

Abnormal anterior corpus callosum white matter integrity in heavy smokers revealed by tract-based spatial statistics

Fuchun Lin¹, Guangyao Wu², Shiqi Yang², Haopeng Peng², Prasanna Ghimire², Ling Zhu², Guobing Liu², and Hao Lei¹

¹State Key Laboratory of Magnetic Resonance and Atomic and Molecular Physics, Wuhan Institute of Physics and Mathematics, Chinese Academy of Sciences, Wuhan, China, People's Republic of, ²Department of Magnetic Resonance Imaging, Zhongnan Hospital, Wuhan University, Wuhan, China, People's Republic of

Introduction Results from recent neuroimaging studies suggest that cigarette smoking is associated with abnormal brain structure, function and metabolism [1-3]. Little is known about the impact of cigarette smoking on the integrity of the white matter of the brain. In this study, we used tract-based spatial statistics (TBSS) method combined with diffusion tensor imaging (DTI) to investigate the microstructural integrity of the white matter in heavy smokers.

Materials and Methods *Subjects:* Thirty-four heavy cigarette smokers (seven females; mean age 46.9±7.3; age range 35-58) and thirty-two nonsmokers (six females; mean age 47.9±8.2; age range 32-58) were recruited from the community by advertisements. All subjects were screened for psychiatric and non-psychiatric medical disorders using the structured clinical interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). The severity of nicotine addiction was assessed by the Fagerström test for nicotine dependence (FTND) that was translated into Chinese. All nonsmokers in this study never had a history of smoking. They had no history of any psychiatric or neurological diseases, had no other substances abuse and were not currently taking any medications. *Image acquisition:* DTI scans were performed with a 3.0-T Siemens Trio MR scanner with the following parameters: TR/TE: 6,000/87 ms; NEX: 4; matrix: 128×128 zero-filled to 256×256; FOV: 24 cm×24 cm; slice thickness: 3 mm without gap; 12 non-collinear gradient encoding directions with b=1000 s/mm². *Data analysis:* DTI data were processed using FDT within FSL (<http://www.fmrib.ox.ac.uk/fsl>). First, the diffusion-weighted images were aligned to the non-diffusion-weighted (b₀) image. Then, the diffusion tensor was estimated and the tensor matrix was diagonalized to obtain its three pairs of eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) and eigenvectors. And then voxel-wise values of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (Da, $Da=\lambda_1$) and radial diffusivity (Dr, $Dr=(\lambda_2+\lambda_3)/2$) were calculated. To identify FA differences between groups, the skeletonized FA data were fed into the TBSS analysis [4]. In brief, the FA maps were first normalized to the MNI space. Then, the registered FA images were averaged to generate a mean FA image, and the mean FA image was applied to create a mean FA skeleton image. The mean FA skeleton was further thresholded by a FA value of 0.2. Following this step, the registered FA data was projected onto the skeleton to create a skeletonized FA map. And then, the skeletonized FA data were fed into voxel-wise statistics analysis based on nonparametric permutation testing approach. The results were corrected at cluster level (t=2) threshold at a level of $p<0.05$ corrected for multiple comparisons. To explore the microstructural mechanisms of FA change, volume-of-interest (VOI) analysis of the TBSS results was performed to investigate the relationship between changes in FA and other diffusivity indices (Da and Dr). In addition, to determine whether there were relationships between clinical measures and diffusion indices for the regions that were significantly different between groups, correlation analysis was performed.

Results There were no differences in the distributions of age, gender and years of education between groups. The mean score on the FTND questionnaire for smokers was 8.85 ±0.70, indicating heavy nicotine dependence. TBSS demonstrated that smokers had significantly lower FA than nonsmokers in the left anterior corpus callosum (Figure 1). There were no white matter regions with increased FA in smokers. Further, VOI analysis found that smokers had a significantly higher Dr ($p=0.002$), and a lower Da ($p=0.0002$) while no changes in MD ($p=0.71$) when compared with nonsmokers. Importantly, we found there was significantly positive correlation between Dr in the region that was significantly different between groups and the duration of smoking ($r=0.378, p=0.033$) in smokers when controlled with the age at smoking onset and gender.

Discussion In this study, we used TBSS to examine the integrity of white matter microstructure in heavy smokers. We found smokers had reduced FA mainly in the left anterior corpus callosum. VOI analysis showed decreased FA in this region as reflected by decreased Da and increased Dr, which was probably caused by axonal loss and disrupted integrity of myelin [5]. These results provide evidences of deficits in white matter integrity of the anterior corpus callosum and may reflect a disruption in the organization of the frontal cortices in smokers. Furthermore, correlation findings suggest that longer exposure to cigarette smoking is associated with decreased microstructural integrity of the anterior corpus callosum, which indicates that DTI may be used as a qualified objective tool to evaluate the effects from chronic cigarette smoking. Further investigations are required to determine the relationship between white matter damages, the functional network affected by chronic cigarette smoking and measures of neurocognitive impairments.

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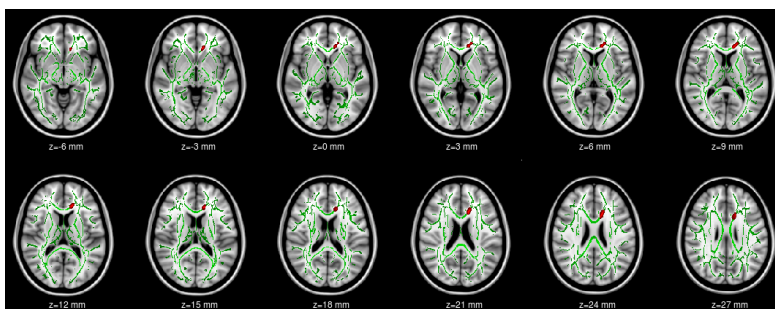


Fig. 1: TBSS analysis of fractional anisotropy (FA) maps. Areas in red are regions where FA was significantly lower in smokers relative to nonsmokers. green: the mean FA skeleton. The left side of the image corresponds to the right hemisphere of the brain.

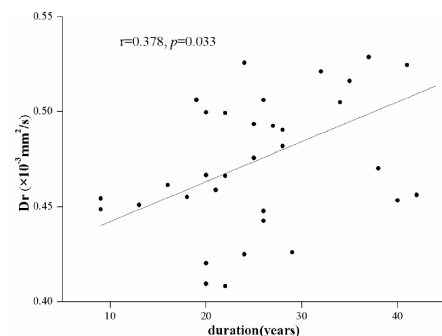


Fig.2: Correlation analysis in smokers. Significant correlation between radial diffusivity (Dr) in the region that was significantly different between groups and the duration of smoking in smokers.