Radiology

Reduced Integrity of Right Lateralized White Matter in Patients with Primary Insomnia: A Diffusion-Tensor Imaging Study[1]

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Purpose: To analyze the integrity of white matter (WM) tracts in primary insomnia patients and provide better characterization of abnormal WM integrity and its relationship with disease duration and clinical features of primary insomnia.

Materials and Methods: This prospective study was approved by the ethics committee of the Guangdong No. 2 Provincial People's Hospital. Tract-based spatial statistics were used to compare changes in diffusion parameters of WM tracts from 23 primary insomnia patients and 30 healthy control (HC) participants, and the accuracy of these changes in distinguishing insomnia patients from HC participants was evaluated. Voxel-wise statistics across subjects was performed by using a 5000-permutation set with family-wise error correction (family-wise error, $P < .05$). Multiple regressions were used to analyze the associations between the abnormal fractional anisotropy (FA) in WM with disease duration, Pittsburgh Sleep Quality Index, insomnia severity index, self-rating anxiety scale, and the self-rating depression scale in primary insomnia. Characteristics for abnormal WM were also investigated in tract-level analyses.

Results: Primary insomnia patients had lower FA values mainly in the right anterior limb of the internal capsule, right posterior limb of the internal capsule, right anterior corona radiata, right superior corona radiata, right superior longitudinal fasciculus, body of the corpus callosum, and right thalamus ($P < .05$, family-wise error correction). The receiver operating characteristic areas for the seven regions were acceptable (range, 0.60–0.74; 60%–74%). Multiple regression models showed abnormal FA values in the thalamus and body corpus callosum were associated with the disease duration, self-rating depression scale, and Pittsburgh Sleep Quality Index scores. Tract-level analysis suggested that the reduced FA values might be related to greater radial diffusivity.

Conclusion: This study showed that WM tracts related to regulation of sleep and wakefulness, and limbic cognitive and sensorimotor regions, are disrupted in the right brain in patients with primary insomnia. The reduced integrity of these WM tracts may be because of loss of myelination.

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Primary insomnia is an independent psychiatric syndrome that refers to difficulties in falling asleep or maintaining sleep for at least 1 month. It is associated with sequelae of daytime impairment or clinically significant distress, and the absence of medical, psychiatric, or environmental causes (1,2). According to an epidemiologic study, insomnia is a remarkably prevalent disorder, and primary insomnia disorder affects 3%–5% of the general adult population (3). Daytime fatigue, mood disruption, and cognitive impairments that affect primary insomnia patients reduce social productivity and quality of life and increase risk of accidents and health care utilization (4–6). Moreover, primary insomnia is a predisposing factor to psychiatric and cognitive disorders, especially depressive and anxiety disorders (7–9). Despite the adverse socioeconomic impacts of primary insomnia, its neurobiological causes and consequences are still elusive.

The development of neuroimaging techniques provided a new avenue of research to detect neuroanatomic and neurobiologic alterations associated with primary insomnia. Functional neuroimaging studies have shown abnormal metabolism and functional connectivity related to the thalamus, amygdala, premotor and sensorimotor cortices, anterior cingulate cortex, and medial prefrontal and insular cortices (10–12). However, current structural neuroimaging studies reported inconsistent results related to abnormal brain volumes in patients with insomnia (13–18). Further studies on structural neuroimaging may be needed to clarify these conclusions.

In vivo structural and functional imaging studies related to insomnia patients have suggested brain abnormalities in the thalamus, sensorimotor cortices, frontal lobe, and limbic brain regions (eg, anterior cingulate cortex, amygdala, and hippocampal). These brain abnormalities may in part be from disruptions in communication between these regions, which would be the case if the integrity of white matter (WM) tracts were impaired.

The purpose of this study was to analyze the integrity of WM tracts in primary insomnia patients and provide better characterization of abnormal WM integrity and its relationship with disease duration and clinical features of primary insomnia.

Advance in Knowledge

- Primary insomnia is associated with reduced integrity of white matter primarily in the right anterior and posterior internal capsule, the anterior coronal radiata, and the right superior corona radiate ($P < .05$, family-wise error correction).

Implication for Patient Care

- This study suggests that primary insomnia is characterized by altered structural connectivity related to regulation of sleep and wakefulness, particularly involving limbic and sensorimotor regions.

