White Matter Alterations in Heart-kidney Imbalance Insomnia and Jiao-tai-wan Treatment: A Diffusion-tensor Imaging Study

Jie Chen
The First Affiliated Hospital of Wenzhou Medical University
Yanxuan Li
The First Affiliated Hospital of Wenzhou Medical University
Nengzhi Xia
The First Affiliated Hospital of Wenzhou Medical University
Caiyun Wen
The First Affiliated Hospital of Wenzhou Medical University
Tianyi Xia
The First Affiliated Hospital of Wenzhou Medical University
Yuandi Zhuang
The First Affiliated Hospital of Wenzhou Medical University
Mengmeng Jiang
The First Affiliated Hospital of Wenzhou Medical University
Yilan Xiang
The First Affiliated Hospital of Wenzhou Medical University
Mingyue Zhang
The First Affiliated Hospital of Wenzhou Medical University
Chenyi Zhan
The First Affiliated Hospital of Wenzhou Medical University
Yunjun Yang
The First Affiliated Hospital of Wenzhou Medical University
Qun Huang (dr_wongq@wzhospital.cn)
Department of Radiology, The First Affiliated Hospital of Wenzhou Medical University, 325000, Wenzhou, China https://orcid.org/0000-0003-1898-0601
Zhengzhong Yuan
The First Affiliated Hospital of Wenzhou Medical University

Research

Keywords: Insomnia, Jiao-tai-wan, traditional Chinese medicine, diffusion-tensor imaging, Magnetic resonance imaging, white matter

Posted Date: January 4th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-136220/v1

Version of Record: A version of this preprint was published at Brain Imaging and Behavior on March 25th, 2022. See the published version at https://doi.org/10.1007/s11682-022-00653-6.

Abstract

Background: Previous studies have reported changes in white matter (WM) microstructures in patients with insomnia. However, few neuroimaging studies have focused specifically on WM tracts in insomnia patients after having received treatment. In this prospective study, diffusion-tensor imaging was used in two samples of heart-kidney imbalance insomnia patients (HKIIPs) who were treated with Jiao-Tai-Wan (JTW) or a placebo to assess the changes in WM tracts.

Methods: Tract-based spatial statistical analyses were first applied to compare the changes in mean diffusivity (MD) and fractional anisotropy (FA) of WM between 75 HKIIPs and 41 healthy control participants. In subsequent randomized, double-blind, placebo-controlled trials, comparisons of MD and FA were also performed in 24 HKIIPs (8 males; 16 females; 42.5 ± 10.4 years) with JTW and 26 HKIIPs (11 males; 15 females; 39.7 ± 9.4 years) with a placebo, with age and sex as covariates.

Results: HKIIPs showed lower MD and FA values of several WM tracts than healthy control participants, such as the bilateral anterior limb of internal capsule, bilateral superior longitudinal fasciculus and bilateral posterior corona radiata. Specifically, FA values in left corticospinal tract (CST) were increased in HKIIPs. After being treated with JTW, HKIIPs showed a trend towards reduced FA values in the left CST.

Conclusions: These results suggest that JTW may reverse WM alterations caused by heart-kidney imbalance insomnia.

Trial registration: Chinese Clinical Trial Registry, ChiCTR1800019239; registered on 1 November 2018-retrospectively registered, http://www.chictr.org.cn/listbycreater.aspx, more than a month after the start of the experiment. The delay was due to lack of experience regarding trail, registration with a data sharing website.

Background

Insomnia is one of the most prevalent subjective complaints of sleep-disordered patients worldwide, and it is reported that approximately 4–20% of the population suffers from insomnia [1–3]. The main characteristic of insomnia is that people with insomnia usually have chronic difficulty falling asleep, difficulty staying sleep, and/or early morning awakening. Insomnia is associated with an increased risk of psychiatric disorders and the quality of an affected patient's life is severely reduced [4–6]. Moreover, chronic insomnia is a predisposing factor for type II diabetes, metabolic syndrome and cardio-cerebrovascular diseases [7, 8]. Although numerous studies have focused on insomnia, the mechanisms underlying the occurrence of insomnia remain poorly understood. According to traditional Chinese medicine (TCM) pattern differentiation, insomnia is mainly caused by disharmony of yin, yang and qi.

Among which, the incompatibility between the heart and kidney is one of the most common pathogenic mechanisms, which can be understood as heart-kidney dysfunction and an imbalance in substance exchange [9, 10].

Current guidelines set cognitive behavioral therapy for insomnia as the preferred treatment for patients who suffer from insomnia [11, 12]. However, poor adherence may diminish its therapeutic effect [13]. Many people cannot address their insomnia without taking a combination of medications. Besides, most therapies only transiently alleviate the symptoms of insomnia instead of delivering a complete cure. The most widely used medications for insomnia are benzodiazepines and benzodiazepine receptor agonists [12]. Still, these therapies incur numerous side effects, including depression, poor memory or forgetfulness, drowsiness and impaired work productivity. In addition, their use is heavily limited by developed tolerance and increased dependency with long-term treatment [12, 14]. So far, guidance for clinicians in choosing the best treatment remains limited, and the search for better treatments is underway. In recent years, increasing evidence has shown that TCM can be effectively applied in the treatment of insomnia [15–17]. It was reported that Jiao-tai-wan (JTW), made of Rhizome Coptidis and Cortex Cinnamomi at a ratio of 10:1, has a remarkable effect in treating of insomnia linked to an incompatibility between heart and kidney [18–20]. Experimental studies have shown that JTW can not only regulate levels of neurotransmitters in the blood, such as orexin A (brain tissue), 5-hydroxy tryptamine(5-HT) and γ-aminobutyric acid, which are all therapeutic targets for insomnia [18, 21], but it may also regulate immune cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor, which are upregulated by sleep loss [22].

