Differences between Smokers and Nonsmokers in Regional Gray Matter Volumes and Densities

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Background: *Magnetic resonance imaging (MRI) studies have demonstrated large-scale brain abnormalities in cigarette smokers, such as ventricular enlargement and atrophy. Converging lines of evidence point to functional differences between smokers and nonsmokers in specific brain regions, namely the lateral prefrontal cortex (PFC), anterior cingulate cortex (ACC), ventral striatum, and thalamus. Using MRI, we examined these regions for differences in gray matter between smokers and nonsmokers.*

Methods: *Thirty-six otherwise healthy adults (19 smokers and 17 nonsmoking control subjects) underwent three-dimensional Fourier-transform spoiled-gradient-recalled acquisition MRI of the brain. Both hand-drawn regions of interest and the computer program voxel-based morphometry were used to assess group differences in regional gray matter volumes and densities, respectively.*

Results: *Smokers had smaller gray matter volumes and lower gray matter densities than nonsmokers in the PFC bilaterally, along with smaller volumes in the left dorsal ACC and lower gray matter densities in the right cerebellum. Smokers also had negative associations between pack-year smoking history and PFC gray matter densities.*

Conclusions: *Smokers and nonsmokers differed in regional gray matter in brain areas previously linked with nicotine dependence. These findings might reflect effects of chronic smoking, predisposing traits that lead to smoking, or some combination of these factors.*

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Key Words: Magnetic resonance imaging, nicotine dependence, voxel-based morphometry, prefrontal cortex, anterior cingulate cortex, ventral striatum

Magnetic resonance imaging (MRI) studies have demonstrated that cigarette smoking history is associated with large-scale structural brain abnormalities. Cigarette usage, as indexed by pack-year smoking history, has been linked with increased sulcal and ventricular grade (Longstreth et al 2000) and atrophy (Longstreth et al 2001) in the elderly. Smoking history is also associated with severity of periventricular white matter hyperintensities in most (Fukuda and Kitani 1996; Kobayashi et al 1997; Liao et al 1997; Longstreth et al 2000; Tsushima et al 2002) but not all (Yamashita et al 1996; Yetkin et al 1993) studies in which this question was examined. In addition, smoking is a risk factor for both silent (Howard et al 1998; Longstreth et al 1998) and symptomatic (Longstreth et al 1998, 2001) stroke. Although these studies have examined large-scale abnormalities, no one has yet reported regional gray matter volume and density differences between otherwise healthy smokers and nonsmoking control subjects.

Converging lines of evidence point to four candidate brain regions that might differ in gray matter volumes and densities between smokers and nonsmokers. Functional MRI (fMRI) and positron emission tomography (PET) studies demonstrate that administration of nicotine (or cigarette smoking) increases activity in the prefrontal cortex (PFC) (Nakamura et al 2000; Stein et al 1998), anterior cingulate cortex (ACC) (Stein et al 1998), ventral striatum (Nakamura et al 2000; Stein et al 1998), and thalamus (Domino et al 2000; Nakamura et al 2000; Rose et al 2003; Stein et al 1998; Zubieta et al 2001). Functional imaging studies also show that smokers exposed to cigarette-related cues have activation of the PFC (Due et al 2002) and ACC (Brody et al 2002). Consistent with these findings in humans are imaging studies of nonhuman primates and rodents, which demonstrate that nicotine administration results in dopamine release in the ventral striatum (Dewey et al 1999; Di Chiara and Imperato 1988) and that the highest density of nicotinic acetylcholine receptors is in the thalamus (Clarke et al 1984; Dávila-García et al 1997; Horti et al 1998; London et al 1985, 1995; Musachio et al 1997). Thus, four regions (the PFC, ACC, ventral striatum, and thalamus) are implicated repeatedly in responses to smoking and smoking cues.

In addition to direct effects of smoking and smoking cues on the candidate brain regions, indirect evidence from behavioral studies strengthens the association between these regions and smoking status. Smokers do not perform as well as nonsmokers on tasks that require working memory (N-back type) (Ernst et al 2001; Spilich et al 1992), which are known to activate the lateral PFC (Braver et al 2001; Meyer-Lindenberg et al 2001; Zurowski et al 2002). Smokers also have higher rates than the general population of impulsivity (Mitchell 1999; Waldeck and Miller 1997), a trait associated with diminished PFC function (Brower and Price 2001). Additionally, smokers have state-dependent (abstinence vs. satiety) alterations in reaction time (Hatsukami et al 1989; Pritchard et al 1992; Shiffman et al 1995), arousal (Parrott and Kaye 1999), motivation (Powell et al 2002), and sustained attention (Rusted et al 2000), which are all functions of the ACC (Bench et al 1993; Critchley et al 2001; Rauch et al 1999).