Materials and Methods

Participants

This prospective study was approved by the ethics committee of the Guangdong No. 2 Provincial People's Hospital. All primary insomnia patients were recruited from the Department of Neurology at Guangdong No. 2 Provincial People's Hospital, Guangzhou, China from April 2010 to April 2014. The inclusion criteria for primary insomnia patients in this study are as follows: *(a)* the patients satisfied the Diagnostic and Statistical Manual of Mental Disorders, version 4 (known as DSM-IV), and a semistandardized psychiatric and sleep-related interview was conducted by an experienced psychiatrist to rule out patients who had other sleep disorders (ie, hypersomnia, parasomnia, or sleep-related movement disorder) or other psychiatric disorders; *(b)* at least 1 month complaining of difficulty falling asleep, maintaining sleep, or early awakening at the same time; *(c)* right-handedness, assessed with the Edinburgh Handedness Inventory (19); *(d)* younger than 60 years; and *(e)* free of any psychoactive medication at least 2 weeks before and during the study. Furthermore, to evaluate the sleep situation and mental status of primary insomnia patients, all participants were asked to complete the Pittsburgh Sleep Quality Index (20), the insomnia severity index (21), the self-rating anxiety scale, and the self-rating depression scale (T.Y.W. and S.M.L, with 3 and 5 years of experience, respectively). Each participant completed informed written consent before undergoing magnetic resonance (MR) imaging. Exclusion criteria included patients who had an abnormal signal in any region of the brain verified by conventional T1- or T2-weighted fluid-attenuated inversion recovery MR imaging; insomnia that was caused by organic disease or severe mental disease secondary to depression or generalized anxiety; and women who were pregnant, nursing, or menstruating. Four patients were excluded because of T2-weighted fluid-attenuated inversion recovery MR images that showed abnormal hyperintense signal in the basal ganglia regions (G.H.J. and J.Z.T., with 25 and 30 years of experiences in neuroradiology) and

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Abbreviations:
FA = fractional anisotropy
FMRIB = Functional Magnetic Resonance of the Brain
HC = healthy control
WM = white matter

Author contributions:
Guarantors of integrity of entire study, S.L., J.T., H.W., M.L., G.J.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, S.L., A.B., H.W., M.L., T.W., G.J.; clinical studies, J.T., T.W., G.J.; experimental studies, S.L., J.T., H.W., T.W., L.X., G.J.; statistical analysis, S.L., R.H.; and manuscript editing, S.L., J.T., A.B., R.H., M.L.

Conflicts of interest are listed at the end of this article.

three patients were excluded because of severe mental disease. Finally, 23 primary insomnia patients (10 men, 13 women; mean age, 41.08 years ± 10.50) were included in this study.

We also recruited 30 age-, hand-, and sex-matched healthy control (HC) participants (18 men, 12 women; mean age, 41.60 years ± 9.48) from the local community by using advertisements. The HC participants were included in the study according to the following criteria: good sleep quality and an insomnia severity index score of less than 7; no brain lesions or prior substantial head trauma, verified by conventional T1- or T2-weighted fluid-attenuated inversion recovery MR imaging; and no history of psychiatric or neurologic diseases. The HC participants were excluded if they were left-handed.

MR Imaging

MR imaging data were obtained by using a 1.5-T MR imager (Achieva Nova-Dual; Philips, Best, the Netherlands) in the Department of Medical Imaging, Guangdong No. 2 Provincial People's Hospital (H.W., with 18 years of experience in MR imaging). Each participant lay supine with the head snugly secured by a belt and foam pads. The diffusion-tensor imaging datasets were acquired in 32 diffusion gradient directions (b = 800 sec/mm^2 along 32 noncollinear directions) with a b value reference image of 0 acquired by using a single-shot twice-refocused spin-echo diffusion echo-planar imaging sequence. The sequence parameters were as follows: repetition time (msec)/echo time (msec), 10700/80; 128 × 128 matrix; field of view, 256 mm × 256 mm; section thickness, 2 mm; isotropic voxel size, 2 mm^3; bandwidth, 2125 Hz/pixel; and 75 transverse sections without gap covered the whole brain. In addition, after diffusion-tensor imaging, we obtained the T1-weighted images and T2-weighted fluid-attenuated inversion recovery images. The sequence parameters for the T1-weighted images were as follows: 25/4.1; flip angle, 30°; 256 × 256 matrix; field of view, 230 mm × 230 mm; section thickness, 1 mm; and 160 transverse sections without gap covered the whole brain. The sequence parameters for the T2-weighted fluid-attenuated inversion recovery images were as follows: 8000/120; inversion time, 2500 msec; field of view, 210 mm × 201 mm; section thickness, 6 mm; and 18 transverse sections without gap covered the whole brain.

Data Analysis

Data preprocessing.—All datasets were analyzed by using a software tool (FSL version 4.1.9, part of the Functional Magnetic Resonance of the Brain [FMRIB] Software Library, Oxford, England; *http://www.fmrib.ox.ac.uk/fsl*) (S.M.L., with 5 years of experiences in MR imaging analysis and interpretation). The Diffusion Toolbox (FMRIB Software Library) was first used to correct for eddy current distortions and head motion by registering the diffusion-weighted images with the first volume of the diffusion data without gradient (b = 0) through the affine transformations. The binary brain mask was then generated from the image with a b value of 0 by using the Brain Extraction Tool (FMRIB Software Library). Finally, DTIfit (FMRIB Software Library) was independently used to fit the diffusion tensor to each voxel to yield fractional anisotropy (FA), mean diffusivity, and axial and radial diffusivity.