Diffusion-tensor imaging (DTI) is a non-invasive method which is widely used to assess alterations in white matter integrity. Although several studies have investigated white matter structures in people with insomnia, the results of these studies remained inconsistent. For instance, Spiegelhalder et al. [23] reported a reduced white matter integrity of bilateral anterior internal capsule in primary insomnia, while Bresser et al. [24] only found decreased fractional anisotropy (FA) values in the right limb of the anterior internal capsule. Kang et al. [25] showed low white-matter integrity between the inferior frontal gyrus and left thalamus in insomnia patients. Li et al. [26] indicated that the integrity of right lateralized white matter in insomnia patients was reduced. Sexton et al. [27] even reported that poor sleep quality was correlated with reduced global FA values. Besides, the effect of insomnia treatment on white matter has not yet been studied.

Therefore, we sought to investigate the alterations in white-matter structure caused by insomnia, and the curative effect of JTW in insomnia based on evidence of white matter integrity.

Methods

2.1 Participants

This prospective study was designed as a double-blind, randomized, placebo-controlled trial and was approved by the Institutional Medical Ethics Committee of No. 1 Affiliated Hospital, Wenzhou Medical University (Approval document #2016045). Heart-kidney imbalance insomnia patients (HKIIPs) were recruited from The First Affiliated Hospital of Wenzhou Medical University from September 2018 to August 2019 through WeChat, flyers and bulletin boards at the hospital. All HKIIPs were asked to

complete the magnetic resonance imaging (MRI) examination, polysomnography (PSG) and Pittsburgh Sleep Quality Index (PSQI) before and after the medication intervention.

The inclusion criteria for HKIIPs were as follows: (a) Aged 18- to 60- years-old, right-handed, male and female, in junior high school or above; (b) According to the DSM-V, insomnia was defined as having difficulty falling asleep, staying asleep or having refreshing sleep, occurring 3 or more times per week, for at least 3 months [28]; (c) A PSQI score of greater than or equal to 7 according to the criteria for insomnia described in CCMD-3 [29]; (d) A Disharmony of Heart and Kidney Scoring System score is greater than 9 [29]; (e)Free of any psychoactive medication or hypnotic or cognitive behavioral therapy for insomnia for at least 2 weeks before the study.

Major exclusion criteria are listed as follows: (a) The presence of any abnormal brain MRI findings; (b) Insomnia caused by changes in lifestyle or environmental factors; (c) A history of serious mental disorders (e.g., anxiety, depression or schizophrenia); (d) Suffering from a physical disorder that affects the central nervous system; (e) Having liver and kidney dysfunction; (f) Alcoholism and/or psychotropic drug addiction; (g) Pregnant, breastfeeding or menstruating women.

The brief flow diagram of the study process is shown in Fig. 1. A total of 80 HKIIPs who passed preliminary screening criteria were recruited to this study. Among these, 2 patients were excluded due to abnormal intracranial occupying signals in their MR images, as diagnosed by two physicians with over 20 years experiences in neuroradiology. In addition, 3 patients were excluded due to severe mental illness. Seventy-five eligible HKIIPs (26 males, 49 females) were included in the present study. HKIIPs were randomly divided into two groups: the JTW group (n = 36) and the placebo group (n = 39). A total of 25 patients were excluded based on the following criteria: no DTI data after treatment (JTW group = 12; placebo group = 11); lack of post-treatment PSQI and PSG data (JTW group = 0; placebo group = 2). Eventually, we obtained a sample of 50 HKIIPs (JTW group = 24, placebo group = 26; 19 men, 31 women).

Forty-one age- and sex-matched healthy controls (HCs; 16 males, 25 females) were also recruited from the local community through advertisements as mentioned above. The inclusion criteria for HC participants were as follows : good sleep quality (PSQI $\leq$ 5); no history of psychiatric or neurologic diseases; and normal conventional MRI findings.

All participants for examination and/or treatment were asked to sign an informed consent form.

2.2 Intervention

A double-blind placebo-controlled drug administration technique was used. Both experimental drugs (JTW) and matched placebos were made by the Kang-ren Pharmaceutical Factory (Shanghai China). JTW were produced as yellowish-brown granules, containing 1.1 g JTW soft extract consisted of Cortex Cinnamomi and Rhizome Coptidis at a ratio of 1:10. The placebos (containing only the excipients, i.e., corn starch, citric acid, lactose hydrate and caramel color) with the same appearance and color as JTW were packaged in identical plastic bags to ensure blinding. HKIIPs ingested 2 g JTW or placebo at 4 pm

and 9 pm daily for a week according to groups, and followed the scheduled examination time at the termination of the medication intervention period.

2.3 Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) used in this study is a retrospective self-rated questionnaire consisting of 19 items. [30] The PSQI was used in this study at the beginning and end of the medicine intervention. The scores obtained at the beginning were recorded as score 1, and the scores obtained at the end were recorded as score 2. A higher PSQI score means worse quality of sleep. Clinical efficacy was calculated according to the following formula: Clinical efficacy = score 2 – score 1.

2.4 Polysomnography

Polysomnography (PSG) was performed at baseline and 1 week later at the end of the medication intervention. All HKIIPs underwent full, in-laboratory PSG by study-certified technicians according to the guidelines of American Academy of Sleep Medicine. Changes in sleep quality were objectively measured by mean changes in all parameters, including total sleep time (TST), sleep efficiency (SE), sleep onset latency (SL), rapid eye movement latency (RL), awakening times (AT), arousal index (AI), rapid eye movement (REM) and 3 parts of non-rapid eye movement (N1,N2 and N3), from baseline to the end of the medication intervention. Clinical effects were assessed by the following formula: Clinical efficacy = parameters after treatment – parameters before treatment. During the recording period, all participants were asked to abstain from alcohol, caffeine and daytime naps.

2.5 MRI

Each participant signed a written consent form before undergoing the MRI examination. All MRI scans were carried out using a 3 T MRI scanner (Philips Achieva TX) with an 8-channel receive-only head coil. Additionally, in order to reduce the effect of scanner noise and head motion, all subjects laid in a supine position with ear plugs and foam pads. The DTI datasets were acquired along 16 gradient directions (b = 1000s/mm2), including five acquisitions without diffusion weighting (b = 0). The sequence parameters were as follows: repetition time (msec) / echo time (msec), 6800 / 93; 128 × 128 matrix; field of view, 256 mm × 256 mm; slice thickness = 3 mm, no gap; and 50 contiguous axial slices. Several other sequences were also scanned, such as T2-weighted images, T1-weighted images, T1- fluid attenuated inversion recovery (FLAIR) images, T2-FLAIR images, and all scans were inspected for motion artefacts and for the absence of pathologic findings by a neuroradiologist.

