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White matter integrity in young smokers: a tract-based spatial statistics study

Dahua Yu[1]*, Kai Yuan[2]*, Baohua Zhang[1], Jixin Liu[2], Minghao Dong[2], Chenwang Jin[3], Lin Luo[4], Jinquan Zhai[4], Ling Zhao[5], Ying Zhao[1], Yu Gu[1], Ting Xue[1], Xin Liu[1], Xiaoqi Lu[1], Wei Qin[2] & Jie Tian[1,6]

Inner Mongolia Key Laboratory of Pattern Recognition and Intelligent Image Processing, School of Information Engineering[1] and Department of Medical Imaging, The First Affiliated Hospital of Baotou Medical College,[4] Inner Mongolia University of Science and Technology, China, Life Sciences Research Center, School of Life Science and Technology, Xidian University, China[2], Department of Medical Imaging, The First Affiliated Hospital of Medical College, Xi'an Jiaotong University, China[3], The 3rd Teaching Hospital, Chengdu University of Traditional Chinese Medicine, China[5] and Institute of Automation, Chinese Academy of Sciences, China[6]

ABSTRACT

Previous diffusion tensor imaging (DTI) studies revealed contradictory effects of smoking on fractional anisotropy (FA). Multiple DTI-derived indices may help to deduce the pathophysiological type of white matter (WM) changes and provide more specific biomarkers of WM neuropathology in the whole brain of young smokers. Twenty-three young smokers and 22 age-, education- and gender-matched healthy non-smoking controls participated in this study. Tract-based spatial statistics was employed to investigate the WM microstructure in young smokers by integrating multiple indices, including FA, mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD). Compared with healthy non-smoking controls, young smokers showed significantly increased FA with increased AD and decreased RD in several brain regions, while no difference in MD was observed. Specifically, the overlapped WM regions with increased FA, increased AD and decreased RD were found in the right posterior limb of the internal capsule, the right external capsule and the right superior corona radiata. Additionally, average FA and RD values in the WM regions mentioned earlier were significantly correlated with pack-years and Fagerström Test for Nicotine Dependence, while no correlation in AD was found. The WM tracts with increased FA may be more associated with RD, rather than AD in young smokers. We suggested that WM properties of several fibres in young smokers may be the biomarker as the cumulative effect and severity of nicotine dependence.

Keywords Diffusion tensor imaging, smoking, tract-based spatial statistics.

Correspondence to: Kai Yuan, Life Sciences Research Center, School of Life Science and Technology, Xidian University, 266 Xinglong Section of Xifeng Road, Xi'an, Shaanxi 710071, China. E-mail: kyuan@xidian.edu.cn. Xiaoqi Lu, Inner Mongolia Key Laboratory of Pattern Recognition and Intelligent Image Processing, School of Information Engineering, Inner Mongolia University of Science and Technology, 7 Arden Street, Baotou, Inner Mongolia 014010, China. E-mail: lxiaoqi@imust.cn

INTRODUCTION

On the basis of current global smoking patterns, about 50 percent of young men and 10 percent of young women are becoming smokers, and relatively few stopping (Jha & Peto 2014). China's first official publication on the harms of smoking as 'China Report on the Health Hazards of Smoking' was released by Ministry of Health in 2012, which declared that China has 350 million Chinese smokers including 14 million young smokers and produces 42 percent of the world's cigarettes. Annual smoking-attributable deaths in China will rise from about 1 million per year now to more than 3 million in 2050 as the young smokers of today reach middle and old age (Jha 2009; Peto *et al.* 2012). Young man spans the age period from late adolescence to adulthood which is associated with the highest prevalence of cigarette smoking, and is also a time of continued brain development, which may be affected by environmental perturbations, like nicotine exposure through cigarettes (Morales *et al.* 2014).

