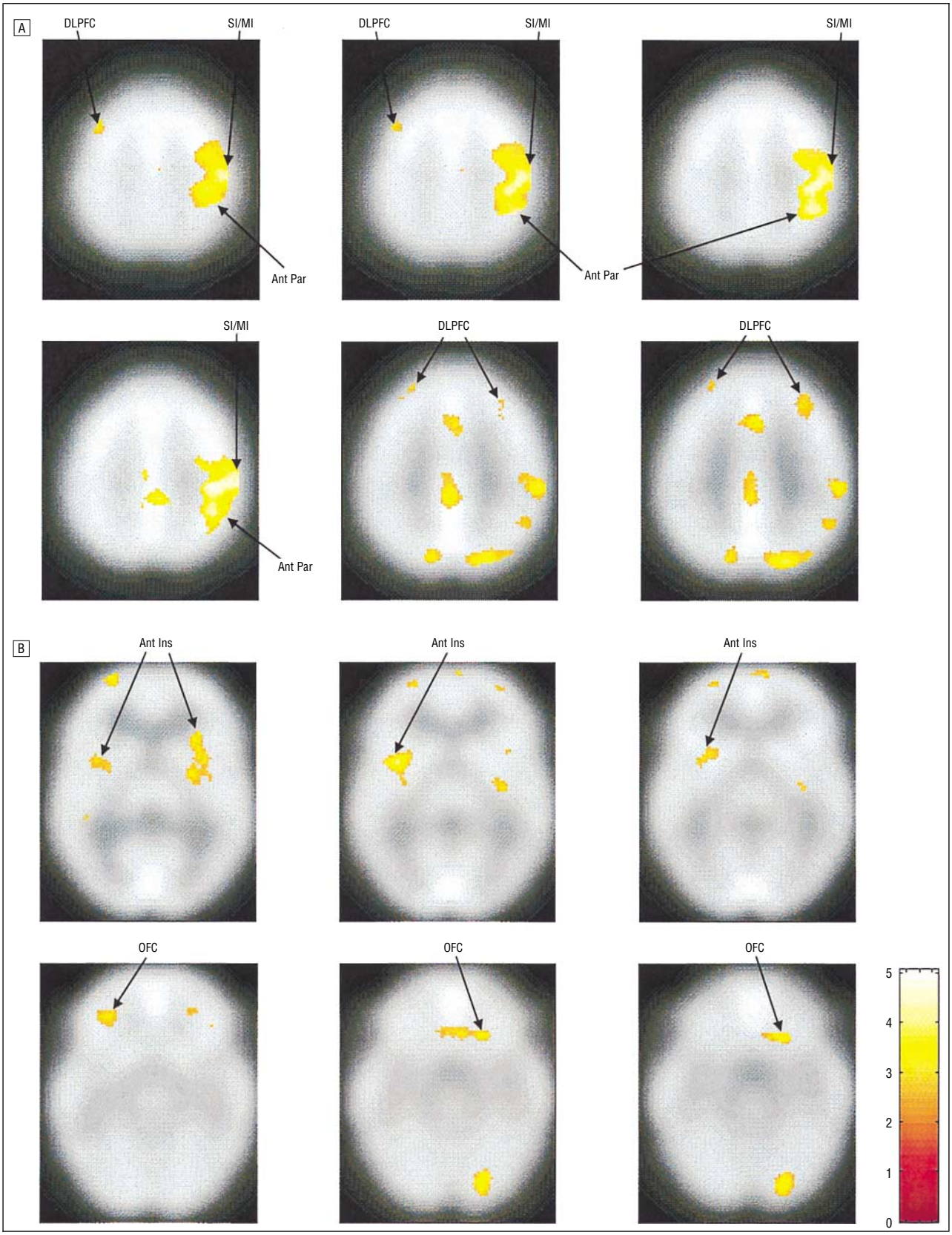

Figure 4. Regions with positive correlations between change in mean craving scores (Urge to Smoke Scale) and change in relative metabolism ($P<.005$, uncorrected) in the heavy smoker group (n=20) using the computer software program Statistical Parametric Mapping (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, England). Hypothesized regions shown include the dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex (OFC), and the anterior insula (Ant Ins) bilaterally. The strong unexpected correlation with right primary sensorimotor cortex (SI/MI) extending to the anterior parietal lobe (Ant Par) is also shown. Unhypothesized regions not passing correction for multiple comparisons are also seen, namely, the posterior cingulate gyrus, the occipital cortex, and the subgenual anterior cingulate gyrus. A, Dorsal findings. B, Ventral findings. Scale represents *Z* score.