2.6 Data analysis

Data preprocessing. —DTI data were preprocessed using tools in FSL (FMRIB Software Library 5.0.9) as follows. Firstly, all DTI images were corrected for distortions caused by eddy current distortions and head motion by using an affine alignment of each diffusion-weighted image to the non-diffusion weighted (b = 0) image by the FMRIB’s Diffusion Toolbox. Secondly, FSL's Brain Extraction Tool (BET) was applied to generate a binary mask from the b0 image and remove any non-brain tissue (fractional intensity

threshold = 0.2)[31]. Finally, a tensor model was fitted locally to each voxel using DTIfit (FSL) and maps of FA and MD were calculated.

Tract-based spatial statistics.—The voxel-wise statistical analysis of DTI data was based on tract-based spatial statistics (TBSS) from the FMRIB Software Library [32], which was used to characterize the microstructure with multiple diffusion measures better than that with FA measures alone. The FA images from all subjects (n = 116) were aligned to a common target FA image (1 × 1 × 1 mm3 MNI152 FMRIB58_FA standard space) using a non-linear registration. Next, a mean FA image was created and thresholded (FA > 0.2) to generate a mean FA skeleton representing the centers of all tracts. Subsequently, each participant's aligned FA images were projected onto the mean FA skeleton for statistical analysis. For better assessment, a TBSS analysis was repeated for MD maps.

2.7 Statistical analysis

Differences in age, PSQI and objective sleep measures on polysomnography between HKIIPs and HCs, JTW and placebo group were analyzed by two-sample, two-tailed t tests. Differences in the proportion of females and males between above groups were determined by a two- tailed Pearson $\chi 2$ test. Differences in clinical efficacy of medication between JTW and placebo group were assessed by two-sample, two-tailed t tests.

A white-matter statistical analysis (covarying for age and sex) was performed, as described in the general linear model (GLM, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/GLM) and permutation analysis of linear models (PALM, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PALM). To correct for multiple-comparisons, a threshold-free cluster enhancement with randomized (5000 permutations) nonparametric testing protocol was used to control for false discovery rates < 0.05 (family-wise error correction, FWE or FDR-correction) using PALM. In addition, we used a cluster-correction to assess possible correlations, using p values < 0.001 and a minimum cluster size of 50 voxels. The Johns Hopkins University (JHU) ICBM-DTI81 White Mater Labels and JHU white-matter tractography atlas were used to locate the specific fibers.

Results

3.1 Demographic characteristics

Table 1 presents the characteristics of the participants in this study. The differences between HC group and HKIIPs group were not significantly different for age ($p = 0.641$) or sex distribution (p = 0.816). Furthermore, HKIIPs had higher PSQI scores than HC participants (12.5 ± 3.0 versus. 2.9 ± 1.4; $p < 0.001$).

Table 1
Demographics and clinical characteristics of all Participants

	All participants			HKIIPs with treatment		
	HKIIPs	HC	*P*	Placebo group	JTW group	*p*
Sex (M/F)	26/49	16/25	0.641	11/15	8/16	0.514
Age (years)	40.3 ± 9.9	40.9 ± 16.1	0.816	39.7 ± 9.4	42.5 ± 10.4	0.328
PQSI	12.5 ± 3.0	2.9 ± 1.4	< 0.001**	11.7 ± 2.9	12.5 ± 3.2	0.401
PSG						
TST (min)	-	-	-	360.1 ± 110.1	374.9 ± 96.0	0.616
SE (%)	-	-	-	67.6 ± 20.8	69.4 ± 16.7	0.740
SL (min)	-	-	-	65.0 ± 72.1	46.5 ± 44.6	0.286
RL (min)	-	-	-	120.3 ± 71.3	170.1 ± 102.1	0.050
AT	-	-	-	15.9 ± 18.4	9.2 ± 8.7	0.107
AI (/hr)	-	-	-	9.7 ± 5.5	9.3 ± 3.8	0.764
N 1 (%)	-	-	-	6.9 ± 3.9	8.1 ± 3.9	0.273
N 2 (%)	-	-	-	61.7 ± 10.3	60.8 ± 14.1	0.796
N 3 (%)	-	-	-	16.3 ± 8.9	17.2 ± 13.4	0.776
REM (%)	-	-	-	15.1 ± 6.3	13.9 ± 4.4	0.425

**p < 0.001; HKIIPs = heart-kidney imbalance insomnia patients; HC = Healthy control; JTW = Jiao-Tai-Wan; PQSI = Pittsburgh Sleep Quality Index; PSG = polysomnography; TST = Total sleep time; SE = Sleep efficiency; SL = Sleep onset latency; RL = Rapid eye movement latency; AT = Awakening times; AI = Arousal index; N = Non-rapid eye movement; REM = Rapid eye movement.

3.2 Whole brain white matter difference

3.2.1 Comparison between HCs and HKIIPs

As shown in Fig. 2 and Table 2, the tract-based spatial statistics analysis demonstrated that when compared with HCs, HKIIPs showed significantly higher FA values in the left corticospinal tract (CST) (Fig. 2a), and significantly lower FA values in several other white matter tracts, including the bilateral superior longitudinal fasciculus (SLF), bilateral anterior limb of internal capsule (ALIC), bilateral anterior and posterior corona radiata (ACR and PCR), bilateral body of corpus callosum (BCC), left cingulum, left posterior thalamic radiation (PTR), right superior corona radiata (SCR), and right CST (Fig. 2b). In addition, the tract-based spatial statistics analysis showed lower MD values in HKIIPs at several fibers, such as bilateral SLF, bilateral PCR, bilateral cingulum, bilateral cerebral peduncle, bilateral CST, bilateral

ALIC, bilateral posterior limb of internal capsule, bilateral PTR, bilateral SCR, left ACR, and left BCC (Fig. 2c).