Previous studies reported structural differences in gray matter between smokers and non-smokers, including decreased gray matter density or volume in the

*Both authors contributed equally to this article.

prefrontal cortex (PFC), anterior cingulate cortex, orbitofrontal cortex and increased gray matter density or volume in the insula (Brody *et al.* 2004; Gallinat *et al.* 2006; Kühn, Schubert & Gallinat 2010; Zhang *et al.* 2011a; Liao *et al.* 2012). Moreover, white matter (WM) microstructure in smokers was investigated and revealed contradictory effects of smoking on fractional anisotropy (FA) in several diffusion tensor imaging (DTI) studies (Jacobsen *et al.* 2007; Paul *et al.* 2008; Gons *et al.* 2011; Liao *et al.* 2011; Zhang *et al.* 2011a,b; Hudkins *et al.* 2012; Kochunov *et al.* 2013; Lin *et al.* 2013; Umene-Nakano *et al.* 2014). In detail, Jacobsen *et al.* investigated adolescent smokers and non-smokers with and without prenatal exposure to maternal smoking and reported adolescent smoking was associated with increased FA in the anterior cortical WM and internal capsule (IC) (Jacobsen *et al.* 2007). In addition, significantly increased FA was also revealed in the corpus callosum (CC), bilateral superior longitudinal fasciculus (SLF), right prefrontal WM and cingulum in smokers (Paul *et al.* 2008; Liao *et al.* 2011; Hudkins *et al.* 2012). Nevertheless, decreased FA in the prefrontal WM, the CC and other WM of smokers were also confirmed (Zhang *et al.* 2011a,b; Lin *et al.* 2013; Umene-Nakano *et al.* 2014). The possible reasons of these inconsistent results may be related to the processing methods, duration of use or the age range of the participants.

As the most frequently used DTI-derived index, FA is highly sensitive to microstructural changes, but not very specific to the types of changes (e.g. radial or axial) (Alexander *et al.* 2007; Thomason & Thompson 2011). To our knowledge, only one recent tract-based spatial statistics (TBSS) study focused on multiple DTI-derived indices in adult smokers (mean age, 40.5 ± 8.6) and reported decreased FA without significant differences in axial diffusivity (AD) and radial diffusivity (RD) (Umene-Nakano *et al.* 2014). However, few studies use multiple DTI-derived indices analysis to specify the pathophysiological features of WM integrity of young smokers. TBSS method along with multiple DTI-derived indices may help deduce the pathophysiological feature of WM changes and provide more specific biomarkers of WM neuropathology in the whole brain of young smokers (Alexander *et al.* 2007; Thomason & Thompson 2011).

MATERIALS AND METHODS

Participants

The young smokers were screened from local high schools and universities following the diagnostic criteria of nicotine dependence in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Nicotine dependence levels were assessed with Fagerström Test for Nicotine Dependence (FTND) (Heatherton *et al.* 1991). All smokers had no attempt to quit or smoking abstinence longer than 3 months in the past year. The age-, education- and gender-matched healthy non-smoking controls were also enrolled. None of healthy non-smoking controls had smoked more than five cigarettes in their lifetime and none in the past 5 years. In order to avoid the effects of second-hand smoke exposure, the healthy non-smoking controls were recruited from non-smoking dormitories and neither of their parents smoked. Exclusion criteria for both groups were: (1) any physical illness such as a brain tumour, obstructive lung disease, hepatitis, or epilepsy as assessed according to clinical evaluations and medical records; (2) any medications currently that may affect cognitive functioning; (3) alcohol or any drug abuse; (4) existence of a neurological disease; and (5) claustrophobia. All of the participants were right-handed as measured by the Edinburgh Handedness Inventory (Oldfield 1971).

At last, 23 young smokers (all men, aged 16–23 years, mean age, 19.6 ± 1.9 years) and 22 matched healthy non-smoking controls (all men, aged 14–23 years, mean age, 19.3 ± 2.4 years) were recruited in our study. This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of the Medical College, Xi'an Jiaotong University. All participants or their parents gave their written informed consent after the experimental procedure was fully explained. Prior to scanning, urine drug screening was performed on all participants to exclude the possibility of substance abuse. Additionally, the expiratory carbon monoxide (CO) levels of all participants were measured using the Smokerlyzer System (Bedfont Scientific, Ltd, Rochester, UK). CO level in expired air was verified as ≥10 ppm in smoking group and ≤3 ppm in non-smoking control group. The clinical and demographic characteristics of participants are shown in Table 1.

Table 1 Clinical details of young smokers and healthy non-smoking controls.