deactivation; (2) the need to rate craving during the uptake period of FDG, which may have affected brain activation and deactivation (although the UTS Scale used herein was relatively brief); and (3) the lack of more detailed measures for the detection of potentially confounding brain functions, such as attention and working memory. Prior studies of attention have observed attentional fixations directly through 1-way mirrors, but such facilities were unavailable for this study. Also, whereas HAM-A ratings showed little variation within groups between the 2 scans, changes in state anxiety that are not well measured by this scale may have contributed to the metabolic changes seen herein; future studies of craving may benefit from using other measures of anxiety.

Several alternative methods could have been used for the present study. Functional MRI and oxygen O_2 15 PET are commonly used for activation studies, and cigarette craving could be examined with these techniques. Fluorine 18–fluorodeoxyglucose PET was chosen herein because of the time course of craving during short-term nicotine withdrawal, which begins within minutes after the last cigarette, can be modified by cues, and is sustained, accommodating the FDG time course. This design allowed us to randomize the order of cue presentation for PET sessions to minimize potential order effects and avoid having to introduce nicotine to alleviate craving, which has been shown to alter regional brain activity in other studies[96,97]; however, the optimal time frame for studying craving with functional imaging is not well established. Other potential design alternatives would be to use mental imagery or audiotapes as cigarette-related cues. Videotapes and exposure to holding a cigarette were chosen based on their ability to induce craving in prior work,[12] but alternatives may prove successful for future studies.

Our results may be important in the interpretation of functional imaging studies of subjects with conditions, such as alcohol and other drug dependence and mood and anxiety disorders,[98-100] that have high rates of nicotine dependence. Studies of these illnesses have found abnormalities in regions similar to those found to activate with cigarette craving. For example, elevated ventral AC and OFC metabolism have been linked to the pathophysiological features of major depression,[101-103] based at least partly on functional imaging studies comparing subjects with depression with healthy controls. Our results point to the need for control and monitoring of cigarette craving status in functional imaging studies in such populations.

Submitted for publication October 19, 2001; final revision received February 20, 2002; accepted February 20, 2002.

This study was supported in part by an Advanced Research Career Development Award from the Department of Veterans Affairs, Washington, DC (Dr Brody); the Tobacco-Related Disease Research Program, Oakland, Calif (Dr Brody); the National Alliance for Research in Schizophrenia and Depression, Great Neck, NY (Drs Brody and Baxter); and the Charles A. Dana Foundation Consortium on Neuroimaging Leadership, New York, NY (Dr Saxena).

Presented in part at the American College of Neuropsychopharmacology Annual Meeting, San Juan, Puerto Rico, December 12, 2000.

We thank Steven M. Berman, PhD, Susan Y. Bookheimer, PhD, and Richard E. Olmstead, PhD, for their suggestions on methods and manuscript preparation; and Naida Quinones and Michael Clark for their technical support in performing PET and MRI scans, respectively.

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REFERENCES

1. Hurt RD, Sachs DP, Glover ED, Offord KP, Johnston JA, Dale LC, Khayrallah MA, Schroeder DR, Glover PN, Sullivan CR, Croghan IT, Sullivan PM. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med.* 1997;337:1195-1202.
2. Killen JD, Fortmann SP, Davis L, Strausberg L, Varady A. Do heavy smokers benefit from higher dose nicotine patch therapy? *Exp Clin Psychopharmacol.* 1999;7:226-233.
3. Hughes JR, Lesmes GR, Hatsukami DK, Richmond RL, Lichtenstein E, Jorenby DE, Broughton JO, Fortmann SP, Leischow SJ, McKenna JP, Rennard SI, Wadland WC, Heatley SA. Are higher doses of nicotine replacement more effective for smoking cessation? *Nicotine Tob Res.* 1999;1:169-174.
4. Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, Smith SS, Muramoto ML, Daughton DM, Doan K, Fiore MC, Baker TB. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med.* 1999;340:685-691.
5. Killen JD, Fortmann SP, Schatzberg AF, Hayward C, Sussman L, Rothman M, Strausberg L, Varady A. Nicotine patch and paroxetine for smoking cessation. *J Consult Clin Psychol.* 2000;68:883-889.
6. Killen JD, Fortmann SP. Craving is associated with smoking relapse: findings from three prospective studies. *Exp Clin Psychopharmacol.* 1997;5:137-142.
7. Swan GE, Ward MM, Jack LM. Abstinence effects as predictors of relapse in smokers. *Addict Behav.* 1996;21:481-490.
8. Niaura R, Abrams DB, Monti PM, Pedraza M. Reactivity to high risk situations and smoking cessation outcome. *J Subst Abuse.* 1989;1:393-405.
9. Catley D, O'Connell KA, Shiffman S. Absentminded lapses during smoking cessation. *Psychol Addict Behav.* 2000;14:73-76.
10. Schuh KJ, Stitzer ML. Desire to smoke during spaced smoking intervals. *Psychopharmacology (Berl).* 1995;120:289-295.
11. Jarvik ME, Madsen DC, Olmstead RE, Iwamoto-Schaap PN, Elins JL, Benowitz NL. Nicotine blood levels and subjective craving for cigarettes. *Pharmacol Biochem Behav.* 2000;66:553-558.
12. Droungas A, Ehrman RN, Childress AR, O'Brien CP. Effect of smoking cues and cigarette availability on craving and smoking behavior. *Addict Behav.* 1995;20:657-673.
13. Mucha RF, Pauli P, Angrilli A. Conditioned responses elicited by cues for smoking. *Can J Physiol Pharmacol.* 1998;76:259-268.
14. Conklin CA, Tiffany ST, Vrana SR. The impact of imagining completed versus interrupted smoking on cigarette craving. *Exp Clin Psychopharmacol.* 2000;8:68-74.
15. Taylor RC, Harris NA, Singleton EG, Moolchan ET, Heishman SJ. Tobacco craving: intensity-related effects of imagery scripts in drug abusers. *Exp Clin Psychopharmacol.* 2000;8:75-87.
16. Mucha RF, Geier A, Pauli P. Modulation of craving by cues having differential overlap with pharmacological effect: evidence for cue approach in smokers and social drinkers. *Psychopharmacology (Berl).* 1999;147:306-313.
17. Sayette MA, Hufford MR. Effects of cue exposure and deprivation on cognitive resources in smokers. *J Abnorm Psychol.* 1994;103:812-818.
18. Morgan MJ, Davies GM, Willner P. The Questionnaire of Smoking Urges is sensitive to abstinence and exposure to smoking-related cues. *Behav Pharmacol.* 1999;10:619-626.
19. Carter BL, Tiffany ST. Cue-reactivity and the future of addiction research. *Addiction.* 1999;94:349-351.
20. Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP. Limbic activation during cue-induced cocaine craving. *Am J Psychiatry.* 1999;156:11-18.
21. Maas LC, Lukas SE, Kaufman MJ, Weiss RD, Daniels SL, Rogers VW, Kukes TJ, Renshaw PF. Functional magnetic resonance imaging of human brain ac-

tivation during cue-induced cocaine craving. *Am J Psychiatry*. 1998;155: 124-126.
22. Garavan H, Pankiewicz J, Bloom A, Cho JK, Sperry L, Ross TJ, Salmeron BJ, Risinger R, Kelley D, Stein EA. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. *Am J Psychiatry*. 2000;157:1789-1798.
23. Wexler BE, Gottschalk CH, Fulbright RK, Prohovnik I, Lacadie CM, Rounsaville BJ, Gore JC. Functional magnetic resonance imaging of cocaine craving. *Am J Psychiatry*. 2001;158:86-95.
24. Volkow ND, Wang GJ, Fowler JS, Hitzemann R, Angrist B, Gatley SJ, Logan J, Ding YS, Pappas N. Association of methylphenidate-induced craving with changes in right striato-orbitofrontal metabolism in cocaine abusers: implications in addiction. *Am J Psychiatry*. 1999;156:19-26.
