



Right arcuate fasciculus and superior longitudinal fasciculus abnormalities in primary insomnia

Wanye Cai^{1,2} · Meng Zhao^{1,2} · Jingjing Liu^{1,2} · Bo Liu³ · Dahua Yu⁴ · Kai Yuan^{1,2,4} 

Published online: 20 July 2019

© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract

Primary insomnia (PI) is a very common phenomenon and associated with functional impairments of attention, memory and mood regulation. However, its neurobiology is poorly understood. To date, the studies about integrity of white matter (WM) tracts in PI patients have been still rare. In the present study, we used Automated Fiber Quantification (AFQ), which reliably and efficiently quantified diffusion measurements at multiple locations along the WM trajectory based on diffusion tensor imaging (DTI), to assess WM diffusion properties differences between 23 PI patients and 32 matched healthy controls in 18 tracts. The relationships between neuroimaging differences and sleep behaviors were explored, including Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index Scale (ISI). Compared with healthy control group, right arcuate fasciculus (Arc) and superior longitudinal fasciculus (SLF) showed significant higher fractional anisotropy (FA), mean diffusivity (MD) and radial diffusivity (RD) along tract length in PI patients (FWE corrected, $p < 0.01$). Axial diffusivity (AD) for PI patients was higher in right Arc and lower in right SLF. Correlation analyses revealed that FA of right Arc and MD of right SLF were negatively correlated with PSQI score in PI patients, and AD of right Arc and FA of right SLF were positively correlated with PSQI score. Negative correlation was observed between FA of right Arc and AD of right SLF and ISI score in PI patients. Our findings can help us to improve the understanding of the neural mechanisms of primary insomnia at abnormalities in WM microstructure.

Keywords Insomnia · White matter · Tractography · Pittsburgh sleep quality index

Introduction

Primary insomnia is an independent psychiatric syndrome that is characterized by difficulties in falling asleep or maintaining

sleep for at least 1 month (Edinger et al. 2004). It is associated with decreased quality of life and reduced work efficiency (Léger et al. 2002; Kyle et al. 2010). In its chronic form, primary insomnia increases the probability of medical disorders like heart disease, high blood pressure, and mental disorders including depression and anxiety (Breslau et al. 1996; Chien et al. 2010; Sarsour et al. 2011).

Recent neuroimaging studies suggested that sleep disturbances were associated with structural and functional brain changes, i.e., reduced gray matter (GM) density or volume particularly in the thalamus, hippocampal, orbitofrontal cortex, superior frontal cortex (Altena et al. 2010; Winkelman et al. 2010; Joo et al. 2013; Stoffers et al. 2012; M. Li et al. 2018). Meanwhile, a number of functional neuroimaging studies showed abnormal resting state functional connectivity (RSFC) of the thalamus, amygdala, premotor and sensorimotor cortices, anterior cingulate cortex, and medial prefrontal cortex and insular (Nofzinger et al. 2004; Huang et al. 2012; Yuan et al. 2013; Yongli Li et al. 2014; Yuan et al. 2016b). Despite great progress, the brain mechanisms of primary insomnia remain elusive, hampering the development of effective treatments. Particularly, the functional repertoire of any

✉ Dahua Yu
fmydh@imust.edu.cn

✉ Kai Yuan
kyuan@xidian.edu.cn

¹ School of Life Science and Technology, Xidian University, Xi'an, Shanxi 710071, People's Republic of China

² Engineering Research Center of Molecular and Neuro Imaging Ministry of Education, Xi'an, People's Republic of China

³ Department of Neurology, The First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou, Inner Mongolia 014010, People's Republic of China

⁴ Inner Mongolia Key Laboratory of Pattern Recognition and Intelligent Image Processing, Information Processing Laboratory, School of Information Engineering, Inner Mongolia University of Science and Technology, Baotou, Inner Mongolia 014010, People's Republic of China

system is ultimately determined by its structural composition. White matter (WM) structures also play a prominent role in regulating brain activity and mediating the functional coupling between brain regions and behavior (Yuan et al. 2016a, 2017; Y. Li et al. 2017; Yuan et al. 2018a, b). To date, the differences in WM diffusion properties of the interested tracts between primary insomnia patients and good sleepers as well as the behavioral implications of such differences remain largely unclear. Therefore, it is of great significance to investigate the underlying neural mechanisms of primary insomnia patients.

Diffusion tensor imaging (DTI), a magnetic resonance imaging (MRI) method, allows for a detailed quantification of WM diffusion properties in WM in multiple directions (Feldman et al. 2010; Basser 1995; Basser and Pierpaoli 2011). Diffusion properties are routinely used for group comparisons between clinical populations and control groups to infer the neurobiology of the disease. Among primary insomnia patients, the abnormalities of WM diffusion properties have been investigated and several studies have revealed significant effects using DTI techniques, i.e. voxel-based analyses (VBA) and tract-based spatial statistics (TBSS) (Spiegelhalder et al. 2014; Shumei Li et al. 2016). They showed that primary insomnia was associated with the reduced FA values compared with healthy controls in multiple brain regions, including the right anterior internal capsule, the right posterior internal capsule, the right anterior corona radiata, the right superior corona radiata, the right superior longitudinal fasciculus, the right thalamus and the corpus callosum. However, these methods have certain limitations. VBA does not have sufficient accuracy at the individual level due to significant changes in the shape of long-range tracts among subjects (Wassermann et al. 2012). TBSS cannot ensure that any voxel corresponds to the same area of the subject, and the consistency of the area defined by the TBSS and the actual location of a tract in the individual's brain are modest (Stephen M. Smith et al. 2006).

In the current study, we apply the automated fiber quantification (AFQ) approach, a novel and sensitive analytic methodology for clinical research and practice, has overcome the above limitation (i.e. VBA and TBSS). DTI has the potential to improve the localization information of WM lesions because it can reveal detailed WM anatomy (Marco Catani et al. 2002; Setsu Wakana et al. 2004). AFQ can capitalize on the precision of tractography for automatically identifying and localizing fiber tracts in individual brain (Yeatman et al. 2012). It can quantize the information of the diffusion measurements at multiple locations along the entire trajectories for analysis. We aim to assess diffusion properties of 20 WM tracts systematically between primarily insomnia patients and healthy good sleepers. We hypothesize that primary insomnia patients would show different diffusion properties within the right arcuate fasciculus (Arc) and right superior

longitudinal fasciculus (SLF) compared with healthy good sleepers, and such abnormalities would be correlated with poor sleep quality.

Methods

Ethics statement

This study was approved by the Ethics Committee of medical research in First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou, China. Informed written contents were obtained from all participants.

Participants

Participants were 27 right-handed adults with primary insomnia (9 males, 18 females; age = 42.11 ± 9.39 years) meeting diagnostic criteria according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) and 39 age-, hand-, and sex-matched healthy control participants (16 males, 23 females; age = 41.08 ± 9.17 years) at the time of scanning (Cooper 2001). The arcuate fasciculus (Arc) could not be tracked in 4 primary insomnia patients and 7 healthy controls due to the consequence of the Arc exhibiting high curvature and great partial voluming with the superior longitudinal fasciculus. Thus, the final number of participants for the primary insomnia group was 23 (6 males, 17 female; age = 41.43 ± 9.47 years) and for the healthy control group was 32 (14 males, 18 females; age = 39.38 ± 9.38 years). Details were shown in Table 1.