We are not aware of any previous reports focusing on regional gray matter in smokers; however, associations between regional gray matter and demographic (and other substance dependence) variables have been reported. Prior studies have examined associations between regional brain volumes and age (Bartzokis et al 2001; Coffey et al 1992; Cowell et al 1994; Jernigan et al 1991, 2001; Mueller et al 1998; Murphy et al 1996; Pfefferbaum et al 1998; Raz et al 1997; Salat et al 2001; Tisserand et al 2000; Van Der Werf et al 2001), gender (Cowell et al 1994; Gur et al 2002a, 2002b; Murphy et al 1996), and intelligence

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(Andreasen et al 1993; Reiss et al 1996), as well as other substance dependencies (Bartzokis et al 2000; Fein et al 2002b; Jacobsen et al 2001a, 2001b; Liu et al 1998). None of these studies reported the effects of smoking status in detail, although one of the aging studies did use smoking status (along with other cardiovascular risk factors) as a single covariate in the statistical analysis (Coffey et al 1992).

Methods and Materials

Subjects

Thirty-six subjects (19 smokers and 17 nonsmoking control subjects), 21–65 years of age, were recruited through local newspaper advertisements. They were initially screened during a semistructured telephone interview to assess smoking, medical, psychiatric, medication, and substance use history. Smokers were defined as those who smoked at least 20 cigarettes per day and met DSM-IV criteria for nicotine dependence. Nonsmoking history was defined as having smoked no more than five cigarettes in a lifetime. Subjects were also screened on the telephone for exclusion criteria (see below). Those who passed these initial screening criteria met with the principal investigator (ALB), and all subjects who participated in the study provided written informed consent after the procedures had been fully explained. The consent form and study procedures were approved by the institutional review board for the Greater Los Angeles Veterans Affairs Healthcare System. Subjects in this study also participated in a separate PET imaging study (Brody et al 2002).

Subjects were excluded for any lifetime history of medical, psychiatric, substance abuse, or medication use thought to affect brain structure or function at the time of scanning. Examples of medical exclusion criteria include primarily neurologic conditions, such as a history of epilepsy or seizures, stroke, or head trauma with loss of consciousness. Potential research participants with any lifetime history of an Axis I psychiatric disorder, as diagnosed by screening questions from the Structured Clinical Interview for DSM-IV (First et al 1995), were excluded. Substance abuse exclusion criteria included alcohol use more than 1 drink equivalent per day, any illicit drug use other than marijuana, or marijuana use more than once per month. Urine toxicology screens were obtained on all subjects with questionable drug abuse history, and subjects were excluded from further participation if their urine toxicology screen was positive. Medication exclusions included any history of regular psychotropic drug usage or any current regular usage of medications with the potential to affect the central nervous system (e.g., β-blockers or analgesic medications).

Clinical ratings obtained before scanning included the 17-item Hamilton Depression Rating Scale (HAM-D; Hamilton 1967), the Hamilton Anxiety Rating Scale (HAM-A; Hamilton 1969), and the Fagerström Test for Nicotine Dependence (FTND; Fagerström 1978; Heatherton et al 1991). Exhaled carbon monoxide levels (Bedfont EC-50, Microsmokerlyzer II, Kent, United Kingdom) were obtained as a rough measure of recent cigarette smoking at the time that rating scales were administered. Handedness was determined with a standard rating scale (Oldfield 1971).

MRI

An MRI scan of the brain was obtained for each subject within 3 days of the clinical interview. The scans were performed on a Vision 1.5-Tesla (Siemens Medical Systems, Iselin, New Jersey) scanner with the following protocol: three-dimensional Fourier-transform spoiled-gradient-recalled acquisition, repetition time = 30 msec, echo time = 7 msec, 30° angle, 256 × 192 view matrix, 23 cm field of view. The acquired volume was reconstructed as contiguous 1.5-mm-thick transaxial slices. Subjects were instructed not to smoke on the morning of the scan; all scans were performed at 7:00 AM, with subjects arriving at the scanner at 6:30 AM.

