Future Integrative Medicine **2024** vol. 000(000) | 000–000 Epub
DOI: 10.14218/FIM.2023.00090

Case Report

Magnetic Resonance Study on Restoration of the Glymphatic System and Brain Network in Insomnia Patients with TCM Physiotherapy: A Case Report

Gengbiao Zhang[1], Lingmei Kong[1], Bixia Wu[1], Xuewen Wang[1], Jin Wang[1], Yian Chen[1], Xinhui Su[2], Jinghua Wu[3,4] and Wenbin Zheng[1*]

[1]Department of Radiology, The Second Affiliated Hospital, Shantou University Medical College, Shantou, China; [2]Department of Neurology, The Second Affiliated Hospital, Shantou University Medical College, Shantou, China; [3]Beijing Jinrou Traditional Chinese Medicine Research Institute, Beijing, China; [4]Shantou Longhu District Jinrou Traditional Chinese Medicine Research Institute, Shantou, China

Received: October 07, 2023 | **Revised:** February 02, 2024 | **Accepted:** February 26, 2024 | **Published online:** March 26, 2024

Abstract

Impairment in the cerebral glymphatic system may be one of the primary etiologic reasons for insomnia. Traditional Chinese medicine (TCM) physiotherapy is helpful for treating insomnia patients, with few side effects; however, its influence on glymphatic system function has not yet been examined. The DTI-ALPS (diffusion tensor image analysis along the perivascular space) technique and structural brain network graph theory analysis are the only current methods that can show the glymphatic system's function and the operating efficiency of the neurofibrillary network in a noninvasive and quantitative manner, but their utility has yet to be proven. We employed DTI-ALPS and structural brain network small-worldness to examine changes in the glymphatic system's function and the network's working efficiency before and after TCM meridian sinew treatment in a 35-year-old female with chronic insomnia. The ALPS index and small-worldness, the Insomnia Severity Index, and the Pittsburgh Sleep Quality Index were collected at various time intervals following therapy. The results showed that the patient's glymphatic system functioning, neurofibrillary network arrangement status, and insomnia symptoms improved during the therapy period. Additionally, her glymphatic system functioning and network status had stabilized and her quality of sleep had improved one month after the treatment ended. Thus, TCM physiotherapy can improve insomnia symptoms, and this report suggests that the corresponding mechanism of action may be achieved by repairing the glymphatic system's function and optimizing the state of neurofibrillary network arrangement, providing a new perspective for the study of the TCM therapeutic mechanism of insomnia.

Introduction

Insomnia is one of the most frequent mental diseases, with World Health Organization data indicating that 10–49% of individuals globally suffer from varying degrees of insomnia. Long-term insomnia not only decreases patients' quality of life and social functioning, but it may also lead to a slew of medical and mental ailments such as cardiovascular disease, cognitive disorders, anxiety, depression, and so on, all of which have major consequences for people's physical and mental health. By clearing potentially dangerous metabolic wastes from the brain during sleep, sleep maintains the basic physiological health of nerve cells.[1] Hence, insomnia can result in a buildup of metabolic wastes that might harm nerve cells, which in turn alters neural network patterning, thus exacerbating metabolic disorders in a vicious cycle. The cerebral glymphatic system regulates brain metabolism, and studies have suggested that insomnia may be linked to glymphatic system dysfunction, as well as anomalies in the patient's nerve fiber network.[2–4] Investigating the relationship between the brain network state, glymphatic system function, and symptoms in insomnia patients can help us understand the mechanism of

Keywords: Insomnia; Traditional Chinese medicine; Meridian sinew therapy; Glymphatic system; Magnetic resonance imaging.

Abbreviations: ALPS, analysis along the perivascular space; DTI, diffusion tensor imaging; ISI, Insomnia Severity Index; MRI, magnetic resonance imaging; PSQI, Pittsburgh Sleep Quality Index; TCM, traditional Chinese medicine.

***Correspondence to:** Wenbin Zheng, Department of Radiology, The Second Affiliated Hospital, Shantou University Medical College, No. 69, Dongxia North Road, Jinping District, Shantou