Clinical details	*Young smokers* (n = *23*)	*Non-smoking healthy controls* (n = *22*)
Age (years)	19.6 ± 1.9	19.3 ± 2.4
Age range (years)	16–23	14–23
Initial smoking age	15.4 ± 1.9	–
Daily consumption (cigarettes/day)	13.4 ± 5.5	–
Exposure (pack-years)	2.5 ± 1.1	–
FTND	6.7 ± 1.3	–

Data are means ± standard deviations. Pack-years = smoking years × daily consumption/20. FTND = Fagerström Test for Nicotine Dependence.

Data acquisition

This experiment was carried out in a 3-T GE scanner (EXCITE, General Electric, Milwaukee, Wisconsin) with an eight-channel phase-array head coil at the First Affiliated Hospital of the Medical College, Xi'an Jiaotong University. During the scan session, restraining foam pads were used to minimize head motion after the heads of the participants were positioned carefully. Prior to the DTI run, T1- and T2-weighted images for each participant were obtained to exclude possible silent lesions in the brain and were examined by two expert radiologists. The diffusion tensor images were acquired with a single-shot echo-planar imaging sequence and the diffusion sensitizing gradients were applied along 30 non-collinear directions ($b = 1000$ s/mm^2) together with an acquisition without diffusion weighting ($b = 0$ s/mm^2). The imaging parameters were 45 continuous axial slices with a slice thickness of 3 mm, repetition time (TR) = 6800 ms, echo time (TE) = 93 ms, data matrix = 128 × 128, field of view (FOV) = 240 × 240 mm^2. Diffusion tensor images were acquired with two averages.

Data analysis

The data processing and analysis in this study were carried out using FMRIB Software Library (FSL) software 4.1.9 (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library, http://www.fmrib.ox.ac.uk/fsl) (Smith *et al.* 2004). Firstly, the eddy current distortion and simple head motion of raw diffusion data were corrected using FMRIB's Diffusion Toolbox (FDT) 2.0. Then, the Brain Extraction Tool (BET) 2.1 of FSL was used for brain extraction. FA, mean diffusivity (MD) and first, second and third eigenvalue maps (L1, L2 and L3 maps) were calculated by fitting a tensor model at each voxel of the diffusion data using FDT. The AD image was the first eigenvalue (L1) map for each participant. The RD image was calculated via the mean of the second and third eigenvalue maps using *fslmaths* command-line utilities. After that, TBSS analyses were performed between healthy non-smoking controls and young smokers. In detail, all of the participants' FA images were nonlinearly registered to the FMRIB58-FA standard-space template (FMRIB Centre University of Oxford, Department of Clinical Neurology, John Radcliffe Hospital Headington, Oxford, UK; http://www.fmrib.ox.ac.uk/fsl/data/FMRIB58_FA.html) and aligned to the Montreal Neurological Institute (MNI) space. The mean image of all aligned FA images was created and thinned to create a skeletonized mean FA image with the threshold at 0.2. Each aligned FA image of all participants was projected onto this skeleton. Next, using the protocol of non-FA Images in TBSS, the MD, AD and RD images were aligned into MNI space and projected onto the mean FA skeleton. After accounting for age effects, the permutation-based non-parametric inferences within the framework of the general linear model were performed to investigate the differences between the two groups. The corrected results used the threshold-free cluster enhancement with the family-wise error (FWE) correction for multiple comparisons corrections ($P < 0.05$, FWE corrected, 5000 permutations). At last, the brain regions in which young smokers showed significantly different DTI properties were overlapped to investigate the more details effect by different DTI indices (Yu *et al.* 2012, 2013). A series of Pearson's correlation analyses were performed to examine the correlation of the mean DTI index values of these overlapped brain regions with pack-years as cumulative effect and FTND as severity of smoking.