MRI Scan Analysis

MRI data were analyzed with two complementary methods: 1) hand-drawn regions of interest (ROIs) to determine gray matter volumes of specific brain structures; and 2) voxel-based morphometry (VBM) (Ashburner and Friston 2000) to measure relative gray matter density. Each method has strengths and limitations (Ashburner and Friston 2001; Bookstein 2001; Friston et al 1994; Steinmetz and Seitz 1991; Tisserand et al 2002). The ROI method gives direct measurement of gray matter volumes of selected structures but is limited by the subjectivity of investigator-defined regional boundaries and the potential for errors in region drawing. Volume-based morphometry measures tissue composition (e.g., gray matter density) and has the advantage of surveying the entire brain without the use of manual techniques; however, this method relies on spatial normalization to a standard brain template, thus deforming structures of interest and comingling effects of tissue composition with those of regional boundaries. Volume-based morphometry has been used to determine differences between cocaine-dependent subjects and normal control subjects (Franklin et al 2002) and has been validated against ROI methods (Good et al 2002; Karas et al 2002) and known structural abnormalities in subjects with degenerative dementias (Burton et al 2002; Busatto et al 2003).

Regions of Interest

For the ROI analysis, six ROIs were hand drawn bilaterally on transaxial MRI slices (Figure 1) by a team of investigators blind to subject identity (GSL, ECS, JCH, and RGN), based on a priori hypotheses derived from the literature cited above. The ROIs were the dorsolateral and ventrolateral prefrontal cortices (DLPFC and VLPFC), dorsal and ventral ACC, ventral striatum, and thalamus. Boundaries for these regions were defined according to standard atlases (Damasio 1995; Mai et al 1997). Because subtle differences in regional boundaries can alter results, each ROI was assigned to a specific region drawer, and all ROIs were reviewed twice by the region drawers and the principal investigator (blinded to subject identity) to improve uniformity of placement. Intrarater reliability with this method (based on replicating three complete ROI sets) was .95.

The DLPFC (roughly corresponding to Brodmann areas [BA] 46/9) and VLPFC (roughly corresponding to BA 45/10) were drawn as the dorsal and ventral halves of the middle frontal gyrus (gray matter), respectively, and were drawn in approximately 10 planes each. The border between DLPFC and VLPFC was at the level of the middle of the body of the caudate nucleus. The anterior border of DLPFC and VLPFC was the superior frontal sulcus, and the posterior border was the inferior frontal sulcus. The inferior border of VLPFC was the level directly above the eyes, where the frontal cortex takes on a convex form unlike its concave appearance in the lower planes. The superior border of the DLPFC was at the level of the middle of the body of the cingulate gyrus. The ventral striatum was drawn in eight planes

