Evaluating the Changes of White Matter Microstructures in Tobacco Addicts Based on Diffusion Tensor Imaging

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Background: The tract-based spatial statistics (TBSS) method was used to investigate the changes of white matter microstructure in tobacco addicts, and to analyze its correlation with smoking index, smoking years, and daily smoking amount.

Material/Methods: Routine magnetic resonance imaging (excluding intracranial lesions) and diffusion tensor imaging (DTI) sequence scanning were performed in 156 nicotine addicts (nicotine dependence group) and 81 non-nicotine addicts (control group) recruited from the study group. TBSS method was used to preprocess DTI data, and age and education level were taken as covariables to statistically analyze relevant parameters between nicotine dependence group and control group, such as fractional anisotropy (FA) value and smoking index. Spearman correlation analysis was performed on smoking status and FA values in brain regions with significant differences between nicotine dependent group and control group, and the test level α was 0.05.

Results: Compared with control group, FA values of white matter in part of the posterior limb of the right inner capsule (r=–0.428, P=0.003), the right superior radiating crown (r=–0.136, P=0.004), the right posterior radiating crown (r=–0.229, P=0.003), the right superior longitudinal bundle (r=–0.474, P=0.002), the right inferior longitudinal bundle (r=–0.354, P=0.003) and the inferior frontal occipital bundle (r=–0.310, P=0.002) were decreased, which were negatively correlated with smoking index (P<0.05).

Conclusions: Nicotine can damage the microstructure of white matter in specific brain regions and damage neurons, with cumulative effects.

MeSH Keywords: Leukoencephalopathies • Magnetic Resonance Imaging • Tobacco Use Cessation • Tobacco Use Disorder

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Background

The harm of tobacco is one of the biggest public health problems facing the world today [1]. Every year, more than 6 million people die from smoking-related diseases. Although people have long known the harm of tobacco, 21% of the world's population still smokes [2], while Chinese male smokers are as high as 316 million [3], more than 1 million people die from smoking-related diseases every year, and more than 2 million are expected per year by 2030 [4]. A survey showed that about 70% of smokers have the intention to quit smoking, 50% of them have tried to quit smoking, but only 5% have succeeded in quitting smoking [5]. Therefore, a thorough understanding of the inherent mechanism of tobacco dependence, the discovery of new therapeutic targets, targeted guidance, and intervention in smoking cessation will help to improve the success rate of smoking cessation.

In recent years, neuroimaging studies on tobacco dependence have shown that tobacco dependence is accompanied by changes in brain structure [6,7], among which the changes in brain white matter structure are closely related to the mechanism of nicotine addiction. Diffusion tensor imaging (DTI) is currently the only non-invasive method to display the microstructure, morphology and density of white matter fibers, in which the fractional anisotropy (FA) value measured by DTI is commonly used to reflect the structural integrity of white matter. At present, there are significant differences between smokers and non-smokers in the microstructure of white matter in local brain regions. However, different studies have shown different FA values in the same brain region [8–15], which needs to be further explored. In addition, previous studies on DTI were mostly analysis based on region of interest (ROI) and voxel. However, the ROI research method had some defects such as highly subjective selection, poor repeatability, results only reflected part of fiber bundles, and required prior assumptions. Voxel based analysis (VBA) had some defects such as registration error and difficulty in smoothing nuclear selection. However, the latest tract-based spatial statistics (TBSS) method is a tracer registration algorithm based on whole-brain fiber bundles, which requires no prior assumptions, no smoothing processing, no requirements on data distribution and accurate registration. It is a promising and reliable method to study the microstructure of white matter. Therefore, based on DTI technology, this study used TBSS method to explore the changes of brain microstructures in nicotine addicts, analyzed the correlation between them and smoking indexes, and further explored the effect of smoking on white matter microstructures, so as to explore effective methods of smoking cessation or clinical intervention targets, and provide targeted, hierarchical and phased manner guidance for smoking cessation.