RESULTS

The WM regions with significantly different DTI properties were identified by the ICBM-DTI-81 white matter labels atlas. Compared with healthy non-smoking controls, the young smokers showed increased FA and decreased RD in the body and splenium parts of CC, bilateral IC, bilateral external capsule (EC), bilateral superior corona radiata (SCR), bilateral posterior corona radiata (PCR), bilateral posterior thalamic radiata (PTR) and the left SLF (Fig. 1a) ($P < 0.05$, FWE corrected); increased AD in the right posterior limb of the internal capsule (PLIC), the right EC and the right SCR (Fig. 1b) ($P < 0.05$, FWE corrected); while no difference in MD was observed. As shown in Fig. 2, the brain regions with increased FA, AD and decreased RD in young smoker group were overlapped and shown as a red colour including the right PLIC, the right EC and the right SCR. These overlapped ROIs may suggest more changed integrity with DTI-derived indices (Alexander *et al.* 2007; Thomason & Thompson 2011). The overlapped brain regions with increased FA and AD were shown as green colour including the right PLIC, the right EC and the right SCR, which may be more associated with axial changes. The overlapped brain regions with increased FA and decreased RD were shown as blue colour including the body and splenium parts of CC, bilateral IC, EC, SCR, PCR, PTR and the left SLF, which may be more associated with radial changes.

Correlation analysis results demonstrated that there were significant negative correlations among the average FA in the right SCR and FTND ($r = -0.4669$, $P = 0.0247$) in young smokers (Fig. 3a). In addition, significant positive correlation was found between FA values in the right SCR and pack-years ($r = 0.5197$, $P = 0.011$) (Fig. 3b). Significant negative correlations between the average RD values and pack-years were found in the right SCR ($r = -0.6176$, $P = 0.0017$) (Fig. 3c), EC ($r = -0.4736$,

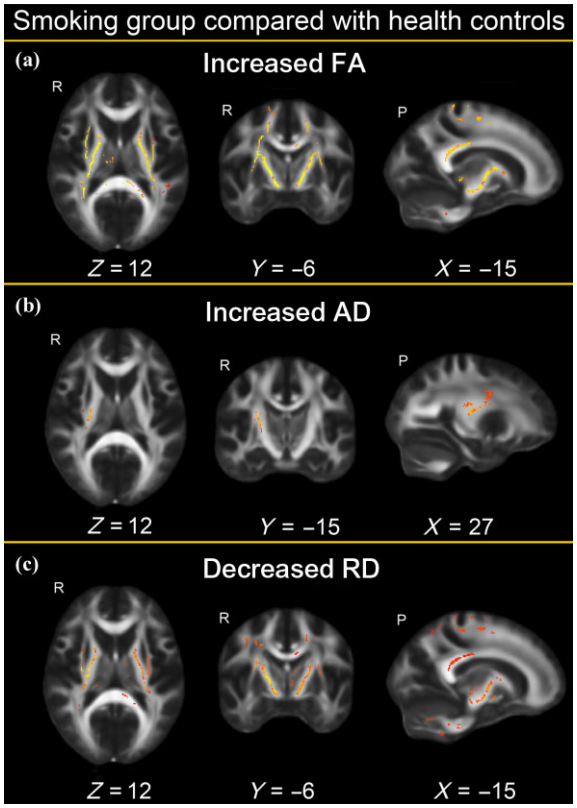

Figure 1 Compared with health non-smoking controls, young smokers showed significantly increased fractional anisotropy (FA) (Fig. 1a), increased axial diffusivity (AD) (Fig. 1b) and decreased radial diffusivity (RD) (Fig. 1c) in multiple brain regions, respectively ($P < 0.05$, FWE corrected), while no difference in mean diffusivity (MD) was observed

$P = 0.0224$) (Fig. 3d) and PLIC ($r = -0.5251$, $P = 0.0101$) (Fig. 3e).