Tract-based spatial statistics.—We used tract-based spatial statistics (22) with multiple diffusion measures to better characterize the microstructure in primary insomnia patients than just with FA measure. Voxel-wise statistical analysis was performed by using tract-based spatial statistics from the FMRIB Software Library (22). The steps were as follows. First, all FA images were aligned to a 1 × 1 × 1 mm target FA image (FMRIB58_FA; FMRIB Software Library) by using nonlinear registration. We checked the aligned FA images to ensure accuracy of the transformations and then all aligned FA images were transformed into the 1 × 1 × 1 mm Montreal Neurologic Institute 152 template by using affine registrations. Then, the mean FA image was created to generate the mean FA skeleton, which is representative of all tracts with a common center. A threshold (FA > 0.2) was applied to the skeleton to include only major fiber bundles. The FA image of each participant was subsequently projected to the mean FA skeleton by searching for the local center of the relevant fiber tract. Finally, voxel-wise statistics across participants (covarying for age and sex) were performed voxel by voxel to detect regions of significant differences in FA by using a 5000-permutation set (Randomize FSL; FMRIB Software Library) with a correction for multiple comparisons (family-wise error correction). The P value indicative of significance with the family-wise error corrected threshold was set at less than .05. Statistically significant regions identified for HC participants versus primary insomnia patients were reported on the basis of the Johns Hopkins University International Consortium of Brain Mapping Diffusion Tensor Imaging 81 and the Harvard-Oxford Subcortical Structural Atlas. Tract-based spatial statistics analysis was repeated for mean diffusivity, axial diffusivity, and radial diffusivity maps. To assess the accuracy of FA values of WM tracts that show differences between the primary insomnia and HC groups, we used receiver operating characteristic curve analysis.

Tract-level comparison.—An entire WM tract was considered to be disrupted if it showed significant clusters detected by the voxel-wise comparison. In the voxel-wise comparison, significant clusters are small segments of the whole WM tract. To verify whether a tract was disrupted, mean FA values of all skeleton voxels of the specific tract were obtained. The Johns Hopkins University International Consortium of Brain Mapping Diffusion Tensor Imaging 81 atlas that we used covered the entire skeletons of major WM tracts. The overlaid region of significant clusters obtained from voxel-wise analysis and the Johns Hopkins University International Consortium of Brain Mapping Diffusion Tensor Imaging 81 atlas with specific WM labeling was used to calculate the mean FA

value that represented the integrity of the whole tract (Fig 1).

Statistical Analysis

Differences in age, duration of education, Pittsburgh Sleep Quality Index, insomnia severity index, self-rating anxiety scale, and self-rating depression scale scores between the primary insomnia and HC groups were assessed by using two-sample two-tailed *t* tests. A two-tailed Pearson χ^2 test was performed to determine differences associated with sex between the two groups. Voxel-wise statistics across participants by using tract-based spatial statistics (covarying for age and sex) were performed by using a 5000-permutation set (Randomize, implemented in FSL; FMRIB Software Library) with a correction for multiple comparisons (family-wise error correction). The *P* value that indicated significance with a family-wise error-corrected threshold was set at less than .05. We applied an exploratory stepwise hierarchical multiple regression (23,24) to analyze the relationships between abnormal FA values in WM tracts with disease duration, Pittsburgh Sleep Quality Index, self-rating anxiety scale, and self-rating depression scale scores. We took the FA value of significant regions between primary insomnia and HC participants as the dependent variable and disease duration, Pittsburgh Sleep Quality Index, self-rating anxiety scale, and self-rating depression scale scores as independent predictor variables, and we used the multiple correlation coefficients to indicate how well the clinical variables for every participant could account for the abnormal FA values. Two-sample two-tailed *t* tests were used in the tract-level analysis to further test whether the mean FA, mean diffusivity, axial diffusivity, and radial diffusivity values in the whole tract between the HC and primary insomnia groups were significantly different.

