Reduced Thickness of Medial Orbitofrontal Cortex in Smokers

Simone Kühn, Florian Schubert, and Jürgen Gallinat

Background: Structural deficiencies within the prefrontal cortex might be related to drug-taking behavior that prevails in smokers. Cortical thickness has been found to be a structural modulator of cerebral function and cognition and a subtle correlate of mental disorders. However, to date an analysis of cortical thickness in smokers compared with never-smokers has not been undertaken.

Methods: We acquired high-resolution magnetic resonance imaging scans from 22 smokers and 21 never-smokers and used FreeSurfer to model the gray-white and pial surfaces for each individual cortex to compute the distance between these surfaces to obtain a measure of cortical thickness. The main cortical folds were aligned across individuals with FreeSurfer's surface-based averaging technique to compare whole brain differences in cortical thickness between smokers and never-smokers.

Results: Relative to never-smokers, smokers showed greater cortical thinning in the left medial orbitofrontal cortex (mOFC). Cortical thickness measures extracted from mOFC correlated negatively with the amount of cigarettes consumed/day and the magnitude of lifetime exposure to tobacco smoke.

Conclusions: The brains of smokers are structurally different from those of never-smokers in a dose-dependent manner. The cortical thinning in mOFC in smokers relative to never-smokers might imply dysfunctions of the brain's reward, impulse control, and decision-making circuits. Related behavioral correlates are suggested to be relevant for smoking initiation and maintenance.

Key Words: Addiction, cortical thickness, orbitofrontal cortex, smoking, nicotine, substance dependence

Worldwide cigarette smoking is a highly prevalent substance-dependence and the leading cause of early preventable deaths in developed countries (1). Magnetic resonance imaging studies have associated tobacco smoking with large-scale structural brain abnormalities. In a study on elderly individuals, smoking has been linked to sulcal as well as ventricular grade and general atrophy (2,3). Moreover, smoking history has been associated with periventricular white matter abnormalities (2,4). More recent studies explored structural differences between smokers and nonsmokers, focusing on regional gray matter (and white matter) volumes as well as densities with voxel based morphometry (VBM) (5–8). Overall they found smaller gray matter volumes and densities for smokers. Gazdzinski *et al.* (8) showed a reduction in parietal and temporal gray matter, which is in line with findings of Durazzo *et al.* (6), reporting smaller temporal, parietal, and neocortical gray matter volume among smokers who were heavy drinkers. By contrast, two studies reported by Gallinat *et al.* (7) and Brody *et al.* (5) found structural deficiencies in anterior cingulate cortex and bilateral prefrontal cortex, next to a multitude of other brain areas.

However, VBM has been shown to be sensitive to a combination of changes in gray matter thickness, intensity, cortical surface area, and cortical folding (9,10). Moreover, VBM is especially susceptible to the degree of smoothing, differences in registration, and choice of normalization template (11,12). Therefore, surface-based morphology analysis has been proposed to assess the contributions of gray matter thinning independently of regional surface area (10). Cortical thickness has previously been found to be associated with normal aging, intelligence, cognitive performance, and mental disorders and is suggested to be a more sensitive parameter with a higher signal-to-noise ratio compared with VBM (9,13–15). Moreover, cortical thickness measures might be easier to interpret than the probabilistic gray matter volumes in VBM (16). In a study by Hutton *et al.* (9) cortical thickness has been shown to provide a more sensitive measure of age-associated decline, compared with the gray matter volume measure typically used in VBM studies. Therefore, cortical thickness might be a more appropriate measure when trying to assess drug-related changes.

We are not aware of any previous studies focusing on regional cortical thickness in smokers compared to nonsmokers. The only related study assessing cortical thickness measures in smokers explored prenatal exposure to maternal cigarette smoking (17). The authors demonstrate that in adolescents with prenatal exposure the likelihood of drug experimentation correlates with thinning of the orbitofrontal cortex (OFC), whereas in nonexposed adolescents OFC thickness is increased with the number of drugs tried. These results, seen in the light of previous studies on various drugs of abuse that have demonstrated structural abnormalities related to OFC (18–20), lead us to suspect that the OFC might be affected by smoking-related structural changes. The current study focuses on possible alterations in cortical thickness in a sample of subjects without mental or medical disorder.