25. Kilts CD, Schweitzer JB, Quinn CK, Gross RE, Faber TL, Muhammad F, Ely TD, Hoffman JM, Drexler KPG. Neural activity related to drug craving in cocaine addiction. *Arch Gen Psychiatry*. 2001;58:334-341.
26. Daglish MR, Weinstein A, Malizia AL, Wilson S, Melichar JK, Britten S, Brewer C, Lingford-Hughes A, Myles JS, Grasby P, Nutt DJ. Changes in regional cerebral blood flow elicited by craving memories in abstinent opiate-dependent subjects. *Am J Psychiatry*. 2001;158:1680-1686.
27. Kraus MA, Kornetsky C. Cue-induced changes in basal local cerebral glucose utilization 13 days after morphine sensitization in the Fischer 344 rat: relevance for drug craving. *Brain Res*. 2000;865:194-201.
28. Bonson KR, Grant SJ, Contoreggi CS, Links JM, Metcalfe J, Weyl HL, Kurian V, Ernst M, London ED. Neural systems and cue-induced cocaine craving. *Neuropsychopharmacology*. 2002;26:376-386.
29. Wang GJ, Volkow ND, Fowler JS, Cervany P, Hitzemann RJ, Pappas NR, Wong CT, Felder C. Regional brain metabolic activation during craving elicited by recall of previous drug experiences. *Life Sci*. 1999;64:775-784.
30. Grant S, London ED, Newlin DB, Villemagne VL, Liu X, Contoreggi C, Phillips RL, Kimes AS, Margolin A. Activation of memory circuits during cue-elicited cocaine craving. *Proc Natl Acad Sci U S A*. 1996;93:12040-12045.
31. George MS, Anton RF, Bloomer C, Teneback C, Drobes DJ, Lorberbaum JP, Nahas Z, Vincent DJ. Activation of prefrontal cortex and anterior thalamus in alcoholic subjects on exposure to alcohol-specific cues. *Arch Gen Psychiatry*. 2001;58:345-352.
32. Volkow ND, Fowler JS, Wolf AP, Hitzemann R, Dewey S, Bendriem B, Alpert R, Hoff A. Changes in brain glucose metabolism in cocaine dependence and withdrawal. *Am J Psychiatry*. 1991;148:621-626.
33. Sell LA, Morris JS, Bearn J, Frackowiak RS, Friston KJ, Dolan RJ. Neural responses associated with cue evoked emotional states and heroin in opiate addicts. *Drug Alcohol Depend*. 2000;60:207-216.
34. Kozlowski LT, Mann RE, Wilkinson DA, Poulos CX. Cravings are ambiguous: ask about urges or desires. *Addict Behav*. 1989;14:443-445.
35. Shiffman S, Johnston JA, Khayrallah M, Elash CA, Gwaltney CJ, Paty JA, Gnys M, Evoniuk G, DeVeaugh-Geiss J. The effect of bupropion on nicotine craving and withdrawal. *Psychopharmacology (Berl)*. 2000;148:33-40.
36. Tiffany ST, Drobes DJ. The development and initial validation of a questionnaire on smoking urges. *Br J Addict*. 1991;86:1467-1476.
37. Willner P, Hardman S, Eaton G. Subjective and behavioural evaluation of cigarette cravings. *Psychopharmacology (Berl)*. 1995;118:171-177.
38. Shadel WG, Niaura R, Brown RA, Hutchison KE, Abrams DB. A content analysis of smoking craving. *J Clin Psychol*. 2001;57:145-150.
39. Gilbert HM, Warburton DM. Craving: a problematic concept in smoking research. *Addict Res*. 2000;8:381-397.
40. Anton RF. What is craving? models and implications for treatment. *Alcohol Res Health*. 1999;23:165-173.
41. Sayette MA, Shiffman S, Tiffany ST, Niaura RS, Martin CS, Schadel WG. The measurement of drug craving. *Addiction*. 2000;95(suppl 2):S189-S210.
42. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for* DSM-IV *Axis I Disorders: Patient Edition (SCID-I/P, Version 2.0)*. New York: Biometrics Research, New York State Psychiatric Institute; 1995.