DISCUSSION

Numerous previous DTI studies reported inconsistent changes in WM properties of smokers (Jacobsen *et al.* 2007; Paul *et al.* 2008; Gons *et al.* 2011; Liao *et al.* 2011; Zhang *et al.* 2011a,b; Hudkins *et al.* 2012; Kochunov *et al.* 2013; Lin *et al.* 2013; Umene-Nakano *et al.* 2014). To the best of our knowledge, few studies investigated WM integrity in young smokers by multiple DTI-derived indices. As a non-invasive access, multiple DTI-derived indices (FA, MD, AD and RD) analysis can offer unique insight into the microstructure of WM tracts in the living brain as a sign of alterations in functional, clinical or behavioural measure (Alexander *et al.* 2007; Thomason & Thompson 2011). In more detail, FA is the most frequently used DTI-derived index, which is highly sensitive to microstructural changes, but not very specific to the types of changes (e.g. radial or axial) (Beaulieu 2002; Alexander *et al.* 2007; Thomason & Thompson 2011). Increased FA or decreased FA may result from several conditions such as myelination, maturation, demyelination, axon loss, gliosis or inflammation observed in a broad spectrum of diseases (Alexander *et al.* 2007). As a supplement, MD, AD and RD may provide more information about the structure of axonal cell membranes and myelin sheaths (Beaulieu 2002; Alexander *et al.* 2007; Thomason & Thompson 2011). As a measure of the average molecular diffusion, MD may be affected by longitudinal diffusion along axons (AD) or the transverse direction of diffusion (RD) (Song *et al.* 2002). In order to maximize specificity, AD indicated longitudinal diffusion along axons, which may be related to the changes of axon or bundle coherence (Beaulieu 2002; Alexander *et al.* 2007; Thomason & Thompson 2011). Moreover, RD indicated perpendicular diffusion, which may be related to the changes of myelin sheaths. Despite of its prominent advantages, voxel-based analysis analysis of DTI suffers from several limitations, such as imperfect image registration or random selection of smoothing factors (Smith *et al.* 2006). Recently, the TBSS method was employed to investigate the WM abnormality between smokers and healthy non-smoking controls (Zhang *et al.* 2011a,b; Kochunov *et al.* 2013; Lin *et al.* 2013; Umene-Nakano *et al.* 2014), which was more sensitive and robust for detecting WM abnormalities (Smith *et al.* 2006). In present study, the TBSS method with the multiple DTI-derived indices analysis was employed collectively to specify the neurophysiological feature of WM integrity in young smokers. Consistent with previous findings (Jacobsen *et al.* 2007; Paul *et al.* 2008; Liao *et al.* 2011; Hudkins *et al.* 2012), young smokers showed similar patterns of increased FA coupled with increased AD and decreased RD in several WM tracts, while no difference in MD was observed (Fig. 1).

Previous DTI studies revealed contradictory effects of smoking on FA in several brain regions. Compared with healthy non-smoking controls, smokers showed increased FA in the CC, IC, SLF, CR, right prefrontal WM and cingulum (Jacobsen *et al.* 2007; Paul *et al.* 2008; Liao *et al.* 2011; Hudkins *et al.* 2012). Whereas, decreased FA in the prefrontal WM and CC was also reported in other previous studies (Zhang *et al.* 2011a,b; Lin *et al.* 2013; Umene-Nakano *et al.* 2014). In present study, our results validated increased FA with decreased RD in the body and splenium parts of CC, bilateral IC, EC, SCR and SLF in young smokers, which was similar with part of previous studies (Jacobsen *et al.* 2007; Paul *et al.* 2008; Gons *et al.* 2011; Liao *et al.* 2011; Hudkins *et al.* 2012). Both increased (Jacobsen *et al.* 2007; Paul *et al.* 2008; Hudkins *et al.* 2012) and decreased (Lin *et al.* 2013; Umene-Nakano *et al.* 2014) FA values in the CC were confirmed, which suggested the CC may play an important role in the nicotine dependence process. As the