Table 2
Results of white matter analysis

Contrast	L/R	Peak region	Cluster size	MNI coordinate		
				X	Y	Z
HKIIPs -HC (FA)	L	CST	47	105	105	69
HC- HKIIPs (FA)			33259			
	L/R	SLF		127/53	95/95	104/105
	L/R	ALIC		108/71	141/142	79/79
	L/R	ACR		113/64	151/150	79/79
	L/R	PCR		116/64	95/95	100/100
	L/R	BCC		102/74	120/118	102/108
	L	Cingulum		97	112	107
	L	PTR		126	70	74
	R	SCR		72	136	106
	R	CST		80	107	50
HC- HKIIPs (MD)			49525			
	L/R	SLF		126/54	100/100	101/100
	L/R	PCR		116/64	99/100	101/101
	L/R	Cingulum		98/82	111/110	106/106
	L/R	CP		102/77	102/102	62/62
	L/R	CST		98/82	101/101	44/44
	L/R	ALIC		107/73	126/126	82/82
	L/R	PLIC		114/66	108/107	82/82
	L/R	PTR		118/61	58/57	84/84
	L/R	SCR		108/73	137/137	109/109
	L	ACR		104	158	62

HKIIPs = heart-kidney imbalance insomnia patients; HC = Healthy control; FA = fractional anisotropy; MD = mean diffusivity; BJT = Before JTW Treatment; AJT = After JTW Treatment; CST = corticospinal tract; SLF = Superior longitudinal fasciculus; ALIC = Anterior limb of internal capsule; ACR = Anterior corona radiata; PCR = Posterior corona radiata; BCC = Body of corpus callosum; PTR = Posterior thalamic radiation; SCR = Superior corona radiata; CP = Cerebral peduncle; PLIC = Posterior limb of internal capsule.

Contrast	L/R	Peak region	Cluster size	MNI coordinate		
				X	Y	Z
	L	BCC		106	119	106
BJT-AJT (FA)	L	CST	85	95	92	127

HKIIPs = heart-kidney imbalance insomnia patients; HC = Healthy control; FA = fractional anisotropy; MD = mean diffusivity; BJT = Before JTW Treatment; AJT = After JTW Treatment; CST = corticospinal tract; SLF = Superior longitudinal fasciculus; ALIC = Anterior limb of internal capsule; ACR = Anterior corona radiata; PCR = Posterior corona radiata; BCC = Body of corpus callosum; PTR = Posterior thalamic radiation; SCR = Superior corona radiata; CP = Cerebral peduncle; PLIC = Posterior limb of internal capsule.

3.2.2 Clinical efficacy after medication

The characteristics of the JTW group and the placebo group are shown in Table 1. There were no significant differences in gender, age, PSQI score or PSG between the two groups. PSQI score and the first stage of non-rapid eye movement (NREM) sleep of HKIIPs decreased significantly after treatment with JTW (Table 3). Additionally, in Fig. 2d, HKIIPs showed decreased FA values in the left CST after JTW treatment, while the white matter structure of the placebo group remained unchanged.

Table 3
Differences in clinical efficacy of medication

	JTW group	Placebo group	*p*
PSQI (TA-TB)	-3.5 ± 2.6	-1.1 ± 2.7	0.002*
PSG (TA-TB)			
TST (min)	35.8 ± 84.1	58.3 ± 100.2	0.398
SE (%)	6.8 ± 15.6	9.9 ± 18.4	0.526
SL (min)	6.4 ± 66.1	-1.7 ± 67.5	0.671
RL (min)	-42.5 ± 104.9	0.6 ± 82.6	0.111
AT	1.4 ± 8.6	5.6 ± 17.2	0.272
AI (/hr)	0.3 ± 3.9	0.0 ± 5.4	0.827
N 1 (%)	-2.3 ± 3.6	0.4 ± 5.3	0.037*
N 2 (%)	1.9 ± 16.5	-3.6 ± 18.7	0.283
N 3 (%)	-2.0 ± 14.0	2.7 ± 18.6	0.320
REM (%)	2.5 ± 4.6	1.3 ± 6.6	0.442

*$p < 0.05$; TA = After Treatment; TB = Before Treatment; JTW = Jiao-Tai-Wan; PQSI = Pittsburgh Sleep Quality Index; PSG = polysomnography; TST = Total sleep time; SE = Sleep efficiency; SL = Sleep onset latency; RL = Rapid eye movement latency; AT = awakening times; AI = Arousal index; N = Non-rapid eye movement; REM = Rapid eye movement.

Discussion

In this study, we assessed the differences in white matter integrity between HKIIPs and HCs, in addition to the curative effect of JTW on white matter integrity in HKIIPs.

4.1 Analysis of white matter changes in HKIIPs

Our findings showed increased FA values in the left CST of HKIIPs compared with HCs. This is consistent with the hyperarousal theory of insomnia which assumes that increased cognitive and physiological arousal leads to difficulty in initiating or maintaining sleep [33]. Autonomic, neuroendocrine, electrophysiological, neuroimmunological, and neuroimaging findings confirm increased arousal levels in patients with primary insomnia [34, 35]. A study of cortical excitability indicated that chronic insomnia patients showed a globally increased excitability, with larger motor evoked potential sizes to stimulation compared with control participants [36]. In addition, it is reported that a lower corticospinal excitability is related to a smaller CST volume [37]. Considering that the CST is of paramount importance in the somatic motor system and increased FA values can be attributable to improved axon density and fiber

coherence, we boldly speculate that the increased FA of CST in HKIIPs was associated with increased cortical excitability. Conversely, our study also found that the FA and MD values of a large number of fiber bundles in bilateral brain were decreased in HKIIPs. One possible explanation for our findings is the presence of insomnia-associated neuroinflammation involving white matter. A meta-analysis showed that insomnia is associated with increased systemic inflammation markers [38]. In addition, the proinflammatory interleukin IL-6 was highly expressed in the brain of sleep-disordered mice [39]. Higher levels of circulating inflammatory markers are correlated with lower FA values in the brain [40]. Neuroinflammation and low FA values have also been reported in mouse models of craniocerebral trauma [41]. Thus, we believe that the decrease in FA and MD in the white matter of HKIIPs may be due to neuroinflammation. It is worth noting that the FA values of bilateral CST in HKIIPs showed inconsistent trends, whereby the FA value of right CST was decreased, while the left showed the opposite pattern. This may be due to the fact that the amount by which the FA value increased, due to the excitability in the dominant hemisphere, was much greater than the amount by which it decreased due to neuroinflammation.