43. Hepple J, Robson P. The effect of caffeine on cue exposure responses in exsmokers. *Addiction*. 1996;91:269-273.
44. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Psychol*. 1967;6:278-296.
45. Hamilton M. Diagnosis and rating of anxiety. *Br J Psychiatry*. 1969;3:76-79.
46. Shiffman SM, Jarvik ME. Smoking withdrawal symptoms in two weeks of abstinence. *Psychopharmacology (Berl)*. 1976;50:35-39.
47. Sweeney CT, Pillitteri JL, Kozlowski LT. Measuring drug urges by questionnaire. *Addict Behav*. 1996;21:199-204.
48. Woods RP, Mazziotta JC, Cherry SR. MRI-PET registration with automated algorithm. *J Comput Assist Tomogr*. 1993;17:536-546.
49. Friston KJ, Worsley KJ, Frackowiak RSJ, Mazziotta JC, Evans AC. Assessing the significance of focal activations using their spatial extent. *Human Brain Mapp*. 1994;1:214-220.
50. Nadeau SE, Crosson B. A guide to functional imaging of cognitive processes. *Neuropsychiatry Neuropsychol Behav Neurol*. 1995;8:143-162.
51. Rajkowska G, Goldman-Rakic PS. Cytoarchitectonic definition of prefrontal areas in the normal human cortex, II: variability in locations of areas 9 and 46 and relationship to the Taliarach Coordinate System. *Cereb Cortex*. 1995;5:323-337.
52. Steinmetz H, Seitz RJ. Functional anatomy of language processing: neuroimaging and the problem of individual variability. *Neuropsychologia*. 1991;29: 1149-1161.
53. Tailarach J, Tournoux P. *Co-planar Stereotaxic Atlas of the Human Brain*. New York, NY: Thieme-Stratton Inc; 1988.
54. Kimbrell TA, George MS, Parekh PI, Ketter TA, Podell DM, Danielson AL, Repella JD, Benson BE, Willis MW, Herscovitch P, Post RM. Regional brain activity during transient self-induced anxiety and anger in healthy adults. *Biol Psychiatry*. 1999;46:454-465.
55. Chua P, Krams M, Toni I, Passingham R, Dolan R. A functional anatomy of anticipatory anxiety. *Neuroimage*. 1999;9(pt 1):563-571.
56. Sturm W, de Simone A, Krause BJ, Specht K, Hesselmann V, Radermacher I, Herzog H, Tellmann L, Muller-Gartner HW, Willmes K. Functional anatomy of intrinsic alertness: evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere. *Neuropsychologia*. 1999;37:797-805.
57. Naito E, Kinomura S, Geyer S, Kawashima R, Roland PE, Zilles K. Fast reaction to different sensory modalities activates common fields in the motor areas, but the anterior cingulate cortex is involved in the speed of reaction. *J Neurophysiol*. 2000;83:1701-1709.
58. Rauch SL, Shin LM, Dougherty DD, Alpert NM, Orr SP, Lasko M, Macklin ML, Fischman AJ, Pitman RK. Neural activation during sexual and competitive arousal in healthy men. *Psychiatry Res*. 1999;91:1-10.
59. Stoleru S, Gregoire MC, Gerard D, Decety J, Lafarge E, Cinotti L, Lavenne F, Le Bars D, Vernet-Maury E, Rada H, Collet C, Mazoyer B, Forest MG, Magnin F, Spira A, Comar D. Neuroanatomical correlates of visually evoked sexual arousal in human males. *Arch Sex Behav*. 1999;28:1-21.
60. Critchley HD, Mathias CJ, Dolan RJ. Neural activity in the human brain relating to uncertainty and arousal during anticipation. *Neuron*. 2001;29:537-545.
61. Bench CJ, Frith CD, Grasby PM, Friston KJ, Paulesu E, Frackowiak RS, Dolan RJ. Investigations of the functional anatomy of attention using the Stroop test. *Neuropsychologia*. 1993;31:907-922.
62. Keilp JG, Herrera J, Stritzke P, Cornblatt BA. The Continuous Performance Test, Identical Pairs version (CPT-IP), III: brain functioning during performance of numbers and shapes subtasks. *Psychiatry Res*. 1997;74:35-45.