Results

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the participants in this study are shown in Table 1. The HC and

Figure 1

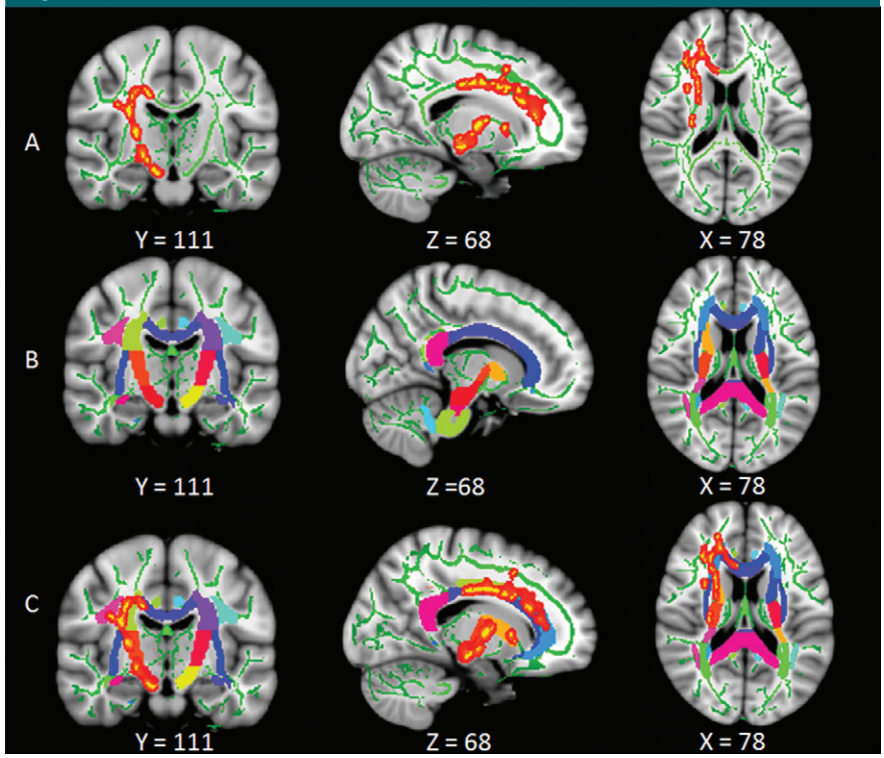

Figure 1: Tract-based analysis for whole WM tracts. *A,* Significant differences in WM detected from analysis of tract-based spatial statistics. Results are shown overlaid on the Montreal Neurologic Institute 152-T1 template and the mean FA skeleton (green). *B,* The Johns Hopkins University International Consortium of Brain Mapping Diffusion Tensor Imaging 81 atlas that covers the entire skeletons of major WM tracts is shown overlaid on the Montreal Neurologic Institute 152-T1 template. *C,* The overlaid region of significant clusters obtained from tract-based spatial statistics analysis and the Johns Hopkins University International Consortium of Brain Mapping Diffusion Tensor Imaging 81 atlas. The overlapping WM labeling from the Johns Hopkins University International Consortium of Brain Mapping Diffusion Tensor Imaging 81 atlas was used to extract the whole WM and to calculate the mean FA value that represents the integrity of the whole tract.

Table 1

Demographics and Clinical Characteristics of All Participants

Parameter	Primary Insomnia Patients	HC Participants	*P* Value
Sex			.80
No. of men	10	18	
No. of women	13	12	
Age (y)	41.08 ± 10.50 (0.46)	41.60 ± 9.48 (0.32)	.85
Duration (mo)	18.39 ± 20.35 (4.24)		
Education (y)	10.96 ± 2.92 (0.61)	9.40 ± 3.42 (0.11)	.09
PSQI	13.43 ± 3.20 (0.67)	5.33 ± 0.92 (0.03)	<.001
ISI	19.83 ± 3.49 (0.73)	5.37 ± 1.03 (0.03)	<.001
SAS	47.96 ± 9.78 (2.03)	37.77 ± 4.30 (0.14)	<.001
SDS	52.70 ± 8.91 (1.86)	40.73 ± 4.11 (0.14)	<.001

Note.—Unless otherwise noted, data are mean ± standard deviation; data in parentheses are stand error. There were 23 patients with primary insomnia and 30 HC participants. ISI = insomnia severity index, PSQI = Pittsburgh Sleep Quality Index, SAS = self-rating anxiety scale, SDS = self-rating depression scale.