All primary insomnia patients complained of difficulty falling sleeping, maintaining sleep or early awakening at least 1 month, and had no other sleep disorders (including hypersomnia, parasomnia, sleep-related breathing disorder, sleep-related movement disorder, and circadian rhythm sleep disorder) or other psychiatric disorders. All primary insomnia patients were right-handed, as assessed with the Edinburgh Handedness Inventory and free of any psychoactive medication at least 2 weeks prior to and during the study (Oldfield 1971). The healthy control participants were included in the study according to the following criteria: good sleep quality and a good sleep onset and/or maintenance, lower the total score of Pittsburgh Sleep Quality Index (PSQI) than five (Buysse et al. 1989); at least 3 months without consumption of any stimulants, cigarettes, alcohol or coffee before the current study; and no history of psychiatric or neurologic diseases. The healthy control participants were right-handed.

Exclusion criteria for all participants were as follows: primary insomnia caused by organic disease or severe mental disease secondary to depression or generalized anxiety; history of neurological or other physical diseases such as

Table 1 Demographic and clinical characteristics of all participants

Parameter	Primary Insomnia (PI)		Healthy Control (HC)		<i>p</i> value	
	Pre_PI(<i>N</i> = 27)	Post_PI(<i>N</i> = 23)	Pre_HC(<i>N</i> = 39)	Post_HC(<i>N</i> = 32)		
Gender (M/F)	9/18	6/17	16/23	14/18	0.526	0.517
Age (years)	42.11 ± 9.39	41.43 ± 9.47	41.08 ± 9.17	39.38 ± 9.38	0.526	0.427
Education (years)	12.51 ± 3.72	12.96 ± 3.47	13.21 ± 2.89	13.44 ± 3.03	0.402	0.587
PSQI	13.67 ± 3.5	13.35 ± 3.7	3.54 ± 1.37	4.25 ± 2.14	<0.001*	<0.001*
ISI	17.3 ± 6.44	17.74 ± 6.5	–	–	–	–

Data are mean ± standard deviation (SD). *N* = participates. **p* < 0.05

PSQI Pittsburgh sleep quality index, ISI Insomnia severity index scale

Pre_PI Pre-exclude primary insomnia subject, Post_PI Excluded primary insomnia subject

Pre_HC Pre-exclude healthy control subject, Post_HC Excluded healthy control subject

respiratory, cardiac, renal, hepatic and endocrinal diseases; addiction disorder (i.e. smoking or coffee); any medication that might affect sleep or cerebral function within 2 weeks before the scans; and women who were pregnant, nursing, or menstruating.

All study participants were asked to complete the Insomnia Severity Index (ISI), the Pittsburgh Sleep Quality Index (PSQI) to assess sleep patterns prior to the MRI scanning.

MRI acquisition

The participants underwent MRI scanning after completing all the questionnaires. Meanwhile, MRI scanning was carried out by a professional doctor to control the MRI acquisition time. T1-weighted MRI and DTI data were acquired on a 3 T Philips scanner (Achieva; Philips Medical Systems, Best, The Netherlands) with an eight-channel phase-array head coil to restrict head motion and diminish scanner noise at the First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou, China. First, T1-weighted images for each participant were obtained with the following parameters: repetition time (TR) = 8.5 ms; echo time (TE) = 3.4 ms; flip angle = 12°; in-plane matrix size = 240 × 240; slices = 140; field of view (FOV) = 240 × 240 mm²; slice thickness = 1 mm. Then, the DTIs were acquired: 60 non-collinear directions (*b* = 1000 s/mm²) together with an acquisition without diffusion weighting (*b* = 0 s/mm²). The other imaging parameters were 75 continuous axial slices with a slice thickness of 2 mm and no gap, FOV = 256 × 256 mm², repetition time/echo time = 9400/84 ms, acquisition matrix = 128 × 128. DTI were acquired with two averages, resulting in 2 mm isotropic voxels. Finally, gradient echo-planar images were obtained during cue reactivity with the following parameters (TR = 2000 ms; TE = 30 ms; flip angle = 90°; FOV = 240 × 240 mm²; data matrix = 64 × 64; axial slices = 30; slice thickness = 5 mm and no slice

gap, total volumes = 185). Subsequently, participants were asked how they felt during the scan to eliminate the effect of anxiety on the DTI.

Data preprocessing

DTI data preprocessing software was available as part of open-source mrDiffusion (<http://web.stanford.edu/group/vista/cgi-bin/wiki/index.php/mrDiffusion>) implemented in MATLAB R2015a (Math Works). Eddy current distortions and subject motion in the diffusion tensor images were removed by a 14-parameter constrained non-linear co-registration based on the expected pattern of eddy current distortions given the phase-encode direction of the acquired data (Rohde et al. 2004).

DTI data were aligned to the T1 anatomical scans that had been averaged and rotated to align with the ac-pc plane. Alignment between DTI and T1 data was achieved by registering the *b*₀ images to the resampled T1 image using the same mutual information maximization algorithm used for T1 image co-registration provided through SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>). Resampling was completed by combining the motion correction and the anatomical registration transforms into an omnibus transform and subsequently resampling the data using trilinear interpolation. The rotation component of the omnibus coordinate transform was applied to the diffusion-weighting gradient directions to preserve their orientation with respect to the resampled diffusion images. For each voxel in the aligned and resampled volume, tensors were fit to the diffusion measurements using a robust least-squares algorithm designed to remove outliers and data points corrupted by motion at the tensor estimation step (Chang et al. 2005). We computed the eigenvalue decomposition of the diffusion tensor and the resulting three eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) were used to compute fractional anisotropy (FA), axial diffusivity (AD), mean diffusivity (MD), and radial diffusivity (RD) (Basser and Pierpaoli 2011).

Automating Fiber tract quantification

We used Automatic Fiber Quantification (AFQ) software tools (<https://github.com/jyeatman/AFQ>) in MATLAB R2015a (Math Works) to identify 20 white matter tracts in each participant's brain. AFQ mainly included three steps: (1) whole-brain tract tractography, (2) waypoint region-of-interest (ROI)-based tract segmentation and cleaning, and (3) tract quantification (Fig. 1). Whole-brain tract tractography was performed using a deterministic streamline tracking algorithm (STT) with a fourth-order Runge-Kutta path integration method and 1-mm fixed-step size (Conturo et al. 1999; Press et al. 1994). The tracking algorithm was seeded with a white matter mask defined as all voxels with a total FA value greater than 0.3. For a given tract group, tracts that intersected ROI were identified (Wakana et al. 2007). Each identified tract was then scored based on its correspondence to the standard tract probability map. Low-scoring tracts were discarded. The given tract groups were then limited to the central portion of the tracts that crossed the waypoint ROIs. Next, 100 equidistant points along each tract were identified and the position of the tract group core was determined by the average position of each node. At each node, the diffusion properties (i.e. FA, RD, AD and MD) were calculated by taking a weighted average across all tracts belonging to the tract. The contribution of each tract to the average was weighted by the probability of

the tract as a fascicle member, calculated as the Mahalanobis distance from the tract core. Figure 1 shows a visualization of this concept. Yeatman et al. described AFQ in more detail (Yeatman et al. 2012).