63. Davis KD, Taylor SJ, Crawley AP, Wood ML, Mikulis DJ. Functional MRI of pain- and attention-related activations in the human cingulate cortex. *J Neurophysiol*. 1997;77:3370-3380.
64. Benedict RH, Lockwood AH, Shucard JL, Shucard DW, Wack D, Murphy BW. Functional neuroimaging of attention in the auditory modality. *Neuroreport*. 1998; 9:121-126.
65. Woldorff MG, Matzke M, Zamarripa F, Fox PT. Hemodynamic and electrophysiological study of the role of the anterior cingulate in target-related processing and selection for action. *Hum Brain Mapp*. 1999;8:121-127.
66. Lane RD, Reiman EM, Axelrod B, Yun LS, Holmes A, Schwartz GE. Neural correlates of levels of emotional awareness: evidence of an interaction between emotion and attention in the anterior cingulate cortex. *J Cogn Neurosci*. 1998; 10:525-535.
67. Volkow ND, Fowler JS. Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cereb Cortex*. 2000;10:318-325.
68. London ED, Ernst M, Grant S, Bonson K, Weinstein A. Orbitofrontal cortex and human drug abuse: functional imaging. *Cereb Cortex*. 2000;10:334-342.
69. Rauch SL, Jenike MA, Alpert NM, Baer L, Breiter HC, Savage CR, Fischman AJ. Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15–labeled carbon dioxide and positron emission tomography. *Arch Gen Psychiatry*. 1994;51:62-70.
70. Breiter HC, Rauch SL, Kwong KK, Baker JR, Weisskoff RM, Kennedy DN, Kendrick AD, Davis TL, Jiang A, Cohen MS, Stern CE, Belliveau JW, Baer L, O'Sullivan RL, Savage CR, Jenike MA, Rosen BR. Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1996;53:595-606.
71. Cottraux J, Gerard D, Cinotti L, Froment JC, Deiber MP, Le Bars D, Galy G, Millet P, Labbe C, Lavenne F, Bouvard M, Mauguiere F. A controlled positron emission tomography study of obsessive and neutral auditory stimulation in obsessive-compulsive disorder with checking rituals. *Psychiatry Res*. 1996; 60:101-112.
72. Rogers RD, Owen AM, Middleton HC, Williams EJ, Pickard JD, Sahakian BJ, Robbins TW. Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. *J Neurosci*. 1999;19:9029-9038.

73. O'Doherty J, Kringelbach ML, Rolls ET, Hornak J, Andrews C. Abstract reward and punishment representations in the human orbitofrontal cortex. *Nat Neurosci.* 2001;4:95-102.
74. Ernst M, Bolla K, Mouratidis M, Contoreggi C, Matochik JA, Kurian V, Cadet JL, Kimes AS, London ED. Decision-making in a risk-taking task: a PET study. *Neuropsychopharmacology.* 2002;26:682-691.
75. Zald DH, Lee JT, Fluegel KW, Pardo JV. Aversive gustatory stimulation activates limbic circuits in humans. *Brain.* 1998;121:1143-1154.
76. O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F. Representation of pleasant and aversive taste in the human brain. *J Neurophysiol.* 2001;85: 1315-1321.
77. Zatorre RJ, Jones-Gotman M, Evans AC, Meyer E. Functional localization and lateralization of human olfactory cortex. *Nature.* 1992;360:339-340.
78. Zald DH, Pardo JV. Emotion, olfaction, and the human amygdala: amygdala activation during aversive olfactory stimulation. *Proc Natl Acad Sci U S A.* 1997; 94:4119-4124.
79. Levy LM, Henkin RI, Hutter A, Lin CS, Martins D, Schellinger D. Functional MRI of human olfaction. *J Comput Assist Tomogr.* 1997;21:849-856.
80. Qureshy A, Kawashima R, Imran MB, Sugiura M, Goto R, Okada K, Inoue K, Itoh M, Schormann T, Zilles K, Fukuda H. Functional mapping of human brain in olfactory processing: a PET study. *J Neurophysiol.* 2000;84: 1656-1666.