Figure 2

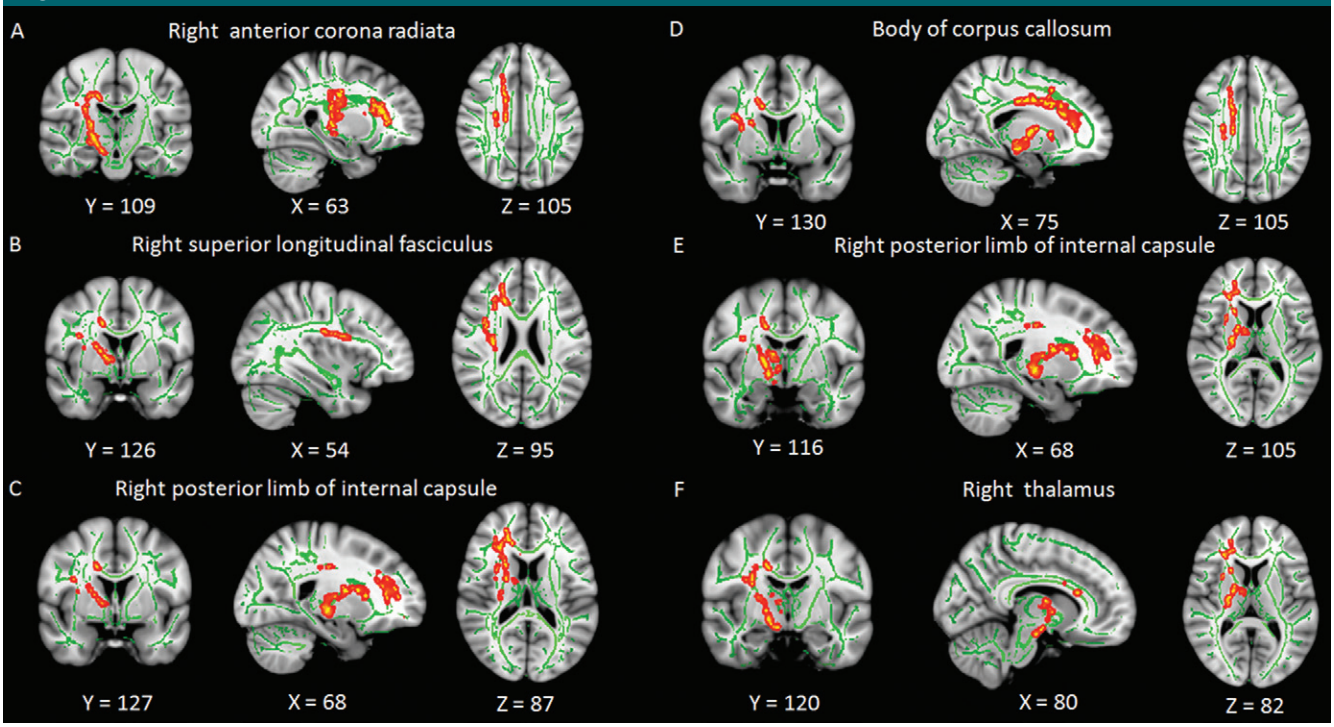

Figure 2: Significant WM clusters obtained from tract-based spatial statistics between primary insomnia and HC groups. Green represents the mean FA skeleton and red-yellow shows clusters with a significant FA reduction in the primary insomnia group ($P < .05$, family-wise error correction). Underlying gray-scale images are the Montreal Neurologic Institute 152-T1 template. Each panel is the best axial, coronal, and sagittal view that shows the specific WM tract.

primary insomnia groups showed no significant differences regarding age ($P = .85$), sex ($P = .80$), and education ($P = .09$). As expected, primary insomnia patients had higher Pittsburgh Sleep Quality Index, insomnia severity index, self-rating anxiety scale, and self-rating depression scale scores than HC participants (Table 1).

Voxelwise Comparison of WM Changes

Results of tract-based spatial statistics analysis consistently showed significantly lower FA values in several WM tracts in primary insomnia patients, including the right anterior limb of the internal capsule, right posterior limb of the internal capsule, right anterior corona radiata, right superior corona radiata, right superior longitudinal fasciculus, and the body of the corpus callosum (Fig 2). In addition, a significantly lower FA value in the right thalamus was also reported from the Harvard-Oxford Subcortical Structural Atlas (Fig 2). The areas under the receiver operating characteristic curve for the six WM tracts (right anterior limb of the internal capsule, right posterior limb of the internal capsule, right anterior corona radiata, right superior corona radiata, right superior longitudinal fasciculus, and body of the corpus callosum) and the right thalamus were 0.70 (70%), 0.74 (74%), 0.67 (67%), 0.65 (65%), 0.71 (71%), 0.60 (60%), and 0.64 (64%), respectively. There were no significant differences in WM tracts in the mean diffusivity, axial diffusivity, and radial diffusivity measures between the primary insomnia and HC groups after the family-wise error correction.

Tract-level Comparison of WM Changes

The voxel-wise comparison showed that five of six (83%) whole WM tracts in the primary insomnia group had significantly lower FA values except for the body of the corpus callosum compared with the HC group (Table 2). Figure 3 shows the distribution of the six whole WM tracts. In addition, we also found that three whole WM tracts (right anterior limb of the internal capsule, right posterior limb of the internal capsule, and right anterior corona radiata) showed statistically significant greater radial diffusivity values in the primary insomnia patients compared with the HC group (Table 2). There were no statistically significant differences in the mean diffusivity and axial diffusivity measures between the two groups in the tract-level comparison (Table 3).