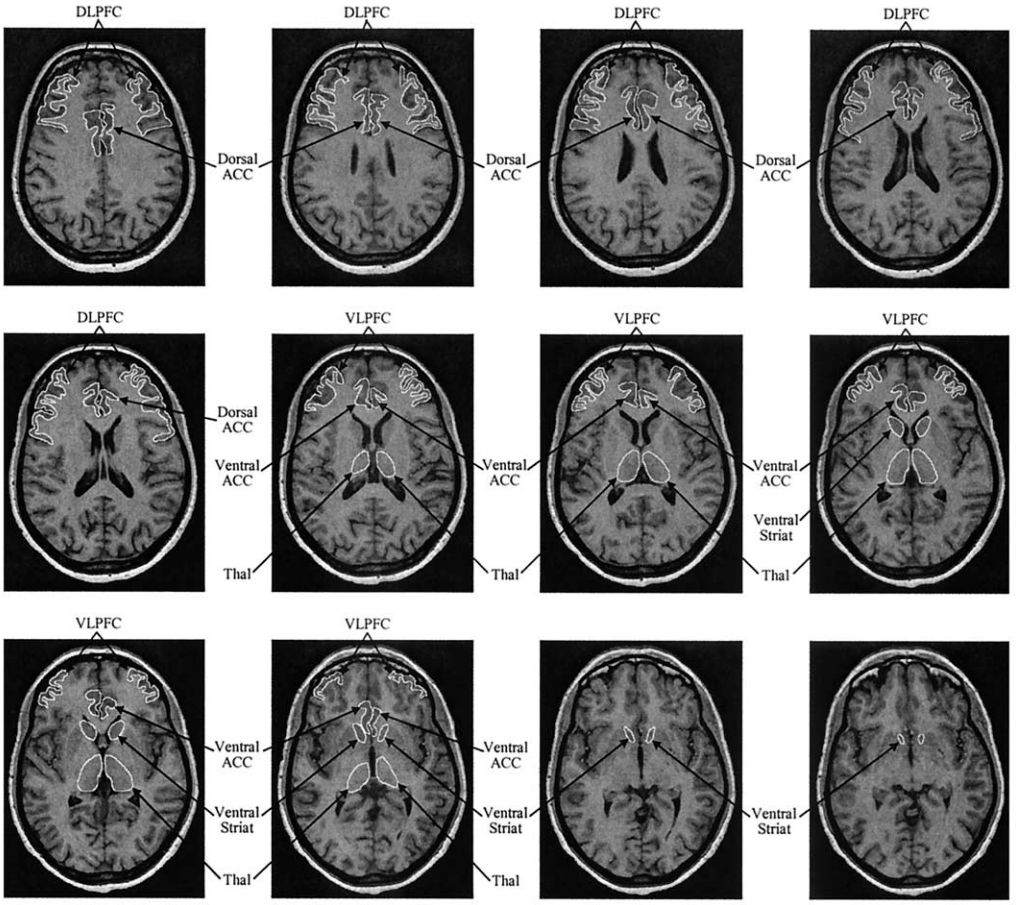

Figure 1. Regions of interest drawn on magnetic resonance images of a study subject. DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; Dorsal ACC, dorsal anterior cingulate cortex; Ventral ACC, ventral anterior cingulate cortex; Striat, striatum; Thal, thalamus.

and consisted of the ventral half of the head of caudate nucleus/nucleus accumbens. The entire thalamus was drawn in 12 planes. Supratentorial whole brain was also drawn in approximately 40 planes so that ratios of ROI to global volume could be determined.

For each ROI, volume was determined by multiplying the area of each drawn region (mm^2) by the MRI slice thickness (1.5 mm) and summing the volumes of all slices. Region of interest volumes were then divided by whole brain volumes to determine the ratio ROI/global (normalized ROI value) for use in statistical analysis. The distribution and variance of all normalized ROI values were examined and determined to be suitable for parametric analyses.

Voxel-Based Morphometry

The standard method of VBM was performed to determine group differences in regional gray matter density (Ashburner and Friston 2000). To prepare images for VBM, skull stripping was first performed with the use of an automated algorithm from the MEDx 3.3 software program (Sensor Systems, Sterling, Virginia). Statistical parametric mapping (SPM99) was then used to spatially normalize all images to a standardized template obtained from the developers of SPM. Images were then partitioned into gray matter, white matter, and cerebrospinal fluid, with the gray matter partitions being used for analysis (Ashburner and Friston 1997). The SPM option for inhomogeneity correction was applied, along with a 12-mm full width half maximum smoothing kernel and proportional scaling for statistical analysis.

Statistical Analyses

Means (± SDs) were determined for clinical variables of interest and for normalized ROI values. Percent differences in normalized ROI value between smokers and nonsmokers were calculated as the difference between normalized ROI values for the groups divided by the mean normalized ROI value of the groups × 100.

For the ROI analysis, an overall multivariate analysis of covariance (MANCOVA) was performed for the six regions of interest bilaterally, with normalized ROI values used as the dependent variables, smoking status (smoker vs. nonsmoker) as a between-subjects factor, and age and gender as covariates (because of the known effects of these variables on regional brain volumes, as cited above). Based on the MANCOVA results, univariate ANCOVAs were performed for individual ROIs, with the same between-subjects factor and covariates as above, to determine which regions accounted

for the overall significant group difference. Alpha levels were set at $p < .05$ (two-tailed).

A statistical analysis similar to the ROI analysis was performed with VBM (using SPM99) to explore the whole brain for differences in regional gray matter density between smokers and nonsmoking control subjects. The "compare groups" SPM option was used, with age and gender as nuisance covariates, to directly determine regions in which smokers and nonsmokers differed in gray matter density. A statistical threshold of $p < .001$, uncorrected for multiple comparisons, was used for voxels of peak significance, along with a minimum extent threshold of 50 contiguous voxels.