Statistical analyses

First, two sample t-test was used to examine differences between the primary insomnia patients and healthy controls on demographic data and behavior performance. The test was two tailed. Next, the diffusion properties (i.e. FA, RD, AD and MD) mean values from corresponding points along each AFQ-identified tract were compared between the primary insomnia patients and healthy controls using two sample t-test. Then, the between-group differences at each point were tested using the permutation-based nonparametric inferences (5,000 random permutations). The threshold for the statistical significance was set as $p < 0.01$, using threshold-free cluster enhancement (TFCE) with a family-wise error (FWE) correction for multiple comparison corrections (5,000 permutations) (Nichols and Holmes 2001; S. M. Smith and Nichols 2009; Eklund et al. 2016). We extracted the mean values of the nodes showed different diffusion properties for each tract. Then, Pearson correlation was employed to evaluate the correlation between the abnormal properties of localized tracts and clinical variables (i.e. PSQI and ISI) in the sample of primary

Tract Fractional Anisotropy (FA) Profiles

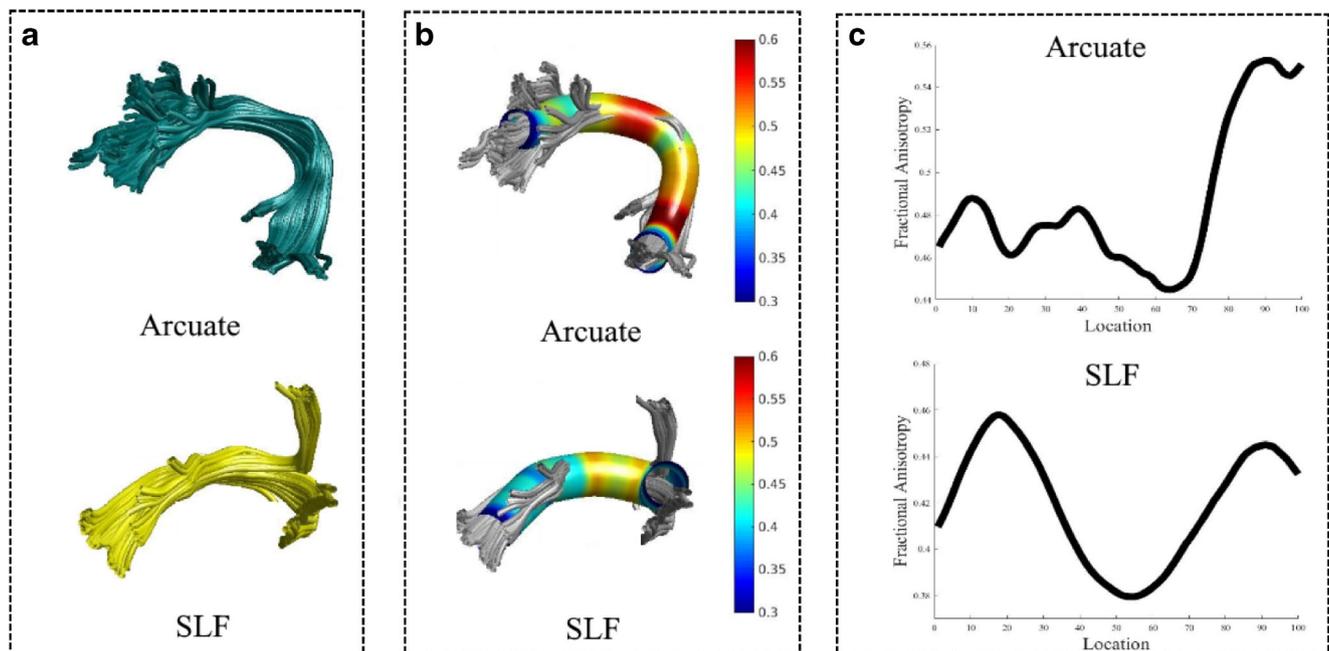


Fig. 1 Tract Fractional Anisotropy (FA) Profile. **a** Arcuate fasciculus (Arc) and superior longitudinal fasciculus (SLF) identified in a representative subject. **b** A three-dimensional rendering is shown for values of FA

along the Arc and SLF. **c** Tract FA Profiles show the FA along the core fiber (y-axis) at each of 100 equidistant points (x-axis) along the Arc and SLF

insomnia. The correlation between the total score of the PSQI and ISI score was checked by using Pearson correlation in the primary insomnia patients.

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of the participants in this study were presented in Table 1. There were no significant differences in gender ($t = 0.62, p = 0.517$), age ($t = 0.79, p = 0.427$), or education ($t = 0.48, p = 0.587$) between primary insomnia and healthy control groups. As expected, the primary insomnia patients had higher the total score of PSQI than healthy controls (PI: $PSQI = 13.35 \pm 3.7$; HC: $PSQI = 4.25 \pm 2.14$).

Fiber tracking

Using automated tract segmentation procedures, we successfully identified 20 tracts in the majority of both the primary insomnia and healthy control groups (Fig. 2). In this study, since the Cingulum hippocampal (HCC) tract was drawn only in 4 primary insomnia patients and 6 healthy controls used by AFQ, the next analysis of the results did not include the left and right HCC tracts. The reason for the tractography results of the two HCC tracts was discussed in more detail below.

Group comparisons of tract properties

Of 18 fiber groups identified by AFQ, two exhibited significantly differences between the primary insomnia and healthy control participants from corresponding points along each tract using two sample t-test ($p < 0.05$): the right arcuate fasciculus (Arc) and right superior longitudinal fasciculus (SLF). Figure 3 specifically showed the effects of comparing the diffusion properties of two tracts between primary insomnia and healthy control groups. Given the high degree of correlation between neighboring points on the tract profile each point should not be treated as an independent comparison (Yeatman et al. 2012). We used the permutation-based nonparametric inferences to appropriately adjust p values given the correlation structure of the data. Then, compared with healthy controls, the primary insomnia patients showed higher FA, MD and RD values in the right Arc (nodes 31–80) and right SLF (nodes 26–85)(FWE corrected, $p < 0.01$). AD values for the primary insomnia patients was higher in the right Arc (nodes 31–80) than healthy controls, and lower in the right SLF (FWE corrected, $p < 0.01$).

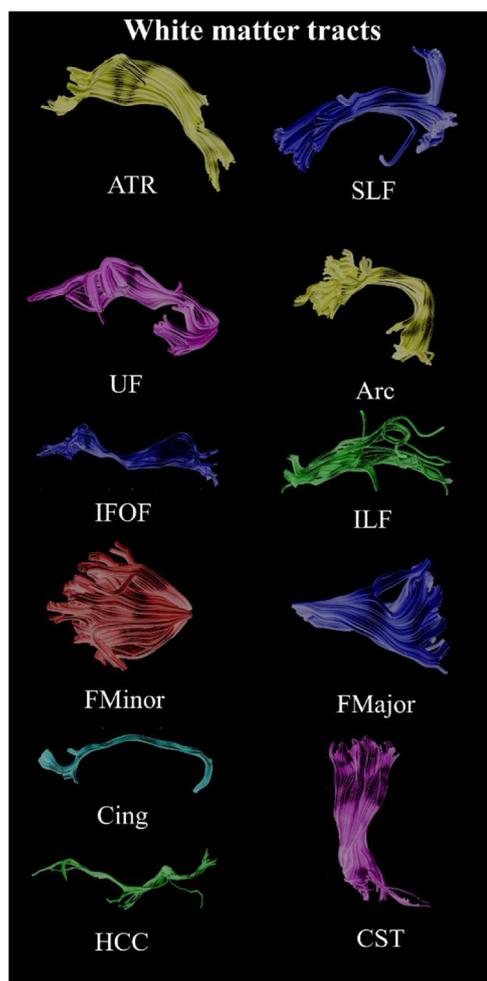


Fig. 2 Tractography of 20 white matter tracts. Single subject results are shown for each of the tracts in the left hemispheric. In the forceps major and minor tracts, the quantification originated in the left hemisphere and proceeded to the right. Panels illustrates the following tracts: *ATR* Anterior thalamic radiation, *SLF* Superior longitudinal fasciculus, *UF* Uncinate fasciculus, *Arc* Arcuate fasciculus, *IFOF* Inferior fronto-occipital fasciculus, *ILF* Inferior longitudinal fasciculus, *Fmajor* Forceps major, *Fminor* Forceps minor, *Cingulum* Cing, *Cingulum hippocampal* (HCC), *CST* Corticospinal tract