Relationship between FA Values Derived from Tract-based Spatial Statistics Results and Clinical Variables

We found that only one variable, disease duration, provided the best fit to the FA value in the right thalamus ($F = 6.60$; $P = .02$; $R^2 = 0.24$). The FA

Table 2

Group Differences in FA and Radial Diffusivity Indexes from Whole WM Tracts

	FA Value			Radial Diffusivity Value		
Tract	Primary Insomnia Patients	HC Patients	*P* Value	Primary Insomnia Patients ($\times 10^{-4}$ mm^2/sec)	HC Patients ($\times 10^{-4}$ mm^2/sec)	*P* Value
ACRR	0.52 ± 0.02	0.55 ± 0.05	.02*	5.05 ± 0.25	4.77 ± 0.61	.04*
ALICR	0.62 ± 0.02	0.65 ± 0.04	.01*	4.12 ± 0.09	3.89 ± 0.58	.04*
PLICR	0.70 ± 0.03	0.74 ± 0.04	.002*	3.60 ± 0.24	3.24 ± 0.66	.02*
SLFR	0.55 ± 0.02	0.58 ± 0.04	.02*	4.92 ± 0.28	4.65 ± 0.64	.07
SCRR	0.54 ± 0.02	0.56 ± 0.05	.04*	4.81 ± 0.34	4.56 ± 0.05	.13
BCCR	0.73 ± 0.02	0.74 ± 0.03	.09	3.74 ± 0.33	3.52 ± 0.60	.12

Note.—Data are mean ± standard deviation. ACRR = right anterior corona radiata, ALICR = right anterior limb of the internal capsule, BCCR = body of the corpus callosum, PLICR = right posterior limb of the internal capsule, SCRR = right corona radiata, SLFR = right superior longitudinal fasciculus.

* Statistically significant

Figure 3

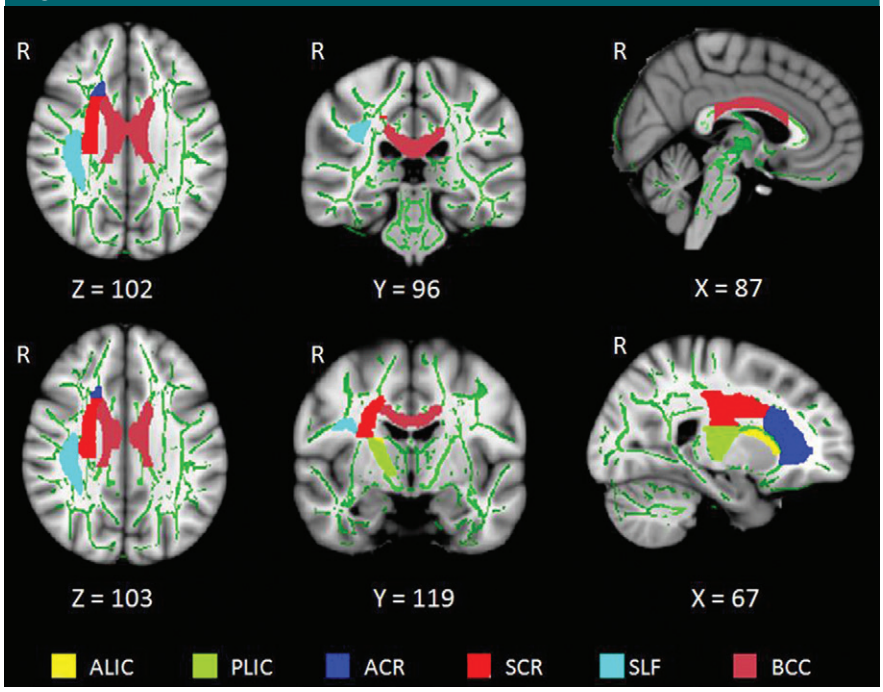

Figure 3: Distribution of the six whole WM tracts in the brain. *ALIC* = anterior limb of the internal capsule, *ACR* = anterior corona radiata, *BCC* = body of the corpus callosum, *PLIC* = posterior limb of the internal capsule, *R* = right side of the brain, *SCR* = superior corona radiata, *SLF* = superior longitudinal fasciculus.

value in the right thalamus was significantly negatively correlated with disease duration ($r = -0.49$; $P = .02$; Fig 4). In addition, we found that two variables, the self-rating depression scale and Pittsburgh Sleep Quality Index scores, provided the best fit to the FA value in the right body of the corpus callosum. ($F = 6.02$; $P = .009$; $R^2 = 0.38$). However, only the self-rating depression scale score was significantly positively correlated with the FA value in right body of the corpus callosum ($r = 0.42$; $P = .04$; Fig 4).