Material and Methods

Study participants

From December 2017 to March 2019, 156 male smokers were recruited through an online platform. All smokers were assessed by Fagerstrom Dependence Test (FTND), correlated smoking index (daily smoking amount×smoking years/20) and alcohol consumption scale. At the same time, 81 healthy adult male non-smokers (volunteers) were recruited as control group. All smokers met the diagnostic criteria for substance dependence in the *Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition* (DSM-V). In addition, inclusion criteria included: 1) healthy males, aged between 20 and 55; 2) daily smoking ≥10, smoking years ≥2; 3) all participants were right-handed; 4) no magnetic resonance examination contraindications. The inclusion criteria for the control group were no more than 10 cigarettes in the lifetime. Exclusion criteria for both groups were: 1) people with psychotic symptoms or family history of mental disorders; 2) people with history of epilepsy or family history of epilepsy; 3) people with history of dependence and behavior (gambling, online games) other than nicotine, such as alcohol and drugs; 4) those who were receiving medication or had taken benzodiazepines within 2 weeks or had received antipsychotics; 5) people with coma history, craniocerebral injury history, brain organic or serious physical diseases, intracranial metal implants or artificial dental implants; 6) people who could not tolerate magnetic resonance examination. The study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Zhengzhou University, and all study participants signed the informed consent form.

Image acquisition and methods

Conventional magnetic resonance imaging (MRI) sequence and DTI image data were collected by using German Siemens Prisma 3.0T MRI equipment and standard 32-channel cranial phased array coil. The study participants were in supine position under natural relaxation. The nasal root was located at the middle line of the coil. The ears were sealed with earplugs and the head was fixed with sponge pads. Before starting the scan, the study participants were told what to pay attention to, close their eyes, keep awake, and do not think.

Scanning parameters: conventional MRI sequences included: axial T_1WI, T_2WI, T_2 FLAIR, DWI (b=0, 1000 s/mm^2), sagittal T_1WI. The parameters were as follows: 1) T_2WI: TR: 5000 ms; TE: 95 ms; FOV: 240×240 mm; layer thickness: 5 mm; interval: 1 mm; number of layers: 20 layers. 2) The DTI sequence scanning parameters were as follows: diffusion gradient directions: 64; b values: 1000 s/mm^2; TR: 9200 ms; inversion time (TI): 900 ms; TE: 72 ms; FOV: 256×256 mm; layer thickness: 2.0 mm;
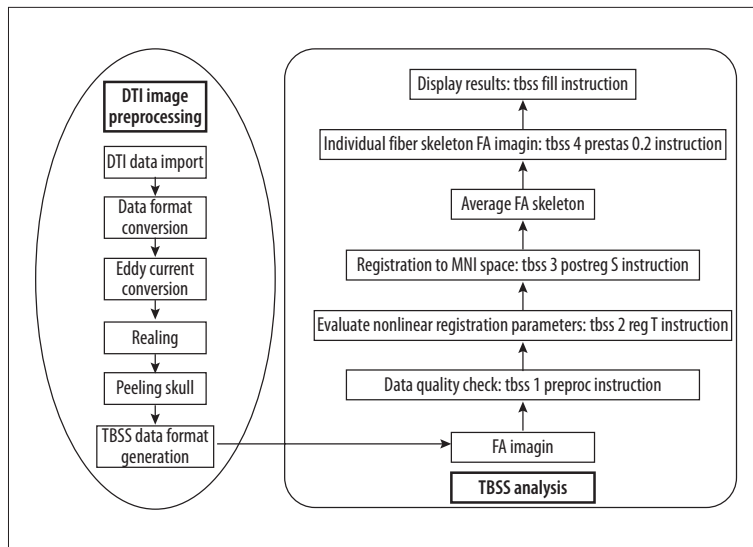
Figure 1. DTI image data processing flow chart. DTI – diffusion tensor imaging; TBSS – tract-based spatial statistics; FA – fractional anisotropy; MNI – Montreal Neurological Institute.

matrix: 128×128; interval: 0 mm; number of layers: 70; FA: 9°; acquisition time: 6 min 50 s.

