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Research report

Voxelwise meta-analysis of gray matter anomalies in chronic cigarette smokers

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HIGHLIGHTS

- We performed meta-analyses of GM anomalies with 11 VBM studies in chronic smokers.
- Lower GM in the PFC and greater GM in the lingual cortex were observed.
- Clinical and demographic variables correlated with GM anomalies in chronic smokers.
- This study reveals a characteristic neuroanatomical pattern in chronic smokers.

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ABSTRACT

Background: Evidence from previous voxel-based morphometry (VBM) studies revealed that widespread brain regions are involved in chronic smoking. However, the spatial localization reported for gray matter (GM) abnormalities is heterogeneous. The aim of the present study was quantitatively to integrate studies on GM abnormalities observed in chronic smokers.
Methods: A systematic search of the PubMed, Web of Knowledge and Science Direct databases from January 1, 2000 to July 31, 2015 was performed to identify eligible whole-brain VBM studies. Comprehensive meta-analyses to investigate regional GM abnormalities in chronic smokers were conducted with the Seed-based *d* Mapping software package.
Results: Eleven studies comprising 686 chronic cigarette smokers and 1024 nonsmokers were included in the meta-analyses. Consistently across studies, the chronic smokers showed a robust GM decrease in the bilateral prefrontal cortex and a GM increase in the right lingual cortex. Moreover, meta-regression demonstrated that smoking years and cigarettes per day were partly correlated with GM anomalies in chronic cigarette smokers.
Conclusions: The convergent findings of this quantitative meta-analysis reveal a characteristic neuroanatomical pattern in chronic smokers. Future longitudinal studies should investigate whether this brain morphometric pattern can serve as a useful target and a prognostic marker for smoking intervention.

1. Introduction

Tobacco use causes serious health, economic and social problems and continues to be a major cause of preventable death throughout the world [1–3]. There is strong evidence that chronic tobacco use has toxic effects on the brain, and on cardiovascular and pulmonary systems [1,2,4,5]. Tobacco smoking in humans is one of the most persistent and widespread addictions. Nicotine in the cigarette is the main addictive ingredient that drives continued tobacco use despite users' knowledge of the harmful consequences [6]. Most disturbingly, dependence on tobacco smoking is still difficult to treat. Complex neural processes underlying tobacco smoking and smoking-induced neural changes have been increasingly recognized [5,7–10]. The mesocorticolimbic system plays a central role in various aspects of nicotine dependence, which is

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mediated by close interactions with glutamatergic, dopaminergic and γ-aminobutyric acidergic systems [8].

Although the effects of chronic tobacco smoking have been well studied in several model systems [8], the effects of chronic tobacco use on brain structures, especially on brain gray matter (GM) anomalies by the voxel-based morphometry (VBM) analysis, have not been fully elucidated. Despite promising preliminary findings across studies, the results are still rather heterogeneous [11–24]. For example, compared with nonsmokers, chronic smokers exhibited lower GM volume or density in the prefrontal cortices [12–14,16–18,20–23], the occipital cortices [12], the insular cortices [19,21–23], the olfactory gyrus [22], the subcortical regions including the amygdala [21], the thalamus [12,17,21,23], and the putamen [21], and the cerebellum [13,15,20,24]. Whereas greater GM or density was observed in the occipital cortex [21], the parietal cortex [23], the insula [14], the putamen [20,24], and the parahippocampus [20]. The discordance might be attributed to differences in clinical and demographic variables, and differences in the imaging protocols employed [12–24]. Thus, a qualitative and quantitative meta-analysis of these original studies to identify consistent or robust GM changes as a common marker in chronic tobacco smokers is of particular importance.

One preliminary meta-analysis of 7 VBM studies completed before April 2012 used the effect-size signed differential mapping tool [25] to demonstrate that GM atrophy in the left anterior cingulate cortex (ACC) was a common structural abnormality in chronic smokers compared to nonsmokers [26]. In recent years, many other original studies with larger samples have addressed the issue. In addition, the statistical technique for meta-analysis of neuroimaging studies have been updated to new version called Seed-based *d* Mapping (SDM). The new version SDM allows for more exhaustive and accurate meta-analyses by using anisotropic kernels during the recreation of the effect size maps to account for the anisotropy in the spatial covariance in addition to combining both peak coordinates and statistical parametric maps [27,28]. A previous meta-analysis [26] did not examine the influence of confounding variables that might lead to heterogeneity in brain GM changes associated with chronic smoking, such as smoking years and cigarettes per day. To overcome these deficits and establish a consistent and reliable GM map in a population of chronic smokers, we performed a more comprehensive meta-analysis by identifying and integrating more recent VBM studies using the newly developed SDM technique. Thus, our meta-analysis is the most current. The findings could advance our understanding of the neuroanatomical substrates of chronic smoking and the pathophysiological mechanisms underlying nicotine dependence, which may help to identify potential targets for smoking cessation interventions.