Discussion

Our findings showed reduced WM integrity, which manifested as lower FA, in some adjacent WM tracts in the right hemisphere in primary insomnia patients compared with HC patients. These impaired WM tracts mainly involve regulation of sleep and wakefulness (anterior limb of the internal capsule), cognitive function (anterior coronal radiata, superior coronal radiata), emotional function (body of corpus callosum), and sensorimotor function (posterior limb of the internal capsule). Tract-level comparison of WM changes revealed the decreased integrity reflected by the increased radial diffusivity in anterior and posterior limb of the internal capsule and anterior coronal radiata tracts. This finding suggests that the mechanism underlying decreased FA in the primary insomnia patients is increased radial diffusivity (ie, loss of myelination), which was not previously well established in the literature. In addition, the abnormal FA value in the right thalamus was associated with disease duration and the abnormal FA value in the body of corpus callosum was associated with both the self-rating depression scale and Pittsburgh Sleep Quality Index scores.

Our current findings are supported by previously published neuroimaging studies focused on different imaging techniques, such as resting-state functional MR imaging, diffusion-tensor imaging, positron emission tomography, and voxel-based morphometry (10–12,14–16,18,25), in primary insomnia. Previous researchers demonstrated that multiple brain regions, especially the frontal, subcortical nuclei, and limbic or parietal lobes, had metabolic, regional, spontaneous activity, and functional and structural connectivity abnormities in primary insomnia. By using the diffusion-tensor imaging technique, a study (25) showed reduced FA values within the right anterior internal capsule and a trend for reduced FA values in the left anterior internal capsule. However, there are two limitations in this diffusion-tensor imaging study: they used voxel-based analysis,

Table 3

Group Differences in Mean and Axial Diffusivity Indexes from Whole WM Tracts

	Mean Diffusivity Value			Axial Diffusivity Value		
Tract	Primary Insomnia Patients ($\times10^{-4}$ mm^2/sec)	HC Patients ($\times10^{-4}$ mm^2/sec)	*P* Value	Primary Insomnia Patients ($\times10^{-4}$ mm^2/sec)	HC Patients ($\times10^{-4}$ mm^2/sec)	*P* Value
ACRR	7.31 ± 0.31	7.06 ± 0.63	.09	12 ± 0.60	12 ± 0.73	.30
ALICR	6.80 ± 0.27	6.61 ± 0.65	.19	12 ± 0.67	12 ± 0.89	.71
PLICR	6.93 ± 0.32	6.62 ± 0.72	.06	13 ± 0.73	14 ± 0.96	.42
SLFR	7.34 ± 0.26	7.12 ± 0.70	.17	12 ± 0.47	12 ± 0.88	.60
SCRR	7.05 ± 0.36	6.84 ± 0.76	.21	11 ± 0.47	12 ± 0.88	.46
BCCR	7.79 ± 0.35	7.54 ± 0.72	.14	16 ± 1.14	16 ± 0.58	.24

Note.—Data are mean ± standard deviation. ACRR = right anterior corona radiata, ALICR = right anterior limb of the internal capsule, BCCR = body of the corpus callosum, PLICR = right posterior limb of the internal capsule, SCRR = right corona radiata, SLFR = right superior longitudinal fasciculus.