DTI image data processing

The DTI imaging data process was as follows: 1) DTI image preprocessing: the original DICOM file was converted to NIFTI format by using cm2nii tool in MRIcron software; eddy current correction, realign (threshold 2 mm or 2 degrees), peeling skull (threshold 0.2) were processed, and finally converted to a special file format recognized by TBSS. 2) TBSS pretreatment: FA images of all participants were registered to standard brain space of Montreal Neurological Institute (MNI) by using FMRIB nonlinear registration. Then, the mean values of all standardized FA images were skeletonized to obtain the average FA skeleton (threshold value 0.2), and the FA data of each participant were projected onto the FA skeleton to obtain the FA fiber skeleton diagram of the white matter of each participant. The projection data was analyzed by a linear model for horizontal statistical analysis, and the name of the fiber bundle skeleton with significant differences between the groups was marked by John Hopkins University (JHU) ICBM-DTI-81 brain white matter atlas, and corresponding records were made. Then, the white matter regions with significant differences were filled by tbss_fill instruction, and the skeleton names of the fibers were recorded. Finally, the template Mask was made based on 3D-T1 BRAVO image, and the FA values and the skeleton names of fibrous bundles with statistical differences were extracted (Figure 1).

Statistical analysis

Taking age and education level as covariates, the general linear model (GLM) in FSL software was used to record the data of nicotine dependence group and control group and generate T test parameters, F test parameters and matrix files. Then, non-parametric test (permutation) was performed by TBSS to obtain the fibrous skeleton with significant differences between groups. Threshold-free cluster enhancement (TFCE) method was used to further perform multiple contrast correction. Statistical results of measurement data were expressed as mean±standard deviation ($\bar{x}\pm s$). Statistical SPSS 21.0 software was used to extract FA values of different brain regions with statistical differences in nicotine dependence group. Spearman correlation analysis was made between FA values and smoking years, daily smoking amount and smoking index (daily smoking amount×smoking years/20). There is a significant difference at $P<0.05$.

Results

Basic clinical data of participants

The participants in this study were all of Han nationality, male, and right-handed. There were 156 cases in nicotine dependence group and 81 cases in control group (Tables 1, 2).

Differences in brain regions between nicotine dependence group and control group

Compared with control group, FA values in the posterior limb of the right inner capsule, the right superior radiating crown, the right posterior radiating crown, the right superior longitudinal bundle, the right inferior longitudinal bundle, the inferior frontal occipital bundle, and the white matter area were decreased, with significant differences (P 0.05). (Figure 2). Then the correlations between different brain regions and smoking years, daily smoking amount and smoking index were analyzed (Table 3).

Table 1. Basic information of subjects.

Group	$\bar{x}\pm s$		P
	Nicotine dependence group (n=156)	Control group (n=81)	
Gender (Male/Female)	156/0	81/0	1.00
Age (years)	37.7±6.9	36.1±7.6	0.10
Education year (years)	13.1±3.9	12.3±4.5	0.15

There is a significant difference at P<0.05.

Table 2. Smoking related data in nicotine dependence group.

Smoking-related characteristics	$\bar{x}\pm s$
Initial smoking age (years)	17.4±2.8
Age span of initial smoking (years)	11–25
Smoking years (years)	20.0±7.4
Smoking years span (years)	3–39
Daily smoking amount (cigarette/day)	21.9±6.7
Daily smoking amount span (cigarette/day)	10–40
FTND (point)	4.3±2.0
FTND span (point)	1–10
Smoking index (daily smoking amount×smoking years/20)	22.1±11.7
Smoking index span	1.8–72.0

FTND – Fagerstrom nicotine dependence test.