Methods and Materials

Participants

Forty-three subjects, 22 smokers and 21 never-smokers, were recruited by means of newspaper advertisements. Never-smokers were naive with respect to tobacco consumption. Demographic and smoking data of the participants are given in Table 1. All subjects were free of medical, neurological, and psychiatric disorders—according to personal interviews (Mini-International Neuropsychi-

From the Faculty of Psychology and Educational Sciences (SK), Department of Experimental Psychology and Ghent Institute for Functional and Metabolic Imaging, Ghent University, Ghent, Belgium; Institute of Cognitive Neuroscience (SK), Department of Psychology, University College London, London, United Kingdom; Physikalisch-Technische Bundesanstalt (FS); and St. Hedwig Krankenhaus (SK, JG), Clinic for Psychiatry and Psychotherapy, Charité University Medicine, Berlin, Germany.

Address correspondence to Simone Kühn, Dr., Department of Experimental Psychology, Ghent University, Henri Dunantlaan 2, 9000 Ghent, Belgium; E-mail: simone.kuhn@ugent.be.

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Table 1. Demographic Characteristics of Smokers and Never-Smokers Studied

	Smokers ($n = 22$)	Never-Smokers ($n = 21$)
Age	31.3 ± 7.8	30.9 ± 8.2
Gender (Female/Male)	14/8	11/10
Cigarettes/Day	13.4 ± 8.8	0
Alcoholic Drinks/Week	3.0 ± 3.2	2.7 ± 2.7
Pack-Years	12.1 ± 13.2	
Fagerström Test for Nicotine Dependence	2.8 ± 1.8	
Age at Start of Smoking, Yrs	16.5 ± 1.9	
Years of Smoking	13.7 ± 8.1	

atric Interview) (21) carried out by a psychiatrist. Control subjects with a family history (first-degree) of axis I disorder were excluded from participation. In addition, exclusion criteria for all subjects were abnormalities in magnetic resonance imaging, general medical disorders, or any clinically relevant abnormalities. Smoking behavior was determined by a questionnaire specifically designed for this purpose (22). All procedures of this study were approved by the ethics committee of the Charité University Medicine Berlin. After complete description of the study to the subjects, informed written consent was obtained from all participants.

Scanning Sequence

Magnetic resonance measurements were carried out on a 3-T scanner (MEDSPEC 30/100, Bruker Biospin, Ettlingen, Germany). The T1-weighted images were acquired with modified driven equilibrium Fourier transform (with echo time = 3.8 msec; repetition time = 20.53 msec; inversion time = 550 msec; nominal flip angle 30°; 128 contiguous slices, 1.5-mm thick; 1-mm in-plane [x–y] resolution).

Data Analysis

Cortical thickness was estimated from the structural magnetic resonance images with FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/) (23, 24), a set of automated tools for reconstruction of brain cortical surface (25).

The segmentation results of FreeSurfer in the hippocampus have been shown to be highly correlated with manual tracings (26). Moreover, there is evidence that differences of approximately .2 mm in cortical thickness are detectable with seven subjects/group and differences in the range of .1 with 26 subjects (27).

First, we used the T1-weighted images to segment cerebral white matter (23) and to estimate the gray-white matter interface. Then, topographical defects in the gray-white estimate were fixed. This gray-white matter estimate was used as the starting point of a deformable surface algorithm searching for the pial surface. The whole cortex of each individual subject was visually inspected for inaccuracies in segmentation and manually corrected if necessary. Interventions were required at the temporal pole only. Local cortical thickness was measured on the basis of the difference between the position of equivalent vertices in the pial and gray-white matter surfaces. The surface of the gray-white matter border was inflated, and differences between subjects in the depth of gyri and sulci were normalized. The reconstructed brain of each subject was morphed and registered to an average spherical surface (24).

