Drug and Alcohol Dependence 129 (2013) 82–87

Contents lists available at SciVerse ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Heavy smokers show abnormal microstructural integrity in the anterior corpus callosum: A diffusion tensor imaging study with tract-based spatial statistics

Fuchun Lin[a], Guangyao Wu[b,*], Ling Zhu[b], Hao Lei[a,**]

[a] Wuhan Center for Magnetic Resonance, State Key Laboratory of Magnetic Resonance and Atomic and Molecular Physics, Wuhan Institute of Physics and Mathematics, Chinese Academy of Sciences, Wuhan 430071, PR China
[b] Department of Magnetic Resonance Imaging, Zhongnan Hospital, Wuhan University, Wuhan 430071, PR China

ARTICLE INFO

Article history:
Received 27 June 2012
Received in revised form
17 September 2012
Accepted 17 September 2012
Available online 11 October 2012

Keywords:
Anterior corpus callosum
Diffusion tensor imaging
Heavy smokers
Tract-based spatial statistics
White matter

ABSTRACT

Background: Abnormal macrostructural brain abnormalities in both gray matter and white matter have been reported in cigarette smokers. However, less is known about white matter microstructure in heavy cigarette smokers. In this study, we used diffusion tensor imaging (DTI) to investigate the integrity of the white matter microstructure in heavy smokers.
Methods: Thirty-four heavy smokers and 34 non-smokers participated in this study. Whole brain analysis of fractional anisotropy (FA) was performed using tract-based spatial statistics (TBSS) to detect abnormal white matter regions between groups. Volume-of-interest (VOI) analysis was used to investigate changes in diffusivity indices in the regions showing FA abnormalities. Multiple regression analysis was applied to assess the relationships between diffusion indices and smoking-related variables in heavy smokers.
Results: Compared with non-smokers, heavy smokers had lower FA in the left anterior (i.e., the genu and rostral body) corpus callosum while exhibiting no areas of higher FA. In the affected region, FA reduction was accompanied by a significantly decreased axial diffusivity and increased radial diffusivity, which suggests that axonal damage and disrupted myelin integrity may be associated with the degraded white matter integrity in heavy smokers. Moreover, significant positive correlations were found between both radial diffusivity and mean diffusivity and the duration of regular smoking.
Conclusions: Our findings suggest that heavy smokers demonstrate abnormal integrity of the white matter microstructure in the anterior corpus callosum, which is related to the duration of regular smoking. In addition, our study may increase the understanding of the neurobiological basis of chronic cigarette smoking.

1. Introduction

Cigarette smoking, a highly prevalent substance dependence, continues to be the leading cause of preventable illness and death worldwide (Danaei et al., 2009; Ezzati and Lopez, 2003; Warner and Mackay, 2006). There is strong evidence that chronic cigarette smoking is a risk factor for stroke, myocardial infarction, lung cancer, and respiratory diseases (Hallstrom et al., 1986; Kannel and Higgins, 1990). Epidemiological and neuropsychological studies also show that cigarette smoking has diverse effects on cognition and the brain (Fagerstrom, 2002; Schmitz et al., 2003; Swan and Lessov-Schlaggar, 2007). Although smoking has serious public health consequences, the effects of chronic smoking on human brain structure and function have not been fully elucidated.

Recent voxel-based morphometry (VBM) neuroimaging studies have sought to identify the effects of smoking on brain structure. These studies have found that smoking is associated with macrostructural brain abnormalities in both gray matter and white matter. Reduced gray matter density/volume was found in the prefrontal cortices, thalamus and cerebellum in smokers (Brody et al., 2004; Gallinat et al., 2006; Liao et al., 2010; Yu et al., 2011; Zhang et al., 2011). Increased white matter volume was reported in the putamen, anterior and middle cingulate cortices, and temporal lobes of smokers (Gazdzinski et al., 2005; Yu et al., 2011). Negative associations between gray matter density/volume in the prefrontal cortex and smoking history have been found in smokers (Brody et al., 2004; Gallinat et al., 2006; Zhang et al., 2011).

Diffusion tensor imaging (DTI) has been used to evaluate the white matter microstructural changes related to cigarette smoking. However, unlike the relatively consistent findings in the VBM studies, discrepancies exist in the literature with respect to DTI

* Corresponding author. Tel.: +86 27 6781 3187; fax: +86 27 6781 3188.
** Corresponding author. Tel.: +86 27 8719 8542; fax: +86 27 8719 9291.
E-mail addresses: wuguangy2002@yahoo.com.cn (G. Wu), leihao@wipm.ac.cn (H. Lei).

0376-8716/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.drugalcdep.2012.09.013

abnormalities in the brains of smokers and how such abnormalities relate to the history of smoking or to the extent of nicotine dependence. A recent study showed that highly nicotine-dependent smokers have reduced fractional anisotropy (FA) in the prefrontal white matter (Zhang et al., 2011), whereas other studies have reported increased FA in the prefrontal white matter, cingulum, genu of the corpus callosum (Hudkins et al., 2012), and fronto-parietal white matter tracts (Liao et al., 2011) in smokers. The FA values in the anterior cingulate cortex and prefrontal white matter were found to be negatively correlated with the degree of nicotine dependence or smoking history in smokers (Hudkins et al., 2012). The higher levels of FA in the white matter, despite negative correlations of FA with smoking-related parameters in smokers, were puzzling (Hudkins et al., 2012). The smokers were also shown to have significantly higher FA in the body and splenium of the corpus callosum, but they showed no change in the FA in the genu of the corpus callosum (Paul et al., 2008).