Association with clinical variables within the primary insomnia group

The correlation between diffusion properties of the right Arc and SLF and clinical variables (i.e. PSQI, ISI) in primary insomnia patients were as follows. The FA value in the right Arc (Fig. 4a, $p = -0.023$) and MD values in the right SLF (Fig. 4c, $p = -0.015$) in primary insomnia patients showed a negative correlation with the total score of the PSQI. The AD value in the right Arc (Fig. 4b, $p = 0.023$) and the FA in the right SLF (Fig. 4c, $p = 0.045$) in primary insomnia patients showed a positive correlation with the total score of the PSQI. A positive correlation was observed between the AD value in the

Diffusion parameters vary along the length of tracts

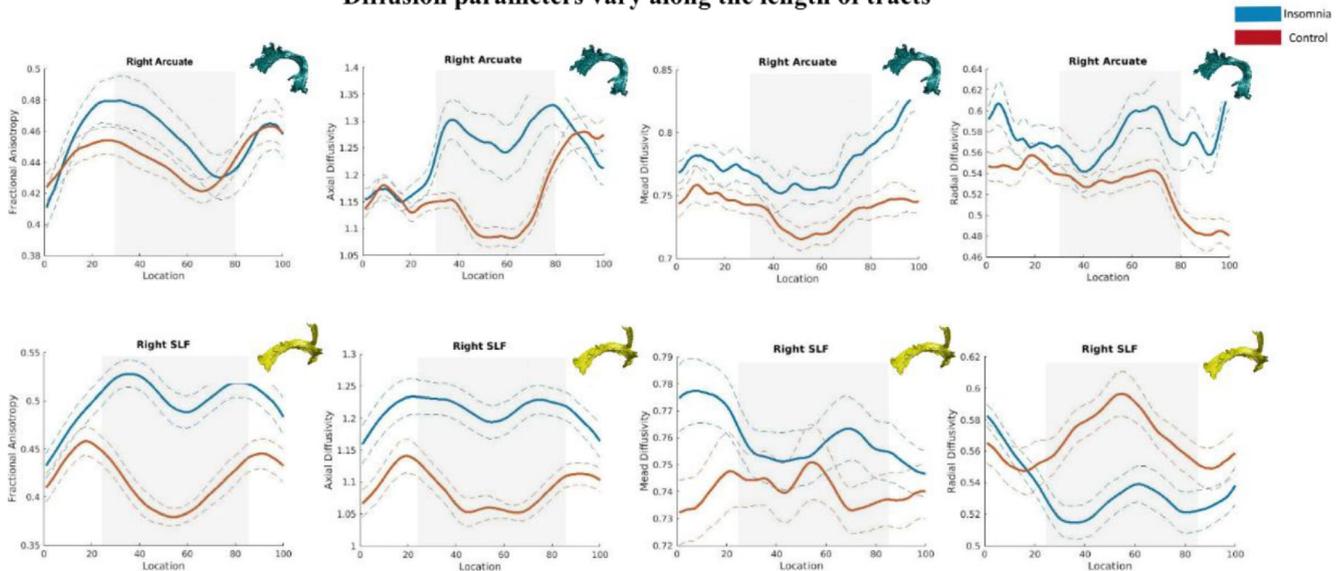


Fig. 3 Group differences vary along the length of tracts. Diffusion parameters vary along the length of the right arcuate fasciculus (Arc) and superior longitudinal fasciculus (SLF) from primary insomnia patients and healthy controls. Each plot depicts AD, RD, MD or FA within 100th nodes of each tract, and indicates a significant effect of each tract

for the diffusion parameter plotted. Shaded gray background indicates a tract segment where mean diffusion properties of the primary insomnia patients are significantly different compared to the healthy controls after FWE correction

right Arc (Fig. 4e, $p = 0.037$) and the FA in the right SLF (Fig. 4f, $p = 0.031$) and ISI score in primary insomnia patients. We also analyzed the correlation between the total score of the

PSQI and ISI score, and the result showed no correlation between the total score of the PSQI and ISI score in primary insomnia patients.

Correlation Analysis

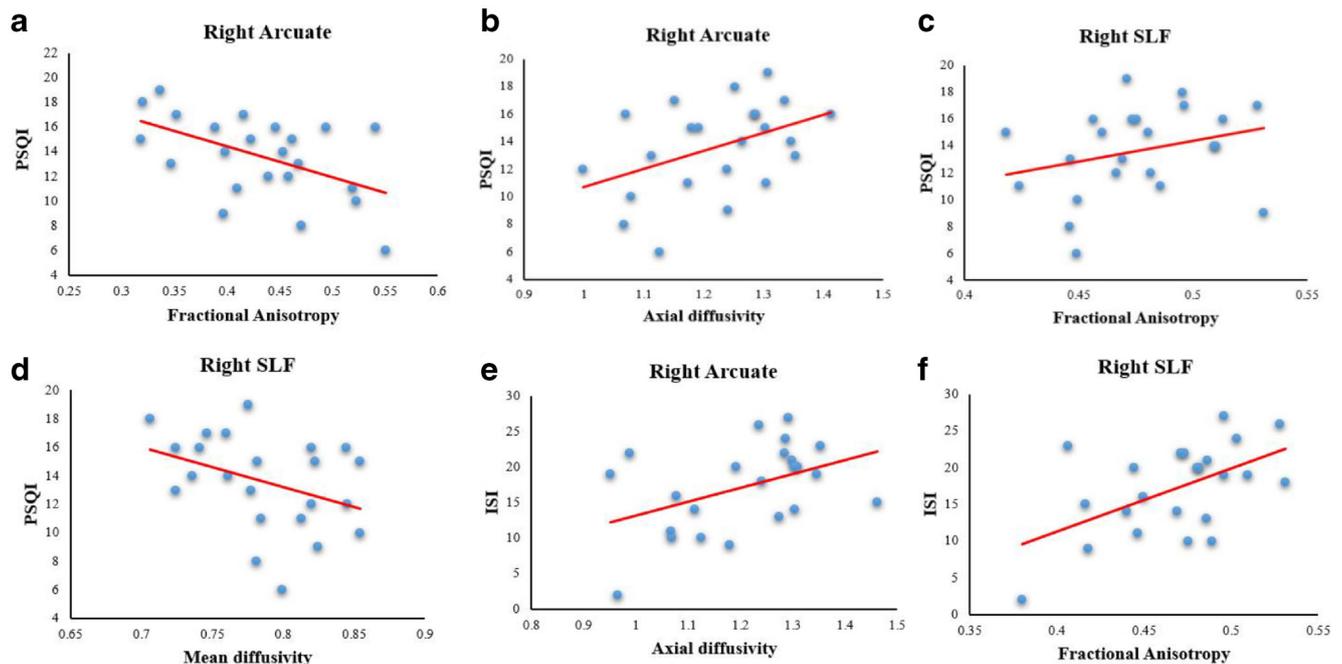


Fig. 4 The correlation between clinical variables and diffusion properties along the arcuate fasciculus (Arc) and superior longitudinal fasciculus (SLF). The FA value in the right Arc (Fig. 4a, $p = -0.023$) and MD values in the right SLF (Fig. 4c, $p = -0.015$) in primary insomnia patients showed a negative correlation with the total score of the PSQI. The AD value in the right Arc (Fig. 4b, $p = 0.023$) and the FA in the right