To obtain cortical thickness difference maps, the data were smoothed on the surface with a Gaussian smoothing kernel with a full-width half maximum of 10 mm. Statistical thickness difference maps were constructed with *t* statistics. We used a general linear model focusing on the main effects of group (smokers vs. never-smokers), controlling for age and gender. Monte Carlo permutation cluster analysis was then performed to correct for multiple comparisons with a cluster threshold of .05; only the surviving cluster is shown.

A region of interest comprising the brain region observed in the whole brain analysis was defined. The average thickness within this region of interest in each subject was subjected to a Pearson product-moment correlation with the reported current amount of cigarettes smoked/day and the magnitude of lifetime exposure to tobacco smoke.

Results

There were no significant differences in age, gender, or alcoholic drinks/week between smokers and never-smokers ($p > .46$) (Table 1).

When computing a whole brain analysis to find differences in cortical thickness between smokers and never-smokers (controlling for age and gender), we found a significant reduction of cortical thickness in the left medial orbitofrontal cortex (mOFC) (−2.5, 26, −20, Talairach coordinates (28) (Figure 1) with an effect size of 1.14 on the basis of Cohen's d (29). There were no regions of significantly increased cortical thickness in never-smokers compared to smokers when using the same thresholding.

Relating cortical thickness in mOFC to the self-reported current amount of cigarette consumption/day revealed a significant negative correlation ($r = -.55$, $p < .001$). This correlation was also present in smokers only ($r = -.51$, $p < .02$) and when controlling for age (partial correlation: $r = -.55$, $p < .001$, partial correlation only on smokers: $r = -.47$, $p < .05$) (Figure 2). Similarly mOFC cortical thickness correlated negatively with the magnitude of lifetime exposure to tobacco smoke (pack-years) ($r = -.52$, $p < .001$; only on smokers: $r = -.53$, $p < .02$; partial correlation controlling for age: $r = -.52$, $p < .001$, partial correlation controlling for age only on smokers: $r = -.47$, $p < .05$) (Figure 3). These correlations were still significant when controlling for the variable alcoholic drinks/week and when excluding the subject with the highest tobacco consumption.

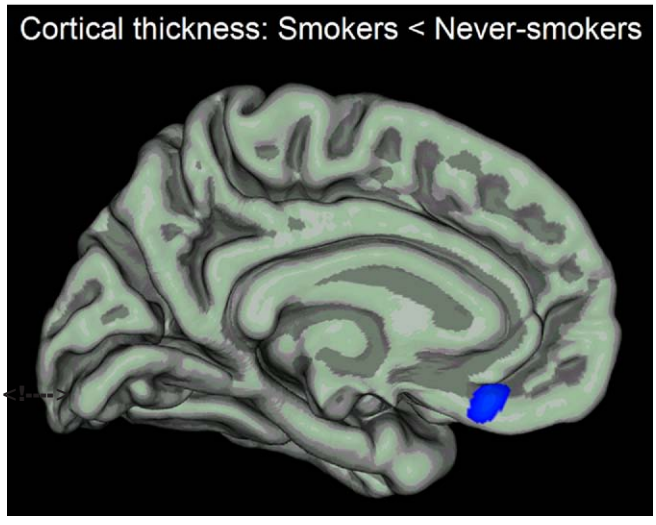

Figure 1. Composite pial representation of the statistically significant cluster of cortical thickness reduction in the left medial orbitofrontal cortex (−2.5, 26, −20) in smokers compared with never-smokers (*p* values corrected for multiple comparisons, $p < .05$).

