

# 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  $\geq 20$  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.

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**D**ESPITE NEW medication options for nicotine dependence, abstinence rates after 6 months or more of treatment remain relatively low at 14% to 35%.<sup>1-5</sup> 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.<sup>6-9</sup>

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.<sup>10,11</sup> 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,<sup>12</sup> audiotapes,<sup>13</sup> mental imagery,<sup>14,15</sup> visual imagery,<sup>16</sup> and exposure to

cigarettes or cigarette-related items.<sup>17,18</sup> A meta-analysis<sup>19</sup> 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),<sup>20-26</sup> amygdala/temporal pole,<sup>20,25,27,28</sup> orbitofrontal cortex (OFC),<sup>20,27-30</sup> and lateral prefrontal cortex (primarily the dorsolateral prefrontal cortex [DLPFC]).<sup>21,22,28,30,31</sup> 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,<sup>24,26,28,32,33</sup> DLPFC,<sup>21,28,30,32</sup> and anterior insula.<sup>29,33</sup> 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<sup>34</sup> and has been used in other research into neurobiological aspects of cigarette craving,<sup>11,35-37</sup> while acknowledging the complexity of the meaning of drug craving.<sup>38-41</sup> 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

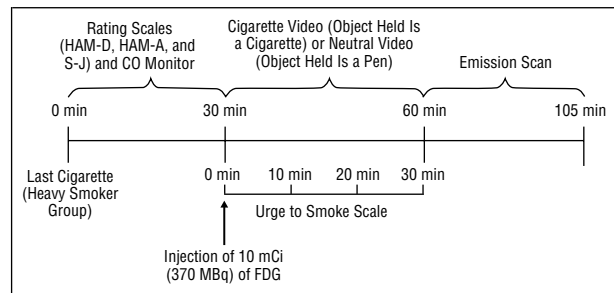
### GENERAL

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  $\geq 20$  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*).<sup>42</sup> Subjects were also excluded if they were taking medication or had any history of or current medical condition that might affect the central ner-



**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.

vous system at the time of scanning (eg, current treatment with a  $\beta$ -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<sup>43</sup> 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.

### 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<sup>44</sup> and the Hamilton Anxiety Rating Scale<sup>45</sup> (HAM-D and HAM-A, respectively) were then administered to all subjects, along with the Shiffman-Jarvik Scale,<sup>46</sup> 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.<sup>12</sup> 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<sup>11</sup> 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<sup>47</sup> 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 milliseconds; echo time, 7 milliseconds; 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.<sup>48</sup>

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 en-

tire 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

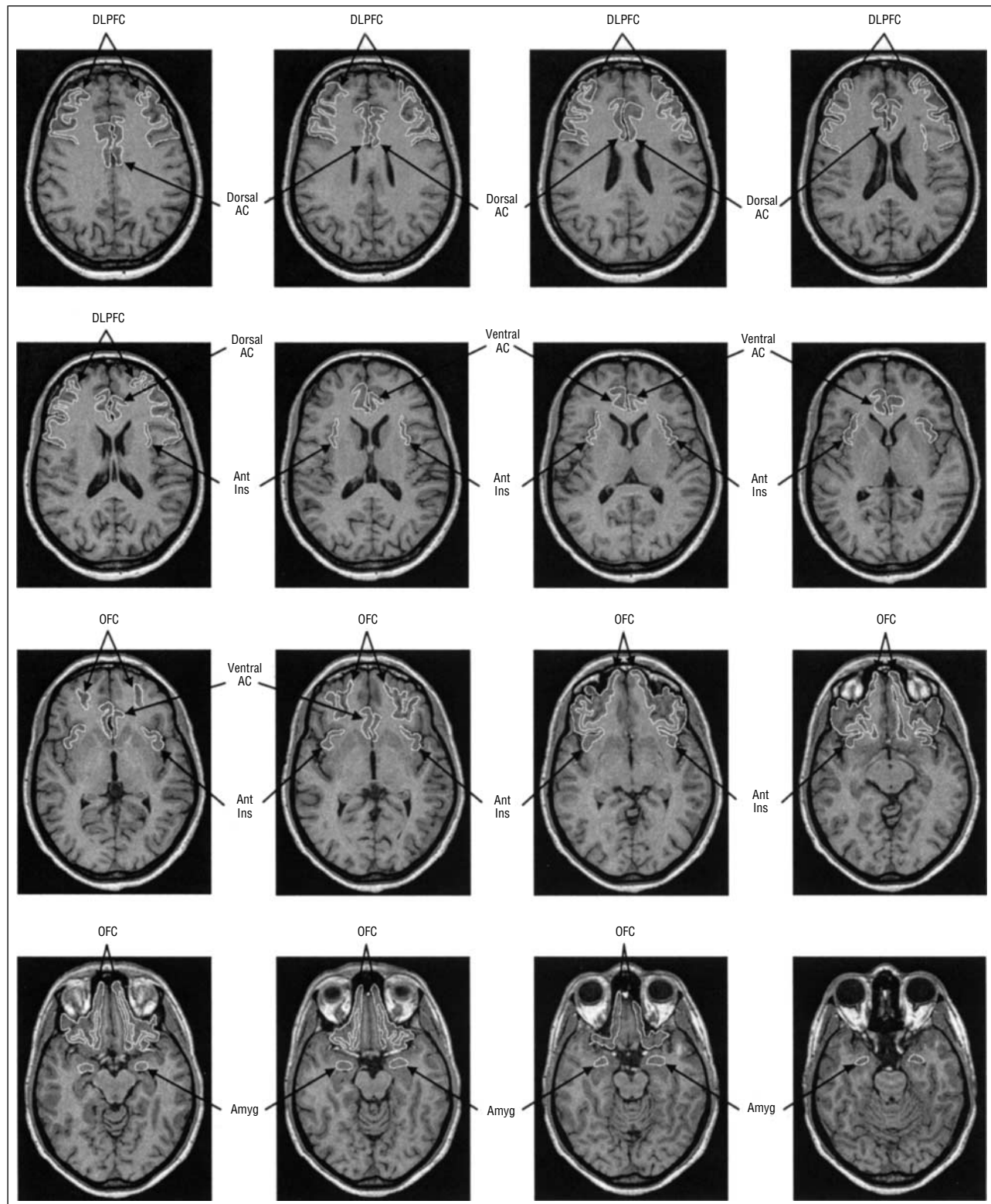
Mean ( $\pm$ SD) scores for all clinical rating scales were determined for the neutral and cigarette cue scans within the heavy smoker and nonsmoking control groups. To examine group differences in clinical data scores and change from the neutral to the cigarette cue scans, repeated-measures analyses 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.<sup>49-52</sup> 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<sup>25,28,33</sup> 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.<sup>53</sup> 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.<sup>20,24,30</sup>