Results

The smoker and nonsmoker groups were similar in age (mean 39.5 ± 10.3 vs. 37.9 ± 12.9 years, respectively), gender (42.1% vs. 41.2% female), ethnicity (74% vs. 64% Caucasian), handedness (0% vs. 6% left-handed), and HAM-D (mean 2.0 ± 2.7 vs. 1.2 ± 1.7) and HAM-A (2.4 ± 2.3 vs. 1.6 ± 1.8) scores. Smokers had higher exhaled carbon monoxide levels (18.3 ± 7.1 vs. 1.9 ± .7 parts per million (ppm), Student t test, $p = 7.1 \times 10^{-9}$), and FTND scores (5.1 ± 1.9 vs. 0 ± 0, Student t test, $p = 6.5 \times 10^{-13}$) than nonsmokers. Smokers smoked an average of 26.2 ± 7.4 cigarettes per day (range, 20–40) and had a mean 31.0 ± 17.9 pack-year smoking history (range, 9–70).

In the overall MANCOVA in which normalized ROIs were used, a significant effect of smoking status was found [$F(12,21) = 3.0$, $p = .013$]. Analyses of covariance performed for individual ROIs revealed that the left DLPFC [$F(1,32) = 6.1$, $p = .019$], left and right VLPFC [$F(1,32) = 8.1$, $p = .008$ and $F(1,32) = 8.9$, $p = .005$, respectively], and left dorsal ACC [$F(1,32) = 4.6$, $p = .039$] had significant between-group differences, indicating that smokers had smaller PFC and left dorsal ACC gray matter volumes than nonsmokers (Table 1). For the DLPFC, smokers had a mean 15.7% smaller normalized gray matter volume on the left and 11.9% on the right. For the VLPFC, smokers had a mean 19.2% smaller gray matter volume on the left and 21.2% on the right. The left dorsal ACC was 18.5% smaller in smokers than nonsmokers. The remaining regions did not have significant between-group differences.

In the VBM analysis, gray matter density was lower in smokers than in nonsmokers in the prefrontal cortices (primarily the bilateral DLPFC but also the left VLPFC) (Table 2 and Figure 2) and also the right medial cerebellum. Not only did a group of voxel clusters pass the predetermined threshold for significance, but clusters in both the left and right DLPFC contained voxels that were significant after the Bonferroni-type correction within the SPM program ($Z = 6.66$, x, y, z = −32, 40, 36, $p = .006$; and $Z = 6.19$, x, y, z = 24, 42, 32, $p = .017$, corrected for multiple comparisons, for the left and right, respectively). There were no regions of gray matter density significantly higher in smokers than in nonsmokers.

As a follow-up to these central study findings, we performed a preliminary analysis to determine associations between pack-year smoking history and regional gray matter volume and density for regions found to be significant in the preceding analyses, while recognizing that this analysis would be limited by a smaller sample size. For the four ROIs found to have significant between-group differences in the above analysis, none had significant Pearson correlation coefficients with pack-year smoking history (all p values ≥ .46). For the VBM analysis of main effect of pack-year smoking history on regional gray matter density, the left ($Z = 5.38$, x, y, z = −54, 14, 26, $p < .0005$, 300 voxels) and right ($Z = 6.06$, x, y, z = 42, 14, 44, $p < .0005$, 371 voxels) prefrontal cortices had clusters of voxels with negative main effects of pack-year smoking history (according to the above significance criteria), indicating that greater pack-year smoking history was associated with lower gray matter densities in these regions.

Table 1. Comparison of Normalized Regions of Interest Values (ROI/Global) between Smokers and Nonsmokers

Region of Interest	Smokers (Mean ± SD)	Nonsmokers (Mean ± SD)	*F* Value (Smoking Status)
DLPFC			
L	9.2 (± 1.6)	10.7 (± 2.1)	6.1[a]
R	9.4 (± 1.8)	10.5 (± 1.8)	3.5
VLPFC			
L	4.4 (± .9)	5.4 (± 1.1)	8.1[b]
R	4.2 (± 1.0)	5.2 (± 1.0)	8.9[b]
DACC			
L	2.7 (± .5)	3.2 (± .9)	4.6[a]
R	2.8 (± .6)	3.0 (± .7)	.3
VACC			
L	2.0 (± .4)	2.2 (± .7)	1.7
R	2.1 (± .4)	2.4 (± .6)	2.4
Ventral Striatum			
L	1.2 (± .2)	1.1 (± .1)	.8
R	1.2 (± .2)	1.2 (± .2)	.1
Thalamus			
L	6.6 (± .9)	6.5 (± .8)	.3
R	6.8 (± .9)	6.7 (± .9)	.1

Actual ROI/global values are values cited in table × 10^{-3}. DLPFC, dorsolateral prefrontal cortex; L, left; R, right; VLPFC, ventrolateral prefrontal cortex; DACC, dorsal anterior cingulate cortex; VACC, ventral anterior cingulate cortex.