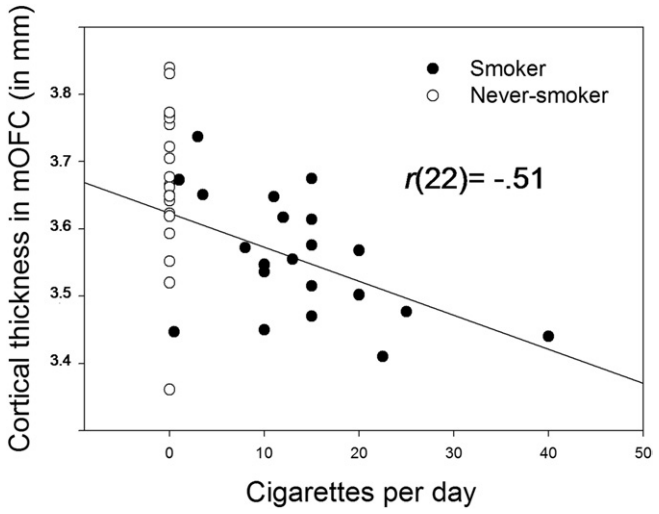

Figure 2. Scatter plot of cortical thickness values extracted from medial orbitofrontal cortex (mOFC) and self-reported current number of cigarettes smoked/day ($r = -.55$, $p < .001$; correlation only on smokers $r = -.51$, $p < .02$; regression line depicted only for smokers).

Discussion

The present study demonstrates a difference in cortical thickness between smokers and never-smokers in the left mOFC. This focal decrease of approximately 3% in cortical thickness was inversely correlated with the current number of cigarettes consumed/day and smoking history, namely the self-reported magnitude of lifetime exposure to tobacco smoke, showing that heavier smoking is associated with more pronounced thinning of gray matter in mOFC. This correlation persists when controlling for weekly alcohol intake. We cannot deduce whether the effect can be attributed to a direct effect of nicotine intake, as is generally the case in studies focusing on structural differences between addicts and nonaddicts. With a correlational approach we cannot rule out that the observed differences between smokers and never-smokers are preconditions that make smokers more vulnerable to become addicted to cigarettes and that keep never-smokers from developing a smoking habit.

The structural differences in gray matter thickness in the mOFC are in line with previous findings that have reported smaller gray matter volumes and densities in smokers compared with nonsmokers (5–8). Our results are particularly in line with the reported differences in prefrontal cortex (5,7). A striking difference from the previous, more-widespread VBM findings is the focality of the cortical thinning, which might be due to a higher sensitivity and specificity of the cortical thickness measure compared with gray matter volume or density (9). Especially these previously observed global structural effects might in part be attributable to cardiovascular effects, because it has been shown that coronary heart diseases increase with smoking (30). In contrast, the focused difference in mOFC in our relatively young and only moderately nicotine-dependent population could be more specific to the direct effects of tobacco use.

The OFC, in particular, has been frequently implicated in addiction to various kinds of drugs for several reasons.

First, several studies on structural deviations in addictions to illegal drugs have implicated abnormalities in OFC. Anatomically, the OFC is a heterogeneous region that has connections with other prefrontal, limbic, sensory, and premotor areas (31) and is linked to the mesolimbic dopamine system that is critical for drug reward (32); therefore it might be prone to be affected by structural changes. Indeed, Tanabe *et al.* (20) reported selective mOFC volume reduction in multisubstance-dependent individuals after prolonged abstinence. This is in line with findings that cocaine addicts show gray matter changes in volume and cortical thickness in OFC (18,19). The laterality of the reported findings is not conclusive. In line with the present finding, Tanabe *et al.* (20) report changes in mOFC with the peak being in the left hemisphere, whereas the findings of Makris *et al.* (19) stress a right hemispheric difference, and Franklin *et al.* (18) report bilateral changes. Moreover, self-administration of amphetamine in rats has been shown to be related to decreased spine density in OFC (33). Our finding of reduced cortical thickness in the mOFC of smokers fits well into these findings on illegal drug addiction.

Second, persistent metabolic and/or neurochemical changes in OFC have been demonstrated in drug addicts (34,35). Acute administration of nicotine during brain imaging in humans has been reported to elicit changes in activation in various brain regions, including anterior cingulate cortex, inferior frontal gyrus, temporal cortex, posterior cingulate gyrus, visual cortex, cerebellum, pons, thalamus, nucleus accumbens, amygdala, and hippocampus (36–39). However, only one study mentions effects on mOFC in smokers, namely when smoking the first cigarette of the day after overnight abstinence (40). This can only be considered as weak evidence in favor of the observed cortical thickness change being a consequence of smoking.