Discussion

Principles and advantages of DTI

Diffusion tensor imaging (DTI) was proposed by Bassar in 1994 and is improved, developed and evolved by diffusion weighted imaging (DWI). DTI uses the diffusion anisotropy of water molecules to image, quantitatively analyze the dispersion of water molecules in tissues, decompose and quantify the signal data of diffusion anisotropy from 3-dimensional perspective, which can display more fine tissue microstructure, i.e., non-invasively display the distribution of white matter, the course of fibrous bundles and the changes of myelin sheath *in vivo*. FA value, commonly used in DTI, is sensitive to neuronal characteristics such as axon size, density, and myelin formation. A study has shown that white matter fibers without pathological changes or damage usually show higher FA values, for the intact myelin sheath restricts the direction of water diffusion. A lower FA value indicates that fewer water molecules undergo directional diffusion, suggesting demyelination of fibers under pathological conditions [16]. FA value is often used to evaluate the microstructure of white matter, and its advantages are as follows: 1) FA has a good contrast between images of gray matter, and the selection of ROI is relatively easy, so the FA value obtained is relatively objective and accurate; 2) FA value does not change with the change of coordinate rotation angle, it represents the physical characteristics of tissue cells, which makes the FA value obtained by the same object in different time, space and imaging equipment have a comparative character, that is, FA image can objectively reflect the structure and partial anisotropy of white matter fibers in the brain. However, the commonly used index mean diffusivity (MD) can
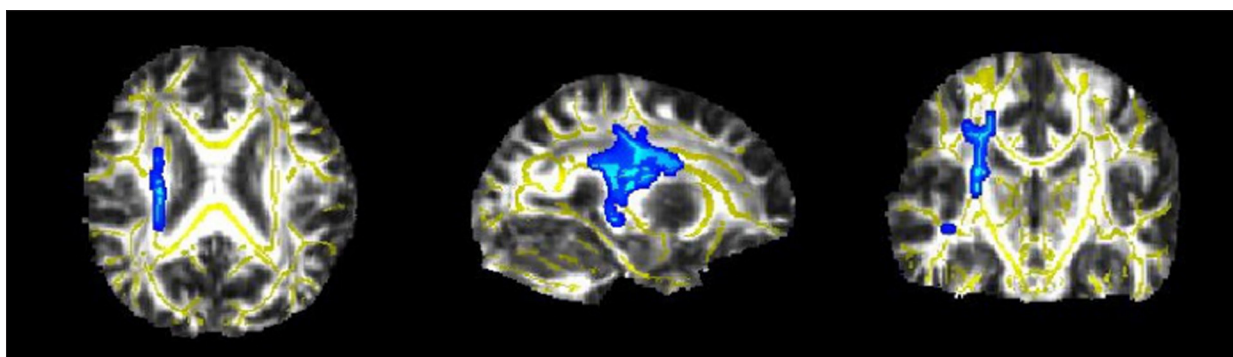

Figure 2. Differences in brain regions between nicotine dependence group and control group. The yellow represented the average FA skeleton and the blue represented the white matter fiber bundle skeleton area with decreased FA value. FA – fractional anisotropy.

Table 3. Correlation analysis of FA value and smoking status between nicotine dependence group and control group.

Brain regions		Smoking year	Daily smoking amount	Smoking index
The posterior limb of the right inner capsule	r	−0.351	−0.342	−0.428
	P	0.003*	0.004*	0.003*
The right superior radiating crown	r	−0.237	−0.226	−0.136
	P	0.001*	0.002*	0.001*
The right posterior radiating crown	r	−0.384	−0.272	−0.229
	P	0.004*	0.002*	0.003*
The right superior longitudinal bundle	r	−0.317	−0.403	−0.474
	P	0.003*	0.002*	0.002*
The right inferior longitudinal bundle	r	−0.358	−0.296	−0.354
	P	0.004*	0.002*	0.003*
The inferior frontal occipital bundle	r	−0.327	−0.364	−0.310
	P	0.003*	0.001*	0.002*

r – correlation; P – significance.

show the change of brain structure but cannot show the difference between gray matter and white matter, and cannot show the deformation of nerve fibers. Therefore, this study was mainly to compare and analyze the difference of white matter structure between nicotine dependent group and control group by FA value.