2. Methods

2.1. Literature search and selection

Systematic and comprehensive searches were conducted in the PubMed, Web of Knowledge and Science Direct databases from January 1, 2000 to July 31, 2015 using a combination of the keywords "voxel*" or "VBM" or "morphometry" or "gray matter" or "grey matter" and "smoking" or "nicotine*" or "tobacco*" or "cigarette*" or "smokers". A manual search of the reference lists of the included studies and relevant scholarly reviews were evaluated for additional potential studies. Studies were included if the following criteria were met: (1) the patient group included chronic cigarette smokers or regular smokers without other substance abuse or dependence; (2) the VBM studies reported a voxelwise comparison between chronic smokers and nonsmokers for GM density or volume; (3) whole-brain results were presented in three-dimensional coordinates (x; y; z) for changes in standard stereotactic space; defined by either Talairach or Montreal Neurological Institute; (4) thresholds for significance were corrected for multiple comparisons or uncorrected with spatial extent thresholds; (5) the sample size in each group was more than 10; and (6) studies were peer reviewed and published in English as an article (not a letter or an abstract). If any two studies included the same or overlapping patients; the study with a larger sample size and more comprehensive data was selected. Studies were excluded if they had at least one of the following deficiencies: (1) sufficient data for the meta-analysis could not be obtained from the original article or after contacting the authors; (2) findings were based only on small volume correction (SVC); (3) the use of the regions of interest (ROI) methods; and (4) the use of a correlation approach to identify GM anomalies. Two authors (H.C. Shi and J.G. Zhong) independently performed the study selection and data extraction using a standardized form; and a third author (L.Q. Sheng) resolved any disagreements. The majority opinion was adopted for final analysis. Our study followed the guidelines of preferred reporting items for systematic reviews and meta-analyses (PRISMA) [29] (Fig. 1).

2.2. Statistical analysis

The meta-analyses were carried out using the SDM software package (http://www.sdm project.com/software/) to analyze VBM studies that investigated regional GM anomalies in chronic cigarette smokers compared to nonsmokers. The SDM methods have been fully validated and described in detail in many studies [25,27,28,30]. The data processing procedure is briefly summarized here (http://www.sdmproject.com/software/tutorial.pdf). First, coordinates of cluster peaks and effect-sizes (derived from e.g., t-values, or equivalently from p-values or z-scores) of GM differences between chronic tobacco smokers and nonsmokers were extracted from each data set according to SDM inclusion criteria. Second, a standard Montreal Neurological Institute (MNI) map of the differences in GM was separately recreated for each study using an anisotropic Gaussian kernel (FWHM = 20 mm), which assigns higher effect sizes to the voxels that were more correlated with peaks. It should be noted that this kernel is different in nature from the smoothing kernel that is used to smooth raw magnetic resonance images because the Gaussian kernel is not intended to smooth any image but rather is used to assign indicators of proximity to reported coordinates [25,30]. To consider the effect of age, we used the mean age of each sample as a covariate when conducting the analysis. Third, a map of the effect size of the variance was derived for each study from its effect size map and its sample size. Fourth, the mean map was obtained by a voxel-wise calculation of the random-effects mean of the study maps that were weighted by the sample size and variance of each study and the between-study heterogeneity. The statistical significance of the analyses was evaluated using standard randomization tests [25,30]. To confirm the findings, a more stringent threshold was set for the meta-analysis maps using a voxel-level threshold of $p < 0.001$ (uncorrected) and a cluster-level threshold of 10 voxels [26].

To determine whether the results remained significant and highly replicable or could be biased by small lenient studies, we performed a systematic, whole-brain, voxel-based jackknife sensitivity analysis by repeating a test as many times as studies have been included, discarding one different study each time, i.e., removing one study and repeating the analyses and subsequently placing that study back and removing another study and repeating the analysis. Similarly, a heterogeneity analysis was performed to determine whether there was significant unexplained between-study variability within the results [25,30].