In this study, we employed DTI combined with tract-based spatial statistics (TBSS) analysis to further investigate how the integrity of white matter microstructure is affected in heavy cigarette smokers. The changes in axial and radial diffusivity in the white matter regions with abnormal FA in heavy smokers were also measured. The relationship between diffusion properties and smoking-related factors in heavy smokers was assessed.

2. Methods

2.1. Subjects

A total of sixty-eight subjects (34 heavy cigarette smokers and 34 healthy non-smoking control subjects) 33–58 years of age participated in this study. All subjects were right-handed as assessed by the Chinese version (Li, 1983) of the Edinburgh handedness inventory (Oldfield, 1971). All subjects were screened for psychiatric and non-psychiatric medical disorders using the mini international neuropsychiatric interview (Sheehan et al., 1998). All recruited participants were healthy and had no history of medical (e.g., cardiac disease) or neurological (e.g., stroke) disorders, mental retardation, drug abuse or dependence (other than nicotine dependence for the heavy smokers), or psychiatric diseases. None of the subjects reported daily consumption of alcohol, experiencing social consequences secondary to alcohol use, or any history with difficulty ceasing alcohol intake. Additional inclusion criteria for heavy smokers were as follows: they met the DSM-IV criteria for nicotine dependence, smoked at least 20 cigarettes per day for at least the past five years and had no period of smoking abstinence longer than 3 months in the past years. The severity of the heavy smokers' nicotine addiction was measured using the Fagerström test for nicotine dependence (FTND; Heatherton et al., 1991). Data concerning other smoking-related factors were also collected as needed. The controls in this sample had smoked no more than five cigarettes in their lifetime. The demographic information for subjects in each group is listed in Table 1.

The study was approved by the Medical Ethics Committee of Zhongnan Hospital of Wuhan University, and written informed consent was given by all participants after a complete description of the measurement and MRI scanning in the study.

2.2. Image acquisition

All subjects were examined using a 3.0-Tesla Siemens Trio MR scanner (Erlangen, Germany). A standard birdcage head coil was used, along with restraining foam pads to minimize head motion and diminish the sounds of the scanner. A single-shot, spin-echo echo-planar imaging technique with alignment of the anterior-posterior commissural plane was performed with the following parameters: repetition time = 6000 ms; echo time = 87 ms; acquisition matrix = 128 × 128 zero-filled to 256 × 256; field of view = 240 mm × 240 mm; slice thickness = 3 mm with no gap; slices = 45; number of repetitions = 4. The integral parallel acquisition technique was used with an acceleration factor of 2. The diffusion sensitizing gradients were applied along 12 non-collinear gradient encoding directions with $b = 1000\ \mathrm{s/mm^2}$, together with an acquisition without diffusion weighting ($b = 0\ \mathrm{s/mm^2}$).

2.3. Data processing

All DTI data were analyzed by the FMRIB's diffusion toolbox (FDT) within FMRIB's Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl). Each diffusion-weighted volume was first aligned to its corresponding non-diffusion-weighted (b_0) image to minimize the image distortion from eddy currents and to reduce simple head motion. The diffusion tensor for each voxel was then estimated by the multivariate linear fitting algorithm, and the tensor matrix was diagonalized to obtain its three pairs of eigenvalues (λ_1, λ_2, λ_3) and eigenvectors. The voxel-wise values of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (Da, Da = λ_1) and radial diffusivity (Dr, Dr = $(\lambda_2 + \lambda_3)/2$) were calculated. FA measures the directionality of water diffusion and the coherence of white matter fiber tracts, MD reflects the overall magnitude of water diffusion, Da quantifies the magnitude of diffusivity along the principal diffusion direction, and Dr measures the magnitude of diffusivity perpendicular to the principal diffusion direction (Basser and Pierpaoli, 1996). These measurements are related to the microstructural organization of the white matter and are often used to infer the structural characteristics of the local tissue environment (Le Bihan, 2003).

Voxel-wise whole brain analysis of FA images was performed by using TBSS, which is an observer-independent method to allow voxel-wise comparisons (Smith et al., 2006). In brief, FA maps of all subjects were normalized to the Montreal Neurological Institute (MNI) space. Then, the registered FA images were averaged to obtain a mean FA image. The mean FA image was applied to create a mean FA skeleton representing the main fiber tracts and the center of all fiber tracts. The mean FA skeleton was further thresholded at a value of 0.2 to exclude non-white matter tissue. Following this step, the aligned FA data for each subject were projected onto the mean skeleton to create a skeletonized FA map by searching the area around the skeleton in the direction perpendicular to each tract, finding the highest local FA value, and then assigning this value to the corresponding skeletal structure. After these steps, the skeletonized FA data were fed into the voxel-wise non-parametric statistical analysis to identify FA differences between groups. The testing was performed by the FSL randomise program, which uses 5000 random permutations (Nichols and Holmes, 2002). Age, gender and educational levels were entered into the analysis as covariates to ensure that any observed differences in FA between groups were independent of age-, gender- and education-related changes. The results were corrected at cluster level ($t = 2$) threshold at $p < 0.05$ corrected for multiple comparisons by controlling for family-wise error rate and were located by the JHU-ICBM-DTI-81 white matter labels atlas in MNI space.

To explore the mechanisms of FA changes, volume-of-interest (VOI) analysis was performed to investigate changes in diffusivity indices (Da, Dr and MD) in the regions with FA abnormalities. The VOI mask was first extracted based on the clusters showing inter-group FA differences using the FSL cluster program, and then back projected to the original images of each subject. The mean values of the diffusivity indices were calculated by the FSL fslmeants program. After confirming normal distribution of the data by a one-sample Kolmogorov–Smirnov test, one-way analysis of covariance with the group as the independent variable and diffusivity indices