SLF (Fig. 4c, $p = 0.045$) in primary insomnia patients showed a positive correlation with the total score of the PSQI. Similarly, a positive correlation was also observed between the AD value in the right Arc (Fig. 4e, $p = 0.037$) and the FA in the right SLF (Fig. 4f, $p = 0.031$) and Insomnia Severity Index (ISI) score in primary insomnia patients

Discussion

Primary insomnia was a naturally occurring clinical condition characterized by disorders of the sleep process (i.e. chronically disturbed sleep and loss of sleep) and cognitive dysfunction (decreased memory function and decreased attention function) (Ohayon 2002; Morin et al. 2009; Riemann et al. 2015). So far, there had been few studies on the white matter (WM) microstructure of the brain in primary insomnia patients (Spiegelhalder et al. 2014; Shumei Li et al. 2016; Lu et al. 2017; Wu et al. 2018). Therefore, its neurological mechanism was still not clear.

The primary purpose of the present study was to determine WM diffusion properties in primary insomnia patients using Automatic Fiber Quantification (AFQ) method. The AFQ method was a more sensitive diffusion tensor imaging (DTI) tractography technique compared to traditional DTI methods, such as the voxel-based analysis (VBA) and the tract-based spatial statistics (TBSS) (Yeatman et al. 2012). It was able to identify equivalent brain WM microstructure in each subject's native space. This avoided a series of problems such as insufficient accuracy at the individual level and the inability to ensure that any voxel corresponds to the same area of the subject. AFQ allowed for the comparison of diffusion properties of multiple locations along the trajectory of each tract (tract profiles). Analyzing tract profile of diffusivity measurements along the trajectory can provide novel insights into the changes of the WM microstructure (Gong et al. 2005; O'Donnell et al. 2009). The AFQ method had been successfully used in many previous disease researches (Johnson et al. 2014; Samson et al. 2016; Keller et al. 2017). By using this method, we observed that primary insomnia patients exhibited significant abnormalities of WM diffusion properties in the right arcuate fasciculus (Arc) and right superior longitudinal fasciculus (SLF). The FA, AD, MD and RD values along the right Arc and the FA, AD and MD values along the right SLF were higher in primary insomnia patients. The RD value along the right SLF was lower in primary insomnia patients.

DTI had become the most common method for quantifying and detecting WM microstructural changes associated with clinical conditions, such as primary insomnia. WM microstructure was typically quantified by calculating fractional anisotropy (FA), axial diffusivity (AD), mean diffusivity (MD) and radial diffusivity (RD). FA indexed the degree of directional preference in water diffusion and consisted of AD and RD. AD and RD respectively quantified the speed of water diffusion along the principal and perpendicular diffusion directions (Heidi et al. 2010; Basser and Pierpaoli 2011). MD was a measure for the average rate of water displacement within a voxel. In the previous DTI researches, as the most frequently used DTI-derived index, FA was highly sensitive to microstructural changes, but not very specific to the types of changes (i.e. radial or axial). Therefore, systematic detection

of the differences in multiple diffusion properties allowed for more comprehensive analysis of WM microstructure anomalies. AFQ method by quantifying multiple WM diffusion properties (i.e. FA, AD, MD and RD) along the entire tract might help deduce the pathophysiological features of WM changes for primary insomnia.

Previous neuroimaging researches that focused on DTI techniques had examined the WM microstructural features in primary insomnia patients, including the VBA and TBSS methods (Spiegelhalder et al. 2014; Shumei Li et al. 2016). However, there were two limitations in these methods: the alignment problems in the VBA method were unresolved (Wassermann et al. 2012); and the TBSS method could not ensure the area it defined corresponds to the same area of individual's brain (Stephen M. Smith et al. 2006). Our study used the AFQ method that could overcome these above limitations (Yeatman et al. 2012). It did not require normalization for the comparison of equivalent WM tracts across subjects. Tracking within native space allowed for the comparison of equivalent tract pathways across individuals even if those tracts were in slightly different locations within the brain. The AFQ method can examine specific tissue property changes through measuring diffusion parameters at multiple locations along each interested tract. Thus, our results were higher in spatial resolution by revealing the specific locations of Arc and SLF between primary insomnia and controls: the Arc was from 31 to 80 nodes, and the SLF was from 26 to 85 nodes. Therefore, AFQ could efficiently and automatically quantify diffusion measurements at multiple locations along the trajectory of a WM tract in individual brain and simultaneously preserved information about the diffusion measurements at different locations on the tracts.

The SLF was a large bundle of association tracts in the WM of each cerebral hemisphere connecting the parietal, occipital and temporal lobes with ipsilateral frontal cortices (Kamali et al. 2014; Wang et al. 2016). The Arc was a bundle of axons that formed part of the SLF. The connectivity of the Arc had been shown to correspond to various functional areas within the temporal, parietal, and frontal lobes (M. Catani and Thiebaut de Schotten 2008; Phillips et al. 2011). These brain regions were well known for its roles in brain functions such as memory integration function, emotional function, and cognitive function (Kimberg and Farah 1993; Stuss et al. 1992; Rowe et al. 2001; E. E. Smith and Kosslyn 2007). Recent neuropsychological and insomnia studies indicated that primary insomnia patients exhibited deficits of memory formation and emotion regulation during sleep compared to healthy good sleepers (Baglioni et al. 2010; Fortier-Brochu et al. 2012). Thence, we hypothesized that abnormality of diffusion properties in right SLF and right Arc might be related to the above clinical features of primary insomnia patients. Notably, we found the diffusion properties of the right Arc (i.e. FA and AD) and right SLF (i.e. FA and MD) were associated with the

total score of the PSQI in primary insomnia patients. The AD value of the right Arc and the FA value of the right SLF were positive correlated with ISI score in primary insomnia patients. These indicated a possible link between the right Arc and right SLF and poor sleep quality. In addition, we also found the ISI score showed a positive correlation with the total score of the PSQI in the primary insomnia patients. From these we hypothesized that primary insomnia severity was closely related to the abnormality of the diffusion properties in the Arc and SLF fiber tracts. These might provide further evidences of potential neurobiological mechanisms for primary insomnia.