4.2 The therapeutic effect of JTW

We found that the FA value in the left CST was decreased in HKIIPs after JTW treatment. This may be attributed to the central inhibitory effect of JTW leading to decreased cortical excitability. JTW antagonizes central excitability by regulating the levels of various neurotransmitters and hormones associated with insomnia [19]. It plays a sedative and hypnotic role by increasing gamma-aminobutyric acid content and receptor expression in the brain of rats. It also increases the level of 5-hydroxytryptamine (5-HT) and decreases the level of norepinephrine (NE) in the brain by inhibiting the hypothalamic–pituitary–adrenal axis (HPA) of insomnia rats, thus exerting its therapeutic effect on insomnia [18]. Our findings may serve to elucidate the underlying therapeutic mechanism of JTW.

4.3 PSQI and PSG results

The PSQI score was used to assess sleep quality and severity of sleep disorders in the past 7 days, while the PSG was mainly used to identify the sleep phases, such as REM, NREM, and wakefulness [29, 42]. The PSQI score of HKIIPs decreased significantly after treatment with JTW, reflecting the effectiveness of JTW in treating insomnia. Although PSG results showed that total sleep time, sleep efficiency and rapid eye movement (REM) sleep of HKIIPs were improved after treatment with JTW, there was no significant difference between the JTW and placebo groups. Better results might be got if giving a longer course of treatment.

Limitations

This study has several limitations. Firstly, the sample size for the HKIIPs was too small. Secondly, the duration of treatment is not long enough, which may lead to no difference in PSG changes between JTW and placebo after treatment.

Conclusion

Our study demonstrates that the increased FA value of the left CST in patients with heart-kidney imbalance insomnia may be associated with the elevated fiber density caused by cortical excitation. JTW plays a central inhibitory role and reduces the fiber density of CST, thus reducing nerve excitability and effectively treating insomnia.

Abbreviations

WM
white matter
HKIIPs
heart-kidney imbalance insomnia patients
HC
healthy control
JTW
Jiao-Tai-Wan
MD
mean diffusivity
FA
fractional anisotropy
CST
corticospinal tract
TCM
traditional Chinese medicine
DTI
Diffusion-tensor imaging
TBSS
tract-based spatial statistics
MRI
magnetic resonance imaging
PSG
polysomnography
PSQI
Pittsburgh Sleep Quality Index
TST
Total sleep time
SE
Sleep efficiency
SL

Sleep onset latency
RL
Rapid eye movement latency;
AT
Awakening times
AI
Arousal index
N
Non-rapid eye movement
REM
Rapid eye movement
BJT
Before JTW Treatment
AJT
After JTW Treatment
SLF
Superior longitudinal fasciculus
ALIC
Anterior limb of internal capsule
ACR
Anterior corona radiata
PCR
Posterior corona radiata
BCC
Body of corpus callosum
PTR
Posterior thalamic radiation
SCR
Superior corona radiata
CP
Cerebral peduncle
PLIC
Posterior limb of internal capsule
5-HT
5-hydroxytryptamine
NE
norepinephrine

Declarations

Ethical approval and consent to participate:

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. This study was approved by the Institutional Medical Ethics Committee of No. 1 Affiliated Hospital, Wenzhou Medical University (Approval document #2016045). Informed consent was obtained from all individual participants included in the study.

Consent for publication:

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no conflict of interest.

Funding:

This study was funded by the National Natural Science Foundation of China (grant no. 81673733); by the Basic Research Project of Wenzhou(Y2020793), China; by the Basic Research Project of Wenzhou(Y2020794), China; by the Health Foundation for Creative Talents in Zhejiang Province (2016), China; and by Project Foundation for the College Young and Middle-aged Academic Leaders of Zhejiang Province (2017), China.

Author Contributions

Qun Huang: Conceptualization, Methodology, Supervision. Zhengzhong Yuan: Conceptualization, Supervision. Jie Chen: Writing - original draft preparation, Formal analysis. Yanxuan Li, Nengzhi Xia: Methodology, Writing - review and editing, Formal analysis. Caiyun Wen, Tianyi Xia, Yuandi Zhuang and Mengmeng Jiang: Investigation, Data curation. Yilan Xiang, Mingyue Zhang, Chenyi Zhan, Yunjun Yang: Resources.

Acknowledgments:

We would like to thank Editage (www.editage.cn) for English language editing.