81. Rolls ET, Critchley HD, Browning A, Hernadi I. The neurophysiology of taste and olfaction in primates, and umami flavor. *Ann N Y Acad Sci.* 1998;855: 426-437.
82. Rolls ET, Baylis LL. Gustatory, olfactory, and visual convergence within the primate orbitofrontal cortex. *J Neurosci.* 1994;14:5437-5452.
83. Bechara A, Damasio H, Damasio AR, Lee GP. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *J Neurosci.* 1999;19:5473-5481.
84. LeDoux JE. Emotional memory systems in the brain. *Behav Brain Res.* 1993; 58:69-79.
85. Augustine JR. Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Res Brain Res Rev.* 1996;22:229-244.
86. Cabeza R, Nyberg L. Imaging cognition II: an empirical review of 275 PET and fMRI studies. *J Cogn Neurosci.* 2000;12:1-47.
87. Roberts TP, Rowley HA. Mapping of the sensorimotor cortex: functional MR and magnetic source imaging. *AJNR Am J Neuroradiol.* 1997;18:871-880.
88. Polonara G, Fabri M, Manzoni T, Salvolini U. Localization of the first and second somatosensory areas in the human cerebral cortex with functional MR imaging. *AJNR Am J Neuroradiol.* 1999;20:199-205.
89. Fink GR, Frackowiak RS, Pietrzyk U, Passingham RE. Multiple nonprimary motor areas in the human cortex. *J Neurophysiol.* 1997;77:2164-2174.
90. Kawashima R, Inoue K, Sugiura M, Okada K, Ogawa A, Fukuda H. A positron emission tomography study of self-paced finger movements at different frequencies. *Neuroscience.* 1999;92:107-112.
91. Carey LM, Abbott DF, Egan GF, Tochon-Danguy HJ, Donnan GA. The functional neuroanatomy and long-term reproducibility of brain activation associated with a simple finger tapping task in older healthy volunteers: a serial PET study. *Neuroimage.* 2000;11:124-144.
92. Bodegard A, Geyer S, Naito E, Zilles K, Roland PE. Somatosensory areas in man activated by moving stimuli: cytoarchitectonic mapping and PET. *Neuroreport.* 2000;11:187-191.
93. Sadato N, Ibanez V, Deiber MP, Hallett M. Gender difference in premotor activity during active tactile discrimination. *Neuroimage.* 2000;11:532-540.
94. Burton H, Abend NS, MacLeod AM, Sinclair RJ, Snyder AZ, Raichle ME. Tactile attention tasks enhance activation in somatosensory regions of parietal cortex: a positron emission tomography study. *Cereb Cortex.* 1999;9:662-674.
95. Bodegard A, Ledberg A, Geyer S, Naito E, Zilles K, Roland PE. Object shape differences reflected by somatosensory cortical activation. *J Neurosci.* 2000; 20:RC51:1-5.
96. Stein EA, Pankiewicz J, Harsch HH, Cho JK, Fuller SA, Hoffmann RG, Hawkins M, Rao SM, Bandettini PA, Bloom AS. Nicotine-induced limbic cortical activation in the human brain: a functional MRI study. *Am J Psychiatry.* 1998;155: 1009-1015.
97. Domino EF, Minoshima S, Guthrie SK, Ohl L, Ni L, Koeppe RA, Cross DJ, Zubieta J. Effects of nicotine on regional cerebral glucose metabolism in awake resting tobacco smokers. *Neuroscience.* 2000;101:277-282.
98. Breslau N. Psychiatric comorbidity of smoking and nicotine dependence. *Behav Genet.* 1995;25:95-101.
99. Black DW, Zimmerman M, Coryell WH. Cigarette smoking and psychiatric disorder in a community sample. *Ann Clin Psychiatry.* 1999;11:129-136.
100. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. *JAMA.* 2000; 284:2606-2610.
101. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. *J Neuropsychiatry Clin Neurosci.* 1997;9:471-481.
102. Drevets WC. Prefrontal cortical-amygdalar metabolism in major depression. *Ann N Y Acad Sci.* 1999;877:614-637.
103. Brody AL, Barsom MW, Bota RG, Saxena S. Prefrontal-subcortical and limbic circuit mediation of major depressive disorder. *Semin Clin Neuropsychiatry.* 2001; 6:102-112.