Advantages of TBSS analysis method

At present, the processing methods of DTI image data include ROI, VBA and TBSS. Among them, the ROI method is sensitive to the change of parameters of small structures, but the ROI drawing method based on the ROI analysis method is time-consuming and laborious, and the accuracy and repeatability of ROI selection are poor, resulting in poor comparability of results. VBA is suitable for exploratory studies on the development and changes of white matter structure in the field of brain science, such as white matter integrity changes in concealed brain diseases (no lesions were found on routine examinations), correlation between white matter development and cognition, but there are 2 major unresolved issues: poor registration (no standard space) and need to be smoothed (no uniform standards for smooth nucleus threshold). The TBSS method first obtained a mean_FA skeleton diagram, and then mapped the FA values of all subjects to the mean_FA skeleton diagram, ensuring that the FA values of each individual element on the skeleton diagram came from the center closest to the white matter fiber bundles. This method only extracts the dispersion index of the white matter skeleton and does not need spatial smoothing processing, to overcome the shortcomings of voxel-based morphological analysis methods in the registration and smoothing process and the disadvantages of ROI selection. It can align and register the main white matter fiber

bundles of different participants, so as to achieve more accurate inter-group comparison, and can more accurately locate the abnormal white matter areas in the brain, providing reliable parameters for quantitative evaluation of white matter lesions, which has a good application prospect in brain science research and clinical practice. Therefore, this study adopted TBSS method to process DTI image data and obtained relatively objective and accurate FA values to compare the differences in the microstructure of white matter between nicotine dependent group and control group.

Relationship between DTI changes of white matter microstructure and tobacco dependence

White matter is a high-speed, fast information superhighway, composed of nerve fibers and myelin sheaths. Nerve fibers form bridges between nerve cells. The myelin sheath is a fatty sheath wrapped around nerve fibers. White matter is usually divided into 3 categories according to the function of nerve fibers: 1) commissural fibers; 2) association fibers; and 3) projective fibers. The commissural fibers are fibers that connect the cerebral hemisphere cortex on both sides, including corpus callosum, anterior commissure, and fornix commissure. Association fibers are the fibers that connect parts of the cortex in the ipsilateral hemisphere, including intra-cortical and subcortical association fibers. The subcortical association fibers are further divided into short association fibers and long association fibers. The long association fibers mainly include frontal occipital bundle, hook bundle, upper longitudinal bundle, lower longitudinal bundle and cingulate belt bundle. Projective fibers are the fibers connecting the deep cortical nucleus group with the brainstem, cerebellum and spinal cord, including the afferent and efferent fibers, which are typically

represented by the corticospinal tract, cortical pontine tract, corticobulbar tract, and optic radiation. Among them, the radial crown is the most typical projective fiber, radiating from the cerebral cortex and finally gathering in the brainstem, which is divided into 3 parts: anterior radiation crown, superior radiation crown, and posterior radiation crown. The anterior radiation crown mainly constitutes the frontal lobo-subcortical circuit [17]. The superior radiation crown is bidirectionally connected to the frontal cortex, brainstem and spinal cord [18]. The posterior radiation crown is mainly visual radiation [19]. The inner capsule connects the cerebral cortex to subcortical structures (basal ganglia, thalamus, and brainstem), including the upper and lower axons. External capsular projective fibers interconnect the prefrontal cortex and basal ganglia of the temporal region. However, tobacco (nicotine) dependence is a chronic addictive disease, which can change the conduction function of certain nerve circuits, i.e., nerve fibers, leading to corresponding pathophysiological changes in white matter. In this study, we focused on nerve fibers and used TBSS method to analyze DTI image data of nicotine addicts and non-nicotine addicts to investigate the effect of nicotine on the microstructure of white matter.