In the current study, we did not analyzed the left and right cingulum hippocampal (HCC) tracts which were reconstructed successfully only in 4 primary insomnia patients and 6 healthy controls. If the two HCC tracts were included in the statistical analysis, the results would be inaccurate. It had been shown that tractography could faithfully reconstruct the cores of WM tracts by using existing anatomical knowledge (Stieltjes et al. 2001; Marco Catani et al. 2002). Whether the WM tracts could be reconstructed successfully was affected by many factors. For instance, the reconstruction of interested tracts was sensitive to the partial volume effect and convolution of axon structures having different orientations in each voxel. In addition to the above, the tractography results could be affected by diseased brains that might have altered DTI parameters. Even if an interested tract had a normal dimensions and 3D trajectory, tractography might not reveal its entire course in the presence of reduced diffusion anisotropy (Hua et al. 2008). The specific reasons for the failure of the HCC fasciculus to be reconstructed in a large number of subjects remained to be studied.

Limitations

We still have certain limitations in the current study. First, this is a cross-sectional study and the direction of the relationship between primary insomnia and disrupted WM integrity remains unclear. Longitudinal studies may help to resolve this question. Second, we only tested the tests associated with sleep and mood in the study. We found that abnormalities in the white matter properties of right Arc and right SLF tracts may be related to the impairments of memory and cognitive function. Therefore, we will use a battery of neuropsychologic tests to comprehensively understand the specific cognitive functions of the primary insomnia patients in future studies.

Conclusions

The study investigated the abnormalities of WM microstructure in major tracts among primary insomnia patients by the AFQ method. The present study showed that primary insomnia was relatively robust to the changes of diffusion properties

along the right Arc and right SLF tracts. Although the significance of these findings for pathophysiologic models of primary insomnia remains to be elucidated, the AFQ method, which had been applied generally in clinical research and practice, has increased the sensitivity to detection of clinical changes and the specificity for the identification of locations of change compared to the methods that summarize an entire tract with a single statistic in primary insomnia. It may provide more specific biomarkers of WM neuropathology for primary insomnia. Therefore, the current results may shed new insights into the neural mechanisms of primary insomnia and provide new clues for primary insomnia treatment in the future.

Acknowledgements This research was supported by the National Natural Science Foundation of China under Grant Nos. 81871426, 81871430, 81571751, 81571753, 61771266, 31800926, 8151650 and 81701780, the Fundamental Research Funds for the Central Universities under the Grant No. JB151204, the program for Young Talents of Science and Technology in Universities of Inner Mongolia Autonomous Region NJYT-17-B11, the Natural Science Foundation of Inner Mongolia under Grant No. 2017MS(LH)0814, the program of Science and Technology in Universities of Inner Mongolia Autonomous Region NJZY17262, the Innovation Fund Project of Inner Mongolia University of Science and Technology No. 2015QNGG03, National Natural Science Foundation of Shaanxi Province under Grant no. 2018JM7075 and the US National Institutes of Health, Intramural Research program Y1AA3009. The authors declare no conflicts of interest.

Compliance with ethical standards

Ethical statements Informed consent was obtained from all individual participants included in the study.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors report no biomedical financial interests or potential conflicts of interest.

References

- Altena, E., Vrenken, H., Van Der Werf, Y. D., van den Heuvel, O. A., & Van Someren, E. J. W. (2010). Reduced orbitofrontal and parietal gray matter in chronic insomnia: A voxel-based morphometric study. *Biological Psychiatry*, *67*(2), 182–185. <https://doi.org/10.1016/j.biopsych.2009.08.003>.
- Baglioni, C., Spiegelhalter, K., Lombardo, C., & Riemann, D. (2010). Sleep and emotions: A focus on insomnia. *Sleep Medicine Reviews*, *14*(4), 227–238. <https://doi.org/10.1016/j.smrv.2009.10.007>.
- Baser, P. J. (1995). Inferring microstructural features and the physiological state of tissues from diffusion weighted image. *NMR in Biomedicine*, *8*, 333–344.
- Basser, P. J., & Pierpaoli, C. (2011). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. 1996. *Journal of Magnetic Resonance*, *213*(2), 560–570. <https://doi.org/10.1016/j.jmr.2011.09.022>.