References

1. Riemann D, Spiegelhalder K, Espie C, Pollmacher T, Leger D, Bassetti C et al (2011) Chronic insomnia: clinical and research challenges–an agenda. Pharmacopsychiatry 44 (1):1-14. doi:10.1055/s-0030-1267978
2. Morin CM, LeBlanc M, Belanger L, Ivers H, Merette C, Savard J (2011) Prevalence of insomnia and its treatment in Canada. Can J Psychiatry 56 (9):540-548. doi:10.1177/070674371105600905
3. Roth T, Coulouvrat C, Hajak G, Lakoma MD, Sampson NA, Shahly V et al (2011) Prevalence and perceived health associated with insomnia based on DSM-IV-TR; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; and Research Diagnostic Criteria/International Classification of Sleep Disorders, Second Edition criteria: results from the America Insomnia Survey. Biol Psychiatry 69 (6):592-600. doi:10.1016/j.biopsych.2010.10.023
4. Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U et al (2011) Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord 135 (1-3):10-19. doi:10.1016/j.jad.2011.01.011
5. Kyle SD, Morgan K, Espie CA (2010) Insomnia and health-related quality of life. Sleep Med Rev 14 (1):69-82. doi:10.1016/j.smrv.2009.07.004
6. Morin CM, Drake CL, Harvey AG, Krystal AD, Manber R, Riemann D et al (2015) Insomnia disorder. Nat Rev Dis Primers 1:15026. doi:10.1038/nrdp.2015.26
7. Knutson KL, Spiegel K, Penev P, Van Cauter E (2007) The metabolic consequences of sleep deprivation. Sleep Med Rev 11 (3):163-178. doi:10.1016/j.smrv.2007.01.002
8. Li M, Zhang XW, Hou WS, Tang ZY (2014) Insomnia and risk of cardiovascular disease: a meta-analysis of cohort studies. Int J Cardiol 176 (3):1044-1047. doi:10.1016/j.ijcard.2014.07.284
9. Poon MM, Chung KF, Yeung WF, Yau VH, Zhang SP (2012) Classification of insomnia using the traditional chinese medicine system: a systematic review. Evid Based Complement Alternat Med 2012:735078. doi:10.1155/2012/735078
10. O'Brien K, Weber D (2016) Insomnia in Chinese Medicine: The Heart of the Matter. The Journal of Alternative and Complementary Medicine 22 (9):684-694. doi:10.1089/acm.2016.0044
11. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M (2008) Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 4 (5):487-504
12. Buysse DJ (2013) Insomnia. JAMA 309 (7):706-716. doi:10.1001/jama.2013.193
13. Matthews EE, Arnedt JT, McCarthy MS, Cuddihy LJ, Aloia MS (2013) Adherence to cognitive behavioral therapy for insomnia: a systematic review. Sleep Med Rev 17 (6):453-464. doi:10.1016/j.smrv.2013.01.001
14. Riemann D, Nissen C, Palagini L, Otte A, Perlis ML, Spiegelhalder K (2015) The neurobiology, investigation, and treatment of chronic insomnia. The Lancet Neurology 14 (5):547-558. doi:10.1016/s1474-4422(15)00021-6
15. Zhang H, Liu P, Wu X, Zhang Y, Cong D (2019) Effectiveness of Chinese herbal medicine for patients with primary insomnia: A PRISMA-compliant meta-analysis. Medicine (Baltimore) 98 (24):e15967. doi:10.1097/MD.0000000000015967

16. Yeung WF, Chung KF, Poon MM, Ho FY, Zhang SP, Zhang ZJ et al (2012) Prescription of chinese herbal medicine and selection of acupoints in pattern-based traditional chinese medicine treatment for insomnia: a systematic review. Evid Based Complement Alternat Med 2012:902578. doi:10.1155/2012/902578
17. Singh A, Zhao K (2017) Treatment of Insomnia With Traditional Chinese Herbal Medicine. Int Rev Neurobiol 135:97-115. doi:10.1016/bs.irn.2017.02.006
18. Huang YF, Bi XN, Zheng W, Zhang T, Wei GJ, Zhang YJ et al (2020) [Regulatory effect of Jiaotai Pills on central and peripheral neurotransmitters in rats with heart-kidney imbalance insomnia]. Zhongguo Zhong Yao Za Zhi 45 (9):2172-2179. doi:10.19540/j.cnki.cjcmm.20191230.402
19. Sun Y, Yang YH, Wang J, Jiang HQ, Cui N, Su BZ et al (2020) [Review of chemical constituents, pharmacological effects and clinical applications of Jiaotai Pills and predictive analysis of its quality marker(Q-marker)]. Zhongguo Zhong Yao Za Zhi 45 (12):2784-2791. doi:10.19540/j.cnki.cjcmm.20200328.201
20. Yue H, Zhou XY, Li CY, Zou ZJ, Wang SM, Liang SW et al (2016) [Intervention effects of Jiaotai pills on PCPA-induced insomnia in rats]. Zhongguo Zhong Yao Za Zhi 41 (18):3451-3456. doi:10.4268/cjcmm20161822
21. Abad VC, Guilleminault C (2018) Insomnia in Elderly Patients: Recommendations for Pharmacological Management. Drugs Aging 35 (9):791-817. doi:10.1007/s40266-018-0569-8
22. Zou X, Huang W, Lu F, Fang K, Wang D, Zhao S et al (2017) The effects of Jiao-Tai-Wan on sleep, inflammation and insulin resistance in obesity-resistant rats with chronic partial sleep deprivation. BMC Complement Altern Med 17 (1):165. doi:10.1186/s12906-017-1648-9
23. Spiegelhalder K, Regen W, Prem M, Baglioni C, Nissen C, Feige B et al (2014) Reduced anterior internal capsule white matter integrity in primary insomnia. Hum Brain Mapp 35 (7):3431-3438. doi:10.1002/hbm.22412
24. Bresser T, Foster-Dingley JC, Wassing R, Leerssen J, Ramautar JR, Stoffers D et al (2020) Consistent altered internal capsule white matter microstructure in insomnia disorder. Sleep. doi:10.1093/sleep/zsaa031
25. Kang JMK, Joo SWJ, Son YDS, Kim HK, Ko KPK, Lee JSL et al (2018) Low white-matter integrity between the left thalamus and inferior frontal gyrus in patients with insomnia disorder. J Psychiatry Neurosci 43 (6):366-374. doi:10.1503/jpn.170195
26. Li S, Tian J, Bauer A, Huang R, Wen H, 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):520-528. doi:10.1148/radiol.2016152038
27. Sexton CE, Zsoldos E, Filippini N, Griffanti L, Winkler A, Mahmood A et al (2017) Associations between self-reported sleep quality and white matter in community-dwelling older adults: A prospective cohort study. Hum Brain Mapp 38 (11):5465-5473. doi:10.1002/hbm.23739
28. Seow LSE, Verma SK, Mok YM, Kumar S, Chang S, Satghare P et al (2018) Evaluating DSM-5 Insomnia Disorder and the Treatment of Sleep Problems in a Psychiatric Population. J Clin Sleep