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

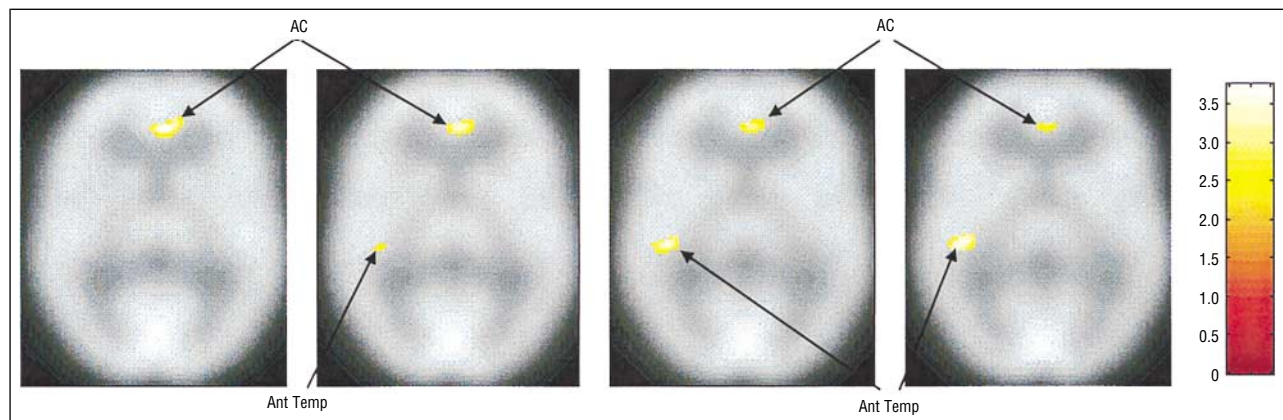
The SPM program revealed an interaction between metabolic increase (from the neutral to the cigarette cue scans) and group (heavy smoker vs nonsmoking control) in the perigenual AC spanning the midline (183 voxels and roughly corresponding to Brodmann areas 24 and 32) ( $P < .001$ ), along with a smaller 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 un-hypothesized 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 ( $1.12 \pm 0.04$  vs  $1.08 \pm 0.06$ ) and right ( $1.12 \pm 0.05$  vs  $1.09 \pm 0.07$ ) ventral AC, while nonsmoking controls had little change in the ventral AC ( $1.08 \pm 0.04$

**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\***

Regions	Heavy Smokers (n = 20)							
	Greater Increases Than Nonsmokers (n = 20)				Within-Group Increases			
	Z Score†	Talairach Coordinates			Z Score†	Talairach Coordinates		
		x	y	z		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  $1.08 \pm 0.05$  on the left and  $1.11 \pm 0.05$  vs  $1.10 \pm 0.06$  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,<sup>54,55</sup> alertness,<sup>56,57</sup> arousal,<sup>58-60</sup> focused attention,<sup>61-65</sup> and awareness of emotional state<sup>66</sup> 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<sup>54-59,62-64,66</sup> of AC function. Previous studies with large regional AC activations similar to the one seen herein include a study of alertness<sup>57</sup> and another of arousal.<sup>60</sup> Heavy smokers may experience an increase in these functions during exposure to cigarette cue stimuli,