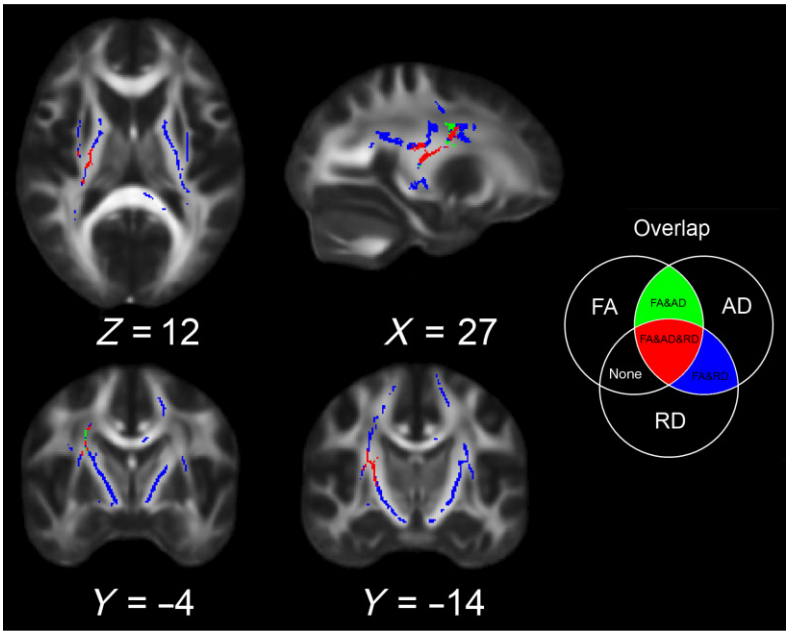

Figure 2 Brain regions with changed diffusion tensor imaging (DTI) properties (Fig. 1) in young smokers were overlapped. The brain regions with increased fractional anisotropy (FA), increased axial diffusivity (AD) and decreased radial diffusivity (RD) were shown in red, including the right posterior limb of the internal capsule (PLIC), the right external capsule (EC) and the right superior corona radiata (SCR). The brain regions with increased FA and decreased radial diffusivity RD were shown in blue, including the body and splenium parts of corpus callosum (CC), bilateral internal capsule (IC), bilateral EC, bilateral SCR, bilateral posterior corona radiata (PCR), bilateral posterior thalamic radiata (PTR) and the left superior longitudinal fasciculi (SLF). The brain regions with increased FA and AD were in green, which were similar as brain regions in red. On the right is the diagrammatic drawing with regards to the colours and the relationship of the overlap

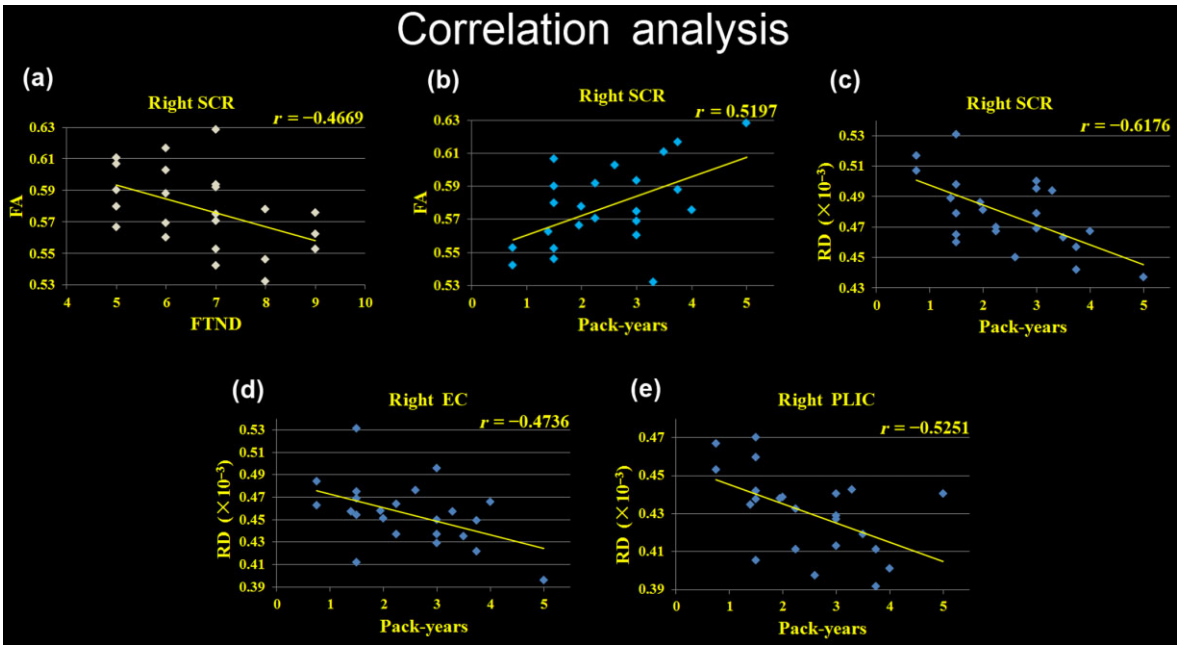

Figure 3 The correlation analysis results demonstrated that there were significant correlations between the smoking properties and the average fractional anisotropy (FA) (Fig. 3a & b) and radial diffusivity (RD) (Fig. 3c–e) values in the overlapped regions with increased FA, increased axial diffusivity (AD) and decreased radial diffusivity (RD). SCR = the superior corona radiata; FTND = Fagerström Test for Nicotine Dependence; pack-years = smoking years × daily consumption/20; EC = the external capsule; PLIC = the posterior limb of the internal capsule