Med 14 (2):237-244. doi:10.5664/jcsm.6942

29. Zeng C, Liu X, Hu L, Feng Y, Xia N, Zeng H et al (2020) Jiao-tai-wan for insomnia symptoms caused by the disharmony of the heart and kidney: a study protocol for a randomized, double-blind, placebo-controlled trial. Trials 21 (1):408. doi:10.1186/s13063-020-04299-x
30. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28 (2):193-213. doi:10.1016/0165-1781(89)90047-4
31. Smith SM (2002) Fast robust automated brain extraction. Human Brain Mapping 17 (3):143-155. doi:10.1002/hbm.10062
32. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE et al (2006) Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31 (4):1487-1505. doi:10.1016/j.neuroimage.2006.02.024
33. Perlis ML, Giles DE, Mendelson WB, Bootzin RR, Wyatt JK (1997) Psychophysiological insomnia: the behavioural model and a neurocognitive perspective. J Sleep Res 6 (3):179-188. doi:10.1046/j.1365-2869.1997.00045.x
34. Riemann D, Spiegelhalder K, Feige B, Voderholzer U, Berger M, Perlis M et al (2010) The hyperarousal model of insomnia: a review of the concept and its evidence. Sleep Med Rev 14 (1):19-31. doi:10.1016/j.smrv.2009.04.002
35. Bonnet MH, Arand DL (2010) Hyperarousal and insomnia: state of the science. Sleep Med Rev 14 (1):9-15. doi:10.1016/j.smrv.2009.05.002
36. van der Werf YD, Altena E, van Dijk KD, Strijers RL, De Rijke W, Stam CJ et al (2010) Is disturbed intracortical excitability a stable trait of chronic insomnia? A study using transcranial magnetic stimulation before and after multimodal sleep therapy. Biol Psychiatry 68 (10):950-955. doi:10.1016/j.biopsych.2010.06.028
37. Lepley AS, Ly MT, Grooms DR, Kinsella-Shaw JM, Lepley LK (2020) Corticospinal tract structure and excitability in patients with anterior cruciate ligament reconstruction: A DTI and TMS study. Neuroimage Clin 25:102157. doi:10.1016/j.nicl.2019.102157
38. Irwin MR, Olmstead R, Carroll JE (2016) Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. Biol Psychiatry 80 (1):40-52. doi:10.1016/j.biopsych.2015.05.014
39. Zhu B, Dong Y, Xu Z, Gompf HS, Ward SA, Xue Z et al (2012) Sleep disturbance induces neuroinflammation and impairment of learning and memory. Neurobiol Dis 48 (3):348-355. doi:10.1016/j.nbd.2012.06.022
40. Rodrigue AL, Knowles EE, Mollon J, Mathias SR, Koenis MM, Peralta JM et al (2019) Evidence for genetic correlation between human cerebral white matter microstructure and inflammation. Hum Brain Mapp 40 (14):4180-4191. doi:10.1002/hbm.24694
41. Missault S, Anckaerts C, Blockx I, Deleye S, Van Dam D, Barriche N et al (2019) Neuroimaging of Subacute Brain Inflammation and Microstructural Changes Predicts Long-Term Functional Outcome

after Experimental Traumatic Brain Injury. J Neurotrauma 36 (5):768-788. doi:10.1089/neu.2018.5704

42. Chen D, Yin Z, Fang B (2018) Measurements and status of sleep quality in patients with cancers. Support Care Cancer 26 (2):405-414. doi:10.1007/s00520-017-3927-x