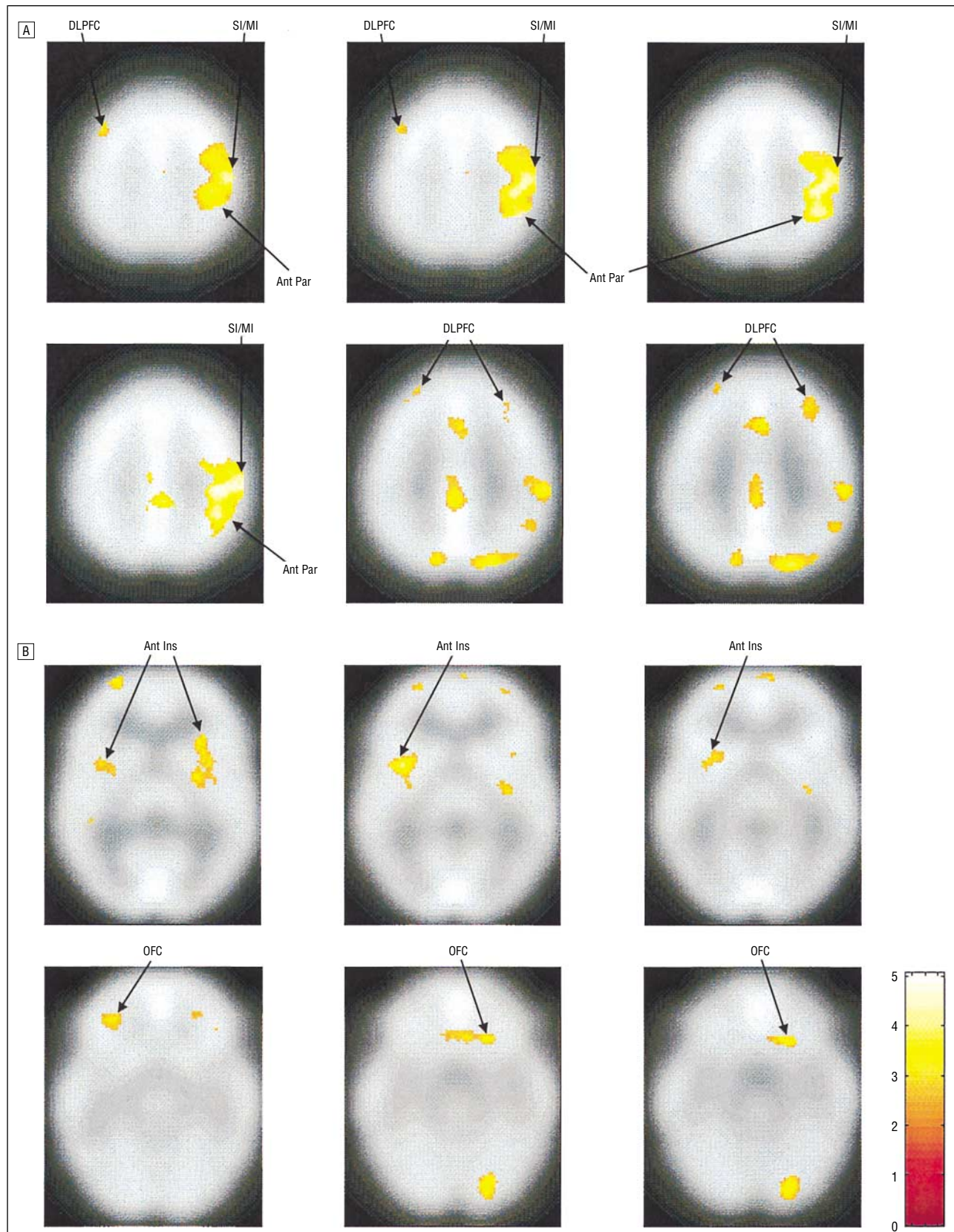
leading to greater relative AC activity (a hypothesis supported by smokers' reports of greater interest in the cigarette cue videotape).

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<sup>67</sup> and in establishing a motivational value of a stimulus based on its potential reward.<sup>68</sup> Activation of the OFC has been demonstrated when subjects with obsessive-compulsive disorder are exposed to obsession-related stimuli<sup>69-71</sup> and when healthy controls are exposed to stimuli requiring decision making that may lead to reward or punishment.<sup>72-74</sup> In addition, gustatory<sup>75,76</sup> and olfactory<sup>77-80</sup> stimuli increase OFC activity, and studies<sup>81,82</sup> 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.<sup>67</sup>

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).<sup>83-85</sup> The DLPFC is associated with encoding and retrieval of episodic memory, sustained attention, and working memory,<sup>86</sup> 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<sup>87,88</sup> and movement<sup>89-91</sup> 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<sup>57,92,93</sup> or bilateral<sup>94,95</sup> 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<sub>2</sub> 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<sup>96,97</sup>; 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,<sup>12</sup> 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,<sup>98-100</sup> 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,<sup>101-103</sup> 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.

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