TBSS is the most objective and accurate method to analyze DTI images at present, but previous research results on DTI are different [20]. Relevant studies have shown that the FA value of white matter is positively correlated with the integrity of axonal myelin sheath and the compactness and parallelism of nerve fibers. Decreased FA value indicates that the integrity of myelin sheath and the compactness of white matter fiber bundles are impaired. The FA values of whole brain white matter structure in nicotine addicts and non-nicotine addicts were studied by TBSS analysis. It was found that the FA values of the posterior limb of the right inner capsule, the right superior radiating crown, the right posterior radiating crown, the right superior longitudinal bundle, the right inferior longitudinal bundle and the inferior frontal occipital bundle in nicotine addicts were lower than those in control group, and were negatively correlated with smoking index. This is consistent with the research results of Zhang et al. [13] on FA value between schizophrenic smokers and age-matched healthy non-smoking control group using TBSS method. This was also similar to the conclusion of Baeza-Loya et al. [21], that is, the FA values of most of the association fibers such as the right superior longitudinal bundle, the right inferior longitudinal bundle and the inferior frontal occipital bundle were reduced. The upper longitudinal bundle is located on the dorsal side of the upper edge of the insula, carries nerve impulses backwards from the frontal lobe to the contact area of the parietal and occipital lobes. The injury might involve the motor language center and the writing language center, and then lead to the symptoms of motor aphasia and agraphia. The lower longitudinal bundle is located in the temporal occipital lobe, adjacent

to the outer side of the inferior horn of the lateral ventricle, extending from the occipital pole to the temporal pole. The lower frontal occipital bundle is located at the bottom of the lateral sulcus, below the plate-like nucleus and the outer capsule, that is, long association fibers connect frontal lobe, parietal lobe, temporal lobe, occipital lobe, and other brain regions, which might lead to motor and postural dysregulation, and motor and sensory aphasia. In addition, the posterior limb of the internal capsule is located between the lenticular nucleus and thalamus in the basal ganglia, where the motor and sensory conduction fibers are highly concentrated. From front to back, the corticospinal tract, the thalamic cortical tract, the occipitotemporal pontine tract, and the visual and auditory radiation fibers pass through the posterior limb. The radial crown refers to the projective fibers radiating from the inner capsule to the cerebral cortex. Therefore, the damaged projective fibers, such as the posterior limb of the inner capsule and the radial crown, might suffer from paresthesia and limb movement disorders. In addition, the study also found that compared with the control group, the FA values of multiple brain regions in the nicotine dependence group decreased, and were negatively correlated with smoking index, smoking years, and daily smoking amount [22]. At the same time, smoking was found to cause FA to decrease with the increase of smoking years.

Conclusions

In conclusion, nicotine can destroy the microstructures of white matter in specific areas of the brain, damage neurons, and its effect has a cumulative effect. The mechanism might be to influence the speed and strength of nerve fiber impulse conduction by changing the physical properties of the myelin sheath in the white matter fiber bundles, so drugs or physiotherapy that support re-myelination are expected to inhibit smoking craving and thus help quit smoking. This result was consistent with the research of Wang et al.

Limitations of the study

This study has the following limitations: 1) all study participants were Han males, and the results might not be applicable to females or to other ethnic smokers. 2) This study showed that the white matter microstructures of nicotine addicts were different from those of a normal control group, but other factors (such as genetic factors, alcohol, etc.) could not be completely excluded. Therefore, it is necessary to expand the sample size and sample population to further refine the study. 3) Limitations of TBSS include that TBSS is only suitable for detecting large fiber bundles, and FA skeleton extraction algorithm might cause skeleton interruption at the intersection of fiber bundles, thus, new methods need to be proposed.

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