main fibre tract interconnecting two cerebral hemispheres, the CC serves as a bridge between bilateral brain regions and has an important role in interhemispheric functional integration and communication of perceptual, cognitive, learned and volitional information (Hofer & Frahm 2006). Increased FA of the CC in present study may be related to shorter exposure to nicotine in the adolescent. More exposure to nicotine in chronic or heavy smokers may have multitude of accumulation effects on WM integrity as decreased FA (Lin *et al.* 2013; Umene-Nakano *et al.* 2014). It may indicate the progress of DTI properties in the CC is affected by smoking nonlinearly during the whole life of smokers.

Furthermore, we found increased FA with decreased RD in the IC and SLF as previous studies of adolescent smokers (Jacobsen *et al.* 2007; Liao *et al.* 2011). The IC connects the cerebral cortex to the subcortical brain structures such as the basal ganglia, thalamus and brainstem, which contain both ascending and descending axons (Axer & Keyserlingk 2000). The SLF is connecting the dorsolateral PFC, occipital, temporal and parietal lobes (Makris *et al.* 2005). With regard to the other fibres, increased FA was also found in the SCR and EC, which was not reported in previous studies. This discrepancy might arise from sample differences, such as duration of cigarette smoking and age. The SCR connects frontal cortex and the brain stem and spinal cord bidirectionally (Schmahmann & Pandya 2009). The EC contains projection fibres interconnecting prefrontal and temporal areas with basal ganglia (Schmahmann & Pandya 2009). All of these fibres mentioned earlier connect the PFC and subcortical regions (basal ganglia and thalamus) as the key nodes. Zhang *et al.* found gray matter density in left PFC was lower in high pack-years smokers and was inversely related to pack-years (Zhang *et al.* 2011a). They also found a significant decrease FA in the left PFC in the high FTND smokers compared with their matched controls (Zhang *et al.* 2011a). The structural abnormalities and functional dysfunction in the PFC and subcortical regions were critical to the reward, craving and cognitive control deficits in addiction including smoking (Goldstein & Volkow 2011). It is noteworthy that these brain regions do not work in isolation. In contrast, the PFC and subcortical regions communicated with each other through dopamine mesocortical and other neurotransmitter pathways to regulate executive functions and behaviours (Volkow *et al.* 2011). Previous studies had found that the information transfer between them was associated with the fibres mentioned earlier. Besides, the changes in the IC, the SCR and the EC had been reported consistently in several addiction studies, such as methamphetamine abusers, adolescent binge drinkers, cocaine-dependent individuals (McQueeny *et al.* 2009; Lane *et al.* 2010; Tobias *et al.* 2010; Bell *et al.* 2011; Baker *et al.* 2013). In the current study, the average FA and RD values of overlapped regions in the right PLIC, the right EC and the right SCR were correlated with FTND and pack-years in young smokers. Therefore, we suggested that WM properties changes of several fibres in young smokers may be the biomarker as the cumulative effect and severity of nicotine dependence.