[a] $p < .05$ by analysis of covariance.

[b] $p < .01$ by analysis of covariance.

Discussion

In this study, smokers had smaller relative cortical gray matter volumes and lower gray matter densities than nonsmokers in the prefrontal cortices (DLPFC and VLPFC). Smokers also had smaller left dorsal ACC volumes and lower right cerebellar gray

Table 2. Coordinates of Peak Voxels Identified by Voxel-Based Morphometry as Having Lower Gray Matter Densities in Smokers than in Nonsmokers

Region	*Z* Score	Coordinates x	y	z	Cluster Size (No. Voxels)
Prefrontal Cortex					
Right	6.19	24	42	32	186
	4.75	16	50	32	
	3.49	8	62	28	
	4.46	34	6	48	162
	4.36	20	34	52	
	3.68	32	18	54	
Left	6.66	−32	40	36	233
	5.06	−52	30	16	50
Cerebellum					
Right	3.69	16	−56	−26	50

$p < .001$, $Z > 3.39$, uncorrected; 50 voxel minimum extent.

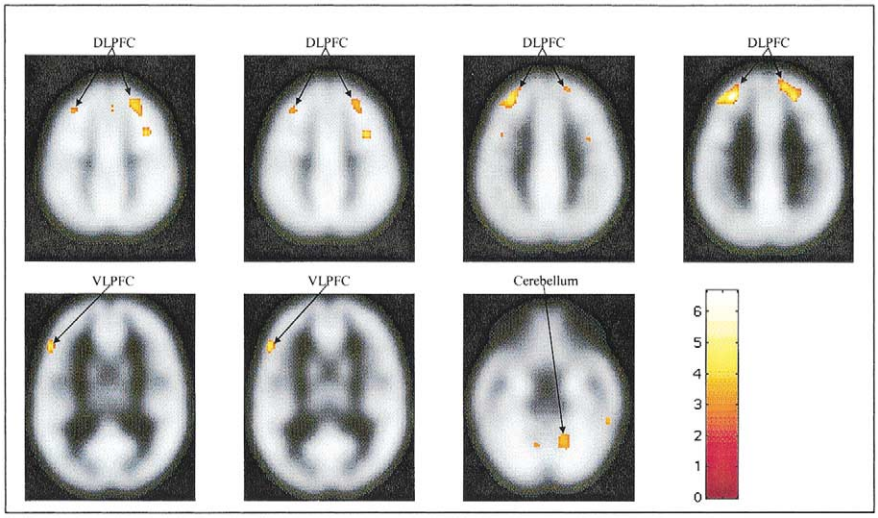

Figure 2. Voxel-based morphometry findings showing brain regions with lower gray matter density in smokers than nonsmokers. Voxels are shown that have significant between-group differences at $p < .001$, uncorrected, after applying age and gender as nuisance covariates. DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex.

matter densities than nonsmokers. No regions were significantly larger or had significantly higher gray matter densities in smokers compared with nonsmokers. The smoker group also had an association between greater pack-year smoking history and lower prefrontal cortical gray matter density.

Differences between groups in PFC gray matter volume and density might be related to direct effects of cigarettes (Nakamura et al 2000; Stein et al 1998) or cigarette cue exposure (Due et al 2002), predisposing factors that contribute to the development of nicotine dependence (Ernst et al 2001; Mitchell 1999; Spilich et al 1992; Waldeck and Miller 1997), or some combination of these factors. As for the possibility that cigarettes and cigarette cue exposure lead to the group differences found here, nicotine-dependent subjects in this study had between a 9 and 70 pack-year smoking history, meaning that even the lowest pack-year smoking history subject in our study had smoked tens of thousands of cigarettes and been exposed to cigarette-related cues many times before brain scanning. Thus, smoking experience represented a substantial difference between groups, lending support for the theory that smoking (and cigarette cue) exposure might have caused the significant PFC (and other) volume and density differences found here. Animal work supports this theory, with studies of nicotine administration in adolescent rodents resulting in both loss of neurons and changes in nicotinic receptor concentration in the cerebral cortex (Slotkin 2002). The preliminary association found here between greater pack-year smoking history and lower PFC gray matter density strengthens this theory.