- Breslau, N., Roth, T., Rosenthal, L., & Andreski, P. (1996). Sleep disturbance and psychiatric disorders—A longitudinal epidemiologic study of young adults. *Society of Biological Psychiatry*, *39*, 411–418.
- Buyse, D. J., Reynolds, C. F., III, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193–213.
- Catani, M., & Thiebaut de Schotten, M. (2008). A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex*, *44*(8), 1105–1132. <https://doi.org/10.1016/j.cortex.2008.05.004>.
- Catani, M., J. Howard, R., Pajevic, S., & Jones, D. K. (2002). Virtual in vivo interactive dissection of white matter fasciculi in the human brain. *NeuroImage*, *17*, 77–94. <https://doi.org/10.1006/nimg.2002.1136>.
- Chang, L. C., Jones, D. K., & Pierpaoli, C. (2005). RESTORE: Robust estimation of tensors by outlier rejection. *Magnetic Resonance in Medicine*, *53*(5), 1088–1095. <https://doi.org/10.1002/mrm.20426>.
- Chien, K.-L., Chen, P.-C., Hsu, H.-C., Su, T.-C., Sung, F.-C., Chen, M.-F., & Lee, Y. T. (2010). Habitual sleep duration and insomnia and the risk of cardiovascular events and all-cause death—report from a community-based cohort. *Sleep*, *33*(2), 177–184.
- Conturo, T. E., Lori, N. F., Cull, T. S., Akbudak, E., Snyder, A. Z., Shimony, J. S., McKinstry, R. C., Burton, H., & Raichle, M. E. (1999). Tracking neuronal fiber pathways in the living human brain. *Proceedings of the National Academy of Sciences*, *96*(18), 10422–10427.
- Cooper, J. (2001). Diagnostic and statistical manual of mental disorders (4th edn, text revision)(DSM-IV-TR) Washington, DC: American Psychiatric Association 2000. 943 pp.£ 39.99 (hb). ISBN 0 89042 025 4. *The British Journal of Psychiatry*, *179*(1), 85–85.
- Eddinger, J. D., Bonnet, M. H., Bootzin, R. R., Doghramji, K., Dorsey, C. M., Espie, C. A., Jamieson, A. O., McCall, W., Morin, C. M., Stepanski, E. J., & American Academy of Sleep Medicine Work Group. (2004). Derivation of research diagnostic criteria for insomnia: Report of an American Academy of sleep medicine work group. *Sleep*, *27*(8), 1567–1596.
- Eklund, A., Nichols, T. E., & Knutsson, H. (2016). Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(33), E4929. <https://doi.org/10.1073/pnas.1612033113>.
- Feldman, H. M., Yeatman, J. D., Lee, E. S., Barde, L. H. F., & Gaman-Bean, S. (2010). Diffusion tensor imaging: A review for pediatric researchers and clinicians. *Journal of Developmental & Behavioral Pediatrics*, *31*, 346–356.
- Fortier-Brochu, E., Beaulieu-Bonneau, S., Ivers, H., & Morin, C. M. (2012). Insomnia and daytime cognitive performance: A meta-analysis. *Sleep Medicine Reviews*, *16*(1), 83–94. <https://doi.org/10.1016/j.smrv.2011.03.008>.
- Gong, G., Jiang, T., Zhu, C., Zang, Y., Wang, F., Xie, S., Xiao, J., & Guo, X. (2005). Asymmetry analysis of cingulum based on scale-invariant parameterization by diffusion tensor imaging. *Human Brain Mapping*, *24*(2), 92–98. <https://doi.org/10.1002/hbm.20072>.
- Heidi, M., Feldman, M., Jason, D., Yeatman, B., Eliana, S., Lee, B., Laura, H. F., Barde, P., & Shayna Gaman-Bean, M. (2010). Diffusion tensor imaging: A review for pediatric researchers and clinicians. *Journal of Developmental & Behavioral Pediatrics*, *31*, 346–356.
- Hua, K., Zhang, J., Wakana, S., Jiang, H., Li, X. S., Reich, D., et al. (2008). Tract probability maps in stereotaxic spaces: Analyses of white matter anatomy and tract-specific quantification. *NeuroImage*, *39*, 336–347. <https://doi.org/10.1016/j.neuroimage.2007.07.053>.
- Huang, Z., Liang, P., Jia, X., Zhan, S., Li, N., Ding, Y., Lu, J., Wang, Y., & Li, K. (2012). Abnormal amygdala connectivity in patients with primary insomnia: Evidence from resting state fMRI. *European Journal of Radiology*, *81*(6), 1288–1295. <https://doi.org/10.1016/j.ejrad.2011.03.029>.
- Johnson, R. T., Yeatman, J. D., Wandell, B. A., Buonocore, M. H., Amaral, D. G., & Nordahl, C. W. (2014). Diffusion properties of major white matter tracts in young, typically developing children. *NeuroImage*, *88*, 143–154. <https://doi.org/10.1016/j.neuroimage.2013.11.025>.
- Joo, E. Y., Noh, H. J., Kim, J.-S., Koo, D. L., Kim, D., Hwang, K. J., Kim, J. Y., Kim, S. T., Kim, M. R., & Hong, S. B. (2013). Brain gray matter deficits in patients with chronic primary insomnia. *Sleep*, *36*(7), 999–1007. <https://doi.org/10.5665/sleep.2796>.
- Kamali, A., Flanders, A. E., Brody, J., Hunter, J. V., & Hasan, K. M. (2014). Tracing superior longitudinal fasciculus connectivity in the human brain using high resolution diffusion tensor tractography. *Brain Structure & Function*, *219*(1), 269–281. <https://doi.org/10.1007/s00429-012-0498-y>.
- Keller, S. S., Glenn, G. R., Weber, B., Kreilkamp, B. A., Jensen, J. H., Helpert, J. A., et al. (2017). Preoperative automated fibre quantification predicts postoperative seizure outcome in temporal lobe epilepsy. *Brain*, *140*(1), 68–82. <https://doi.org/10.1093/brain/aww280>.
- Kimberg, D. Y., & Farah, M. J. (1993). A unified account of cognitive impairments following frontal lobe Damage: The Role of Working Memory in Complex, Organized Behavior. *Journal of Experimental Psychology: General*, *122*(4), 411–428.
- Kyle, S. D., Morgan, K., & Espie, C. A. (2010). Insomnia and health-related quality of life. *Sleep Medicine Reviews*, *14*(1), 69–82. <https://doi.org/10.1016/j.smrv.2009.07.004>.
- Léger, D., Guilleminault, C., Bader, G., Lévy, E., & Paillard, M. (2002). Medical and socio-professional impact of insomnia. *Sleep*, *25*(2), 621–625.
- Li, Y., Wang, E., Zhang, H., Dou, S., Liu, L., Tong, L., Lei, Y., Wang, M., Xu, J., Shi, D., & Zhang, Q. (2014). Functional connectivity changes between parietal and prefrontal cortices in primary insomnia patients: Evidence from resting-state fMRI. *European Journal of Medical Research*, *19*, 32.
- Li, Y., Yuan, K., Guan, Y., Cheng, J., Bi, Y., Shi, S., Xue, T., Lu, X., Qin, W., Yu, D., & Tian, J. (2017). The implication of salience network abnormalities in young male adult smokers. *Brain Imaging and Behavior*, *11*(4), 943–953. <https://doi.org/10.1007/s11682-016-9568-8>.
- Li, M., Wang, R., Zhao, M., Zhai, J., Liu, B., Yu, D., Yuan K. (2018). Abnormalities of thalamus volume and resting state functional connectivity in primary insomnia patients. *Brain Imaging and Behavior*, *1*–9. <https://doi.org/10.1007/s11682-018-9932-y>.
- Lu, F. M., Dai, J., Couto, T. A., Liu, C. H., Chen, H., Lu, S. L., Tang, L. R., Tie, C. L., Chen, H. F., He, M. X., Xiang, Y. T., & Yuan, Z. (2017). Diffusion tensor imaging Tractography reveals disrupted white matter structural connectivity network in healthy adults with insomnia symptoms. *Frontiers in Human Neuroscience*, *11*, 583. <https://doi.org/10.3389/fnhum.2017.00583>.
- Morin, C. M., Be'langer, L., LeBlanc, M. I., Ivers, H., Savard, J. E., Espie, C. A., et al. (2009). The natural history of insomnia—A population-based 3 year longitudinal study. *Archives of Internal Medicine*, *169*(5), 447–453.
- Nichols, T. E., & Holmes, A. P. (2001). Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Human Brain Mapping*, *15*, 1–25.
- Nozinger, E. A., Buyse, D. J., Germain, A., Price, J. C., Miewald, J. M., & Kupfer, D. J. (2004). Functional neuroimaging evidence for hyperarousal in insomnia. *The American Journal of Psychiatry*, *161*(11), 2126–2128.
- O'Donnell, L. J., Westin, C. F., & Golby, A. J. (2009). Tract-based morphometry for white matter group analysis. *NeuroImage*, *45*(3), 832–844. <https://doi.org/10.1016/j.neuroimage.2008.12.023>.