Smoking initiation has been proved most likely to occur during adolescence by several previous studies (Lantz 2003). The brain of adolescent is undergoing a series of significant neurobiological change, which may especially sensitive to outside influences and induce plasticity of nervous system (Gulley & Juraska 2013; Lydon *et al.* 2014; Morales *et al.* 2014). The period from adolescence to adulthood is the most important step of brain maturation, which means the nervous system is in a relatively labile state during this stage of development (Gulley & Juraska 2013; Lydon *et al.* 2014). It may be especially sensitive to experience-induced plasticity, such as nicotine exposure through cigarettes. Nicotine binds to nicotinic acetylcholine receptors (nAChRs), which are widely distributed in the central nervous system (Slotkin 2004). The stimulation of nAChRs may interfere neurodevelopment and regulate brain development possibly by disrupting the trophic actions of acetylcholine (Slotkin 2004). Animal tests demonstrated that nicotine exposure during prenatal or adolescent period may effect on cholinergic neurotransmission, cell signalling, and serotonin receptor expression and disrupt both prenatal period and adolescent brain development (Abreu-Villaça *et al.* 2003; Slotkin *et al.* 2007). The possible mechanism of increased FA and decreased RD in young smokers might be associated that nicotine acting at nAChRs promote glial activity or proliferation or accelerate the brain maturation (Garrido *et al.* 2003; Liu *et al.* 2005). As suggested by Paul *et al.* (2008) and Hudkins *et al.* (2012), this pattern may suggest that developmental maturation of WM during adolescence to adult might be stimulated by nicotine (Barnea-Goraly *et al.* 2005; Ashtari *et al.* 2007). Meanwhile, adolescent engagement in risk taking (including substance use) was proven to be associated with increased WM maturity in the SCR and SLF (Berns, Moore & Capra 2009; Jacobus *et al.* 2013). Berns *et al.* used probabilistic tractography to identify the WM tracts that were related to risk taking in adolescents, including the descending tracts from PFC through the IC, interhemispheric fibres connecting left and right homologous regions through the CC, and fibres connecting prefrontal regions with the temporal lobe (Berns *et al.* 2009). They revealed that adolescents who engage in risk taking or dangerous behaviours may be more impulsive or more sensation-seeking than their age-matched peers, meanwhile, they also have more mature frontal WM tracts as evidenced by increased FA and decreased RD

(Berns *et al.* 2009). Our findings revealed increased FA and decreased RD, which may be associated with accelerated WM maturity of SCR and SLF. Because of the implication of these two fibres in risk taking in adolescents and young adults, we rationally suggested that smoking exacerbate the risk taking behaviour in young individuals.

Moreover, we found increased AD in several WM regions. Correlation analysis showed significant correlations between the smoking properties and the average FA and RD values in the overlapped regions with increased FA, increased AD and decreased RD, while no correlation between smoking properties and average AD values in these regions. It may suggest that RD, rather than AD, was more associated with increased FA in young smokers. Taken together, the solid evidence mentioned earlier might help us explain the discrepancy in smoking DTI studies. Possible explanation might be that shorter exposure to nicotine in the adolescent (Jacobsen *et al.* 2007; Liao *et al.* 2011), light smokers (Paul *et al.* 2008; Hudkins *et al.* 2012) or acute nicotine administration effects (Kochunov *et al.* 2013) may be related with nicotine acting at nAChRs promote glial activity or proliferation as increased FA; while more exposure to nicotine in chronic or heavy smokers may reveal multitude of accumulation effects on WM integrity as decreased FA (Gons *et al.* 2011; Zhang *et al.* 2011a,b; Kochunov *et al.* 2013; Lin *et al.* 2013; Umene-Nakano *et al.* 2014).

Limitation

The study is limited in its cross-sectional design, and it is not possible to infer the causality of the relationships between WM integrity and severity of smoking. The relationships might be bi-directional and related to some latent variables. Another limitation of the study is the relatively small sample size, so the results might not be generalizable to wider populations. Further longitudinal studies with larger sample size would be required to improve the understanding of the neuroimaging findings in the current study.

CONCLUSION

In the current study, we investigated specific features of WM changes in young smokers by employing the TBSS method with multiple DTI indices (i.e. FA, MD, RD and AD). The WM tracts with increased FA in the CC, bilateral IC, EC, SCR and SLF may be more associated with RD, rather than AD. Our result may suggest that developmental maturation of WM during adolescence to adult might be stimulated by nicotine (Barnea-Goraly *et al.* 2005; Ashtari *et al.* 2007). However, a more comprehensive experimental design is needed to reveal the accurate roles of these WM changes in smokers. We hope that our results could improve the understanding of smoking.

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Disclosure/Conflict of Interest

The Authors declare that there is no conflict of interest.

Authors Contribution

DY, KY, WQ, XL and JT conceived and designed the experiments; KY, CJ, LL, JZ, XL and LZ performed the experiments; DY, KY, BZ, MD, JL and YZ analysed the data; DY, KY, WQ wrote the paper; JL, YG and TX provided critical revision of the paper for important intellectual content. All authors critically reviewed content and approved final version for publication.

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