As for predisposing factors that might be associated with lower regional brain gray matter in the PFC, prospective and cross-sectional studies of associations between personality traits and smoking indicate that smokers have higher rates than nonsmokers of impulsivity (Mitchell 1999; Waldeck and Miller 1997), neuroticism (Byrne et al 1995; Hu et al 2000), extraversion (Patton et al 1997; Sieber and Angst 1990), antisociality (Barry et al 1997; Patton et al 1997; Reitsma-Street et al 1985), and novelty seeking (Howard et al 1997; Masse and Tremblay 1997). Evidence for these personality traits being associated with smaller PFC volumes is mixed, with behavioral studies indicating PFC function deficits in impulsive individuals (Brower and Price 2001) and MRI studies of antisocial personality indicating smaller prefrontal cortical volumes (Raine et al 2000) but MRI studies of neuroticism (Knutson et al 2001) and impulsivity (Dolan et al 2002) indicating no association of these personality traits with PFC volumes.

The finding of smaller mean left dorsal ACC volumes in smokers might also be related to activation of this region by chronic smoking (Stein et al 1998) or cigarette cue (Brody et al 2002) exposure, or preexisting differences between smokers and nonsmokers. As noted above, smoking leads to changes in behavioral states associated with ACC function, such as improvements in reaction time (Hatsukami et al 1989; Pritchard et al 1992; Shiffman et al 1995), arousal (Parrott and Kaye 1999), motivation (Powell et al 2002), and sustained attention (Rusted et al 2000). Thus, this region might be stimulated repeatedly by smoking or smoking cues, or might be dysfunctional in some individuals (predisposing them to develop nicotine dependence). Furthermore, the fact that the dorsal ACC subregion was significantly smaller in smokers is not surprising. This subdivision is activated during cognitive/motor tasks, such as the Stroop (Whalen et al 1998), whereas smoking history is associated with diminished cognitive flexibility (Kalmijn et al 2002) and functioning (Cervilla et al 2000; Elwood et al 1999; Schinka et al 2002) and reduced psychomotor speed (Kalmijn et al 2002). The cerebellar finding was unexpected, but at least one prior imaging study (Domino et al 2000) did find relative cerebellar activation (in a region overlapping with the one found here) in response to nicotine administration, perhaps indicating chronic stimulation of this region as well.

The findings in this report might aid in the interpretation of studies of brain structure and tissue composition in populations with high rates of nicotine dependence. For example, subjects with depression (Breslau 1995, Breslau et al 1998; de Leon et al 1995, 2002; Glassman et al 1990; Lasser et al 2000), schizophrenia (de Leon et al 1995, 2002; Herran et al 2000; Hughes et al 1986), and other substance dependencies (Bobo 1989; Breslau 1995; Lasser et al 2000) have rates of nicotine dependence much higher than those of the general population. Magnetic resonance imaging studies of these illnesses (Ananth et al 2002; Coffey et al 1993a, 1993b; Fein et al 2002a, 2002b; Hulshoff et al 2002; Kumar et al 1997; Pfefferbaum et al 1998; Suzuki et al 2002) have reported reduced prefrontal cortical gray matter compared with normal control subjects, but they did not focus on the potential confounding role of nicotine dependence. If future prospective studies show that nicotine dependence causes reductions in gray

matter, such findings will point to the need to control for nicotine dependence in studies of these illnesses.

The central limitations of this study were a modest sample size and the absence of sequential MRI scans. A larger, longitudinal study would allow for evaluation of whether volumetric differences between smokers and nonsmokers reflect a biological predisposition to smoking, an effect of smoking, or some combination of these factors. Another limitation is the degree of psychometric characterization of study subjects, which could provide more detail about the complex interplay between smoking, cognitive function, personality characteristics, and regional brain volumes.

Despite these limitations, the present study had several strengths, including the use of relatively stringent thresholds for significance, and similarities in study findings with the use of two independent methods of MRI analysis. Our results indicate significant regional gray matter volume and density differences between smokers and nonsmokers, a potentially important association with smoking behavior that has not yet been widely studied.

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