Third, functional imaging studies demonstrated activation of OFC together with other limbic areas when addicted subjects were exposed to stimuli associated with the abused drug. This has been demonstrated for smoking-related stimuli in smokers (41–46) as well as for other drugs of abuse (e.g., cocaine) (47,48). These findings could imply that mOFC cortical thinning is rather a consequence of smoking then a predisposition for addiction.

Fourth, the compulsive drug-seeking behavior often observed in addicts and the persistence of it despite known negative outcomes bears resemblance to the behavior of individuals with damage to the OFC. Those frontal lobe lesions have been associated with a lack of impulse control and a tendency for delay discounting (devaluation of rewards as a function of delay) as well as risky decision-making (49,50). Moreover, impulsiveness has been shown

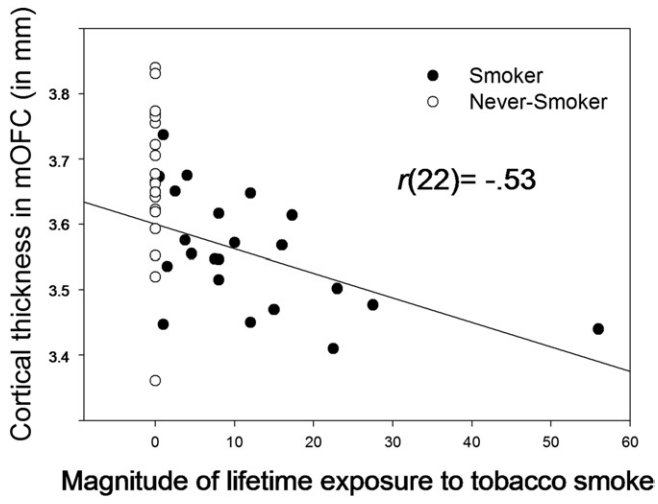

Figure 3. Scatter plot of cortical thickness values extracted from medial orbitofrontal cortex (mOFC) and self-reported magnitude of lifetime exposure to tobacco smoke (pack-years) ($r = -.52$, $p < .001$; correlation only on smokers $r = -.53$, $p < .02$; regression line depicted only for smokers).

to be inversely related to OFC volume (51). Smokers have been shown to score higher on impulsiveness measures and to show signs of disinhibition, in line with the idea of deficiencies in OFC due to nicotine intake (52–55). Furthermore, smokers have been demonstrated to be more prone to delay discounting, which is broadly accepted as a measure of impulsiveness (56–59). In the domain of risk-taking, smokers have been shown to perform poorly in gambling tasks (60–62), but there is at least one study that does not show this association (63).

But we found no significant correlations between cortical thickness in left mOFC and measures of interindividual differences (impulsivity [64]; sensation seeking [65]; NEO Five-Factor Inventory [66]; anxiety [67]; and depression, Beck Depression Inventory [68]).

Another function that has been associated with the integrity of OFC is sensitivity to reward and punishment and, in particular, the assignment of emotional valence to environmental stimuli that signal reward or punishment (69,70). Several studies have reported deficits in reward processing in smokers (71–73). Taken together, the observed changes in mOFC thickness might mediate these neurocognitive deviations commonly reported in smokers. Further research is needed to relate the structural changes in mOFC found in smokers to the behavior of subjects in, for example, gambling tasks.

In conclusion, we found a circumscribed thinning of mOFC in smokers compared with never-smokers that was inversely correlated with the amount of cigarettes smoked/day. This is to our knowledge the first study reporting cortical thickness data in this population. Contextualizing our results within previous studies on various drugs of abuse that have demonstrated structural, functional, and behavioral abnormalities related to OFC, we conclude that OFC is an important target of drug-induced structural changes, not only because of illegal drug use but also because of the most prevalent substance dependence: tobacco smoking.

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