- Ohayon, M. M. (2002). Epidemiology of insomnia: What we know and what we still need to learn. *Sleep Medicine Reviews*, 6(2), 97–111. <https://doi.org/10.1053/smr.2002.0186>.
- Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, 9(1), 97–113.
- Phillips, O. R., Clark, K. A., Woods, R. P., Subotnik, K. L., Asarnow, R. F., Nuechterlein, K. H., Toga, A. W., & Narr, K. L. (2011). Topographical relationships between arcuate fasciculus connectivity and cortical thickness. *Human Brain Mapping*, 32(11), 1788–1801. <https://doi.org/10.1002/hbm.21147>.
- Press, W. H., Teukolsky, S. A., Vetterling, W. T., & Flannery, B. P. (1994). Numerical recipes in C++: The art of scientific computing. *Wiley on behalf of the Royal Economic Society*, 104(424), 725–726.
- Riemann, D., Nissen, C., Palagini, L., Otte, A., Perlis, M. L., & Spiegelhalter, K. (2015). The neurobiology, investigation, and treatment of chronic insomnia. *The Lancet Neurology*, 14(5), 547–558. [https://doi.org/10.1016/s1474-4422\(15\)00021-6](https://doi.org/10.1016/s1474-4422(15)00021-6).
- Rohde, G. K., Barnett, A. S., Bassler, P. J., Marengo, S., & Pierpaoli, C. (2004). Comprehensive approach for correction of motion and distortion in diffusion-weighted MRI. *Magnetic Resonance in Medicine*, 51(1), 103–114. <https://doi.org/10.1002/mrm.10677>.
- Rowe, A. D., Bullock, P. R., Polkey, C. E., & Morris, R. G. (2001). 'Theory of mind' impairments and their relationship to executive functioning following frontal lobe excisions. *Brain*, 124, 600–616.
- Samson, A. C., Dougherty, R. F., Lee, I. A., Phillips, J. M., Gross, J. J., & Hardan, A. Y. (2016). White matter structure in the uncinate fasciculus: Implications for socio-affective deficits in autism Spectrum disorder. *Psychiatry Research: Neuroimaging*, 255, 66–74. <https://doi.org/10.1016/j.psychres.2016.08.004>.
- Sarsour, K., Kalsekar, A., Swindle, R., Foley, K., & Walsh, J. K. (2011). The association between insomnia severity and healthcare and productivity costs in a health plan sample. *Sleep*, 34(4), 443–450.
- Setsu Wakana, M., Hangyi Jing, P., Lidia, M., Nagae-Poetscher, M., Peter, C. M., van Zijl, P., & Susumu Mori, P. (2004). Fiber tract-based atlas of human white matter anatomy. *Radiology*, 230, 77–87.
- Shumei Li, M., Junzhang Tian, M., Andreas Bauer, M., Ruiwang Huang, P., Hua Wen, M., Meng Li, M., et al. (2016). Reduced integrity of right lateralized white matter in patients with primary insomnia: A diffusion-tensor imaging study. *Radiology*, 280(2). <https://doi.org/10.1148/radiol.2016152038>.
- Smith, E. E., & Kosslyn, S. M. (2007). Cognitive psychology-mind and brain. *New Jersey: Prentice Hall*, 21, 194–199,349.
- Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage*, 44(1), 83–98. <https://doi.org/10.1016/j.neuroimage.2008.03.061>.
- Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., Watkins, K. E., Ciccarelli, O., Cader, M. Z., Matthews, P. M., & Behrens, T. E. J. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage*, 31(4), 1487–1505. <https://doi.org/10.1016/j.neuroimage.2006.02.024>.
- Spiegelhalter, K., Regen, W., Prem, M., Baglioni, C., Nissen, C., Feige, B., Schnell, S., Kiselev, V. G., Hennig, J., & Riemann, D. (2014). Reduced anterior internal capsule white matter integrity in primary insomnia. *Human Brain Mapping*, 35(7), 3431–3438. <https://doi.org/10.1002/hbm.22412>.
- Stieltjes, B. E., Kaufmann, W., Peter, C. M., van Zijl, P., Fredericksen, K. D., Pearlson, G., Solaiyappan, M., et al. (2001). Diffusion tensor imaging and axonal tracking in the human brainstem. *NeuroImage*, 14, 723–735. <https://doi.org/10.1006/nimg.2001.0861>.
- Stoffers, D., Moens, S., Benjamins, J., van Tol, M. J., Penninx, B. W., Veltman, D. J., et al. (2012). Orbitofrontal gray matter relates to early morning awakening: A neural correlate of insomnia complaints? *Frontiers in Neurology*, 3, 105. <https://doi.org/10.3389/fneur.2012.00105>.
- Stuss, D. T., Gow, C. A., & Hetherington, C. R. (1992). "no longer gage": Frontal lobe dysfunction and emotional changes. *Journal of Consulting and Clinical Psychology*, 60(3), 349–359.
- Wakana, S., Caprihan, A., Panzenboeck, M. M., Fallon, J. H., Perry, M., Gollub, R. L., Hua, K., Zhang, J., Jiang, H., Dubey, P., Blitz, A., van Zijl, P., & Mori, S. (2007). Reproducibility of quantitative tractography methods applied to cerebral white matter. *NeuroImage*, 36(3), 630–644. <https://doi.org/10.1016/j.neuroimage.2007.02.049>.
- Wang, X., Pathak, S., Stefaneanu, L., Yeh, F. C., Li, S., & Fernandez-Miranda, J. C. (2016). Subcomponents and connectivity of the superior longitudinal fasciculus in the human brain. *Brain Structure & Function*, 221(4), 2075–2092. <https://doi.org/10.1007/s00429-015-1028-5>.
- Wassermann, D., Rathi, Y., Bouix, S., Kubicki, M., Kikinis, R., Shenton, M., et al. (2012). White matter bundle registration and population analysis based on Gaussian processes. *InfProcess Med Imaging*, 22, 320–332.
- Winkelman, J. W., Benson, K. L., Buxton, O. M., Lyoo, I. K., Yoon, S., O'Connor, S., et al. (2010). Lack of hippocampal volume differences in primary insomnia and good sleeper controls: An MRI volumetric study at 3 tesla. *Sleep Medicine*, 11(6), 576–582. <https://doi.org/10.1016/j.sleep.2010.03.009>.
- Wu, Y., Liu, M., Zeng, S., Ma, X., Yan, J., Lin, C., Xu, G., Li, G., Yin, Y., Fu, S., Hua, K., Li, C., Wang, T., Li, C., & Jiang, G. (2018). Abnormal topology of the structural connectome in the limbic Cortico-basal-ganglia circuit and default-mode network among primary insomnia patients. *Frontiers in Neuroscience*, 12, 860. <https://doi.org/10.3389/fnins.2018.00860>.
- Yeatman, J. D., Dougherty, R. F., Myall, N. J., Wandell, B. A., & Feldman, H. M. (2012). Tract profiles of white matter properties: Automating fiber-tract quantification. *PLoS One*, 7(11), e49790. <https://doi.org/10.1371/journal.pone.0049790>.
- Yuan, K., Jin, C., Cheng, P., Yang, X., Dong, T., Bi, Y., Xing, L., von Deneen, K. M., Yu, D., Liu, J., Liang, J., Cheng, T., Qin, W., & Tian, J. (2013). Amplitude of low frequency fluctuation abnormalities in adolescents with online gaming addiction. *PLoS One*, 8(11), e78708. <https://doi.org/10.1371/journal.pone.0078708>.
- Yuan, K., Qin, W., Yu, D., Bi, Y., Xing, L., Jin, C., & Tian, J. (2016a). Core brain networks interactions and cognitive control in internet gaming disorder individuals in late adolescence/early adulthood. *Brain Structure & Function*, 221(3), 1427–1442. <https://doi.org/10.1007/s00429-014-0982-7>.
- Yuan, K., Yu, D., Bi, Y., Li, Y., Guan, Y., Liu, J., Zhang, Y., Qin, W., Lu, X., & Tian, J. (2016b). The implication of frontostriatal circuits in young smokers: A resting-state study. *Human Brain Mapping*, 37(6), 2013–2026. <https://doi.org/10.1002/hbm.23153>.
- Yuan, K., Yu, D., Cai, C., Feng, D., Li, Y., Bi, Y., Liu, J., Zhang, Y., Jin, C., Li, L., Qin, W., & Tian, J. (2017). Frontostriatal circuits, resting state functional connectivity and cognitive control in internet gaming disorder. *Addiction Biology*, 22(3), 813–822. <https://doi.org/10.1111/adb.12348>.
- Yuan, K., Yu, D., Zhao, M., Li, M., Wang, R., Li, Y., Manza, P., Shokri-Kojori, E., Wiers, C. E., Wang, G. J., & Tian, J. (2018a). Abnormal frontostriatal tracts in young male tobacco smokers. *NeuroImage*, 183, 346–355. <https://doi.org/10.1016/j.neuroimage.2018.08.046>.
- Yuan, K., Zhao, M., Yu, D., Manza, P., Volkow, N. D., Wang, G. J., & Tian, J. (2018b). Striato-cortical tracts predict 12-h abstinence-induced lapse in smokers. *Neuropsychopharmacology*, 43(12), 2452–2458. <https://doi.org/10.1038/s41386-018-0182-x>.