Figures

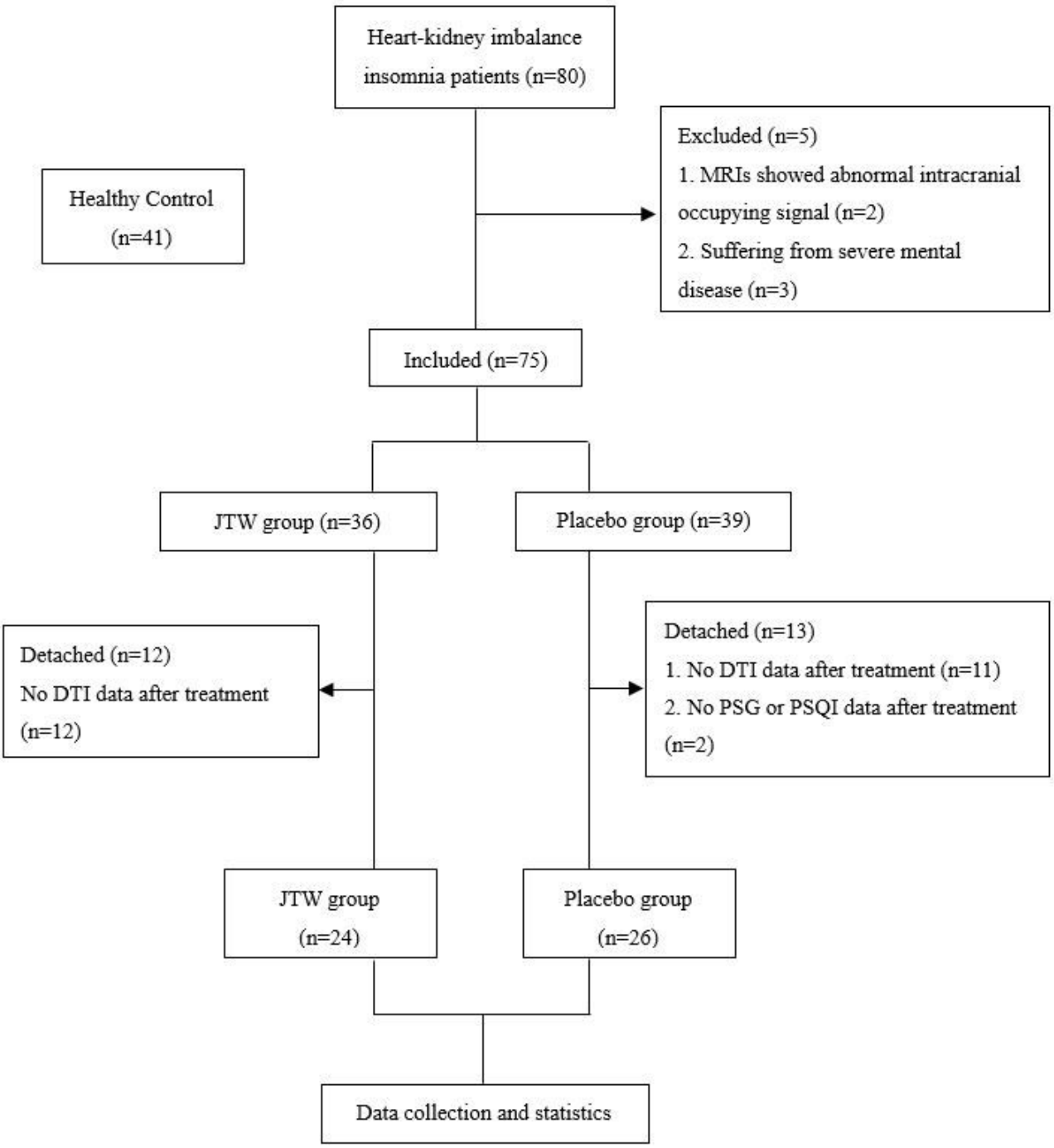

Figure 1

Flowchart representing study patients' selection.

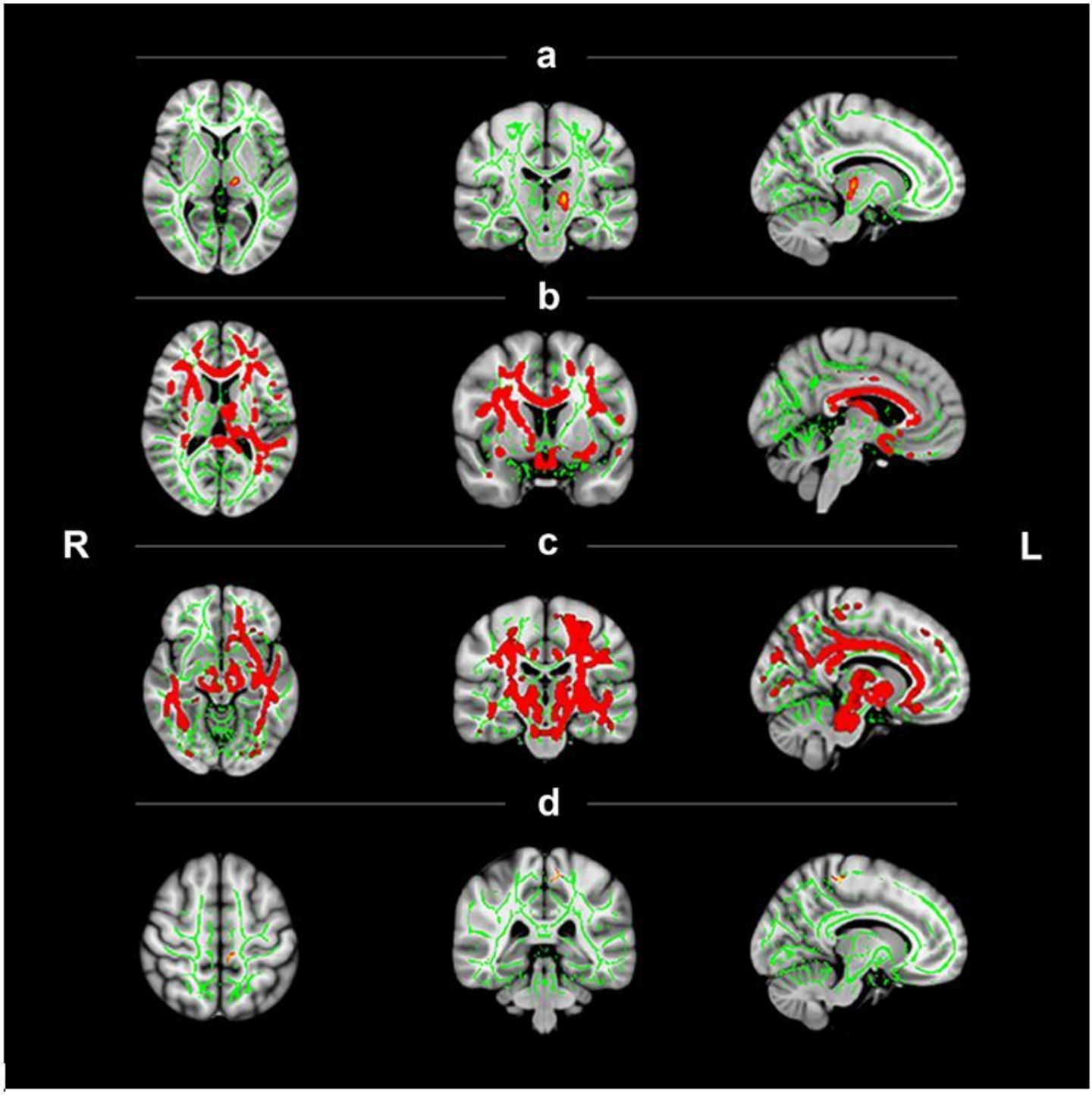

Figure 2

Tract-based spatial statistics analysis showing increased or decreased fractional anisotropy (FA) and mean diffusivity (MD) values in different white matter (WM) tracts of heart-kidney imbalance insomnia patients (HKIIPs). Green represents the mean FA or MD skeleton across all participants. Red yellow depicts the WM tracts whose FA or MD values were significantly changed ($p < 0.05$, family-wise error correction). a WM tracts with increased FA values in HKIIPs compared with health control (HC); b WM

tracts with decreased FA values in HKIIPs compared with HC; c WM tracts with decreased MD values in HKIIPs compared with HC; d WM tracts with decreased FA values in JTW group compared with placebo group.