Figure 4

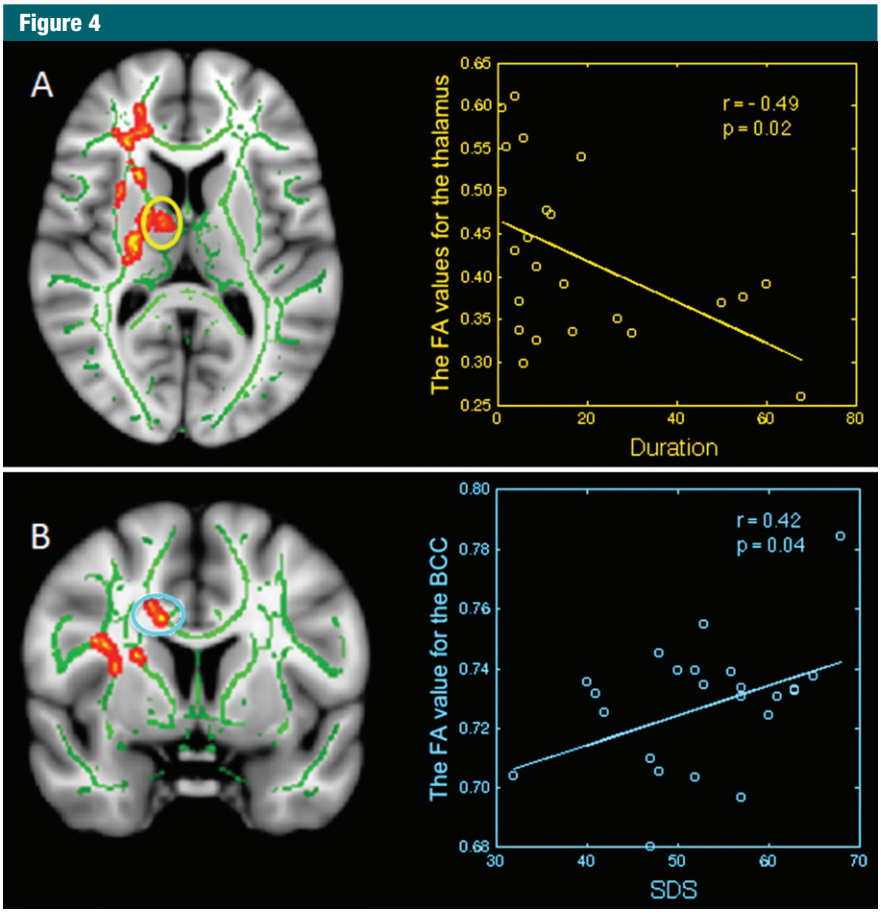

Figure 4: Relationship between mean FA and disease duration and clinical features in primary insomnia; region-of-interest maps (left side) are displayed with the corresponding graphs (right side). *A,* Significant negative correlation between FA values for the right thalamus with disease duration in primary insomnia. *B,* Significant positive correlation between FA values for the body of the corpus callosum with self-rating depression scale scores *(SDS)* in primary insomnia. *BCC* = body of the corpus callosum.

in which alignment problems are unresolved; and they only used the FA measure, and additional causes for the reduction in integrity of the WM tract are not clear. Our study used tract-based spatial statistics that can overcome the limitations of the voxel-based analysis and found reduced FA value in the anterior limb of the internal capsule. In addition, our study found that the FA value in the thalamus was reduced, and the FA value in the thalamus was negatively correlated with duration of primary insomnia, which indicated that FA in the thalamus is progressively reduced with disease duration. This could point to an involvement of thalamus in the pathologic structure of primary insomnia, which is particularly critical because important constituents of the biologic clock are located in the thalamus (26). Apart from FA measures, we found radial diffusivity measures attributed to reduced WM integrity, which suggests that a loss of myelination (27,28) in the primary patients is causative for the increased radial diffusivity and consecutively for the reduced FA in the WM tracts.

Previous studies (29–31) suggested that the anterior corona radiata and superior corona radiata are associated with functions of the executive network. Primary insomnia patients often undergo a decline in executive ability, attention, and working memory in daytime (32,33). Our results therefore suggest that reduced integrity in

anterior corona radiata and superior corona radiata are associated with daytime dysfunction in primary insomnia. Alterations in the sensorimotor cortex in primary insomnia patients were reported in functional neuroimaging studies (12,34). In this study, all enrolled primary insomnia patients reported difficulties falling asleep and reduced daytime activity. Thus, our and previous results suggest that reduced FA values in the posterior limb of the internal capsule may be part of the underlying neurobiological pathologic structure responsible for the long-term difficulties in sleep initiation and daytime fatigue. The reduced FA value in the body of the corpus callosum, as observed in our study, may be related to emotional and sleep perturbations in primary insomnia patients (7–9). We also found a significant positive correlation between FA values in the body of the corpus callosum and self-rating depression scale scores, which further support the view that impaired integrity in the body of the corpus callosum might be related to depressed mood in primary insomnia.

There are several limitations in our study. First, the sample size is relatively small. In this study, we found that the integrity of WM in primary insomnia patients was primarily affected in the right hemisphere. This might be an indication for a lateralized pathologic structure in primary insomnia. It is also noteworthy that the receiver operating characteristic area values for the six WM tracts that we examined showed only modest accuracies to distinguish the insomnia patients from HC participants, although these WM tracts are related to the emergence of insomnia and may contribute to the structural connectivity of primary insomnia. Thus, further studies with a larger statistical power will have to verify these results. Second, 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. Third, we only tested the sleep- and mood-related tests in the study, and it might be better to use a battery of neuropsychologic tests (eg, digit-symbol test, line-tracing test, and serial-dotting test) to comprehensively understand the specific cognitive functions of the primary insomnia patients.

In summary, our study suggests that primary insomnia is associated with reduced WM integrity primarily in the right anterior and posterior internal capsule, the anterior coronal radiata, and the right superior corona radiata. Although the significance of these findings for pathophysiologic models of primary insomnia remains unclear, our study suggests that primary insomnia is characterized by altered structural connectivity related to regulation of sleep and wakefulness, particularly involving limbic cognitive function and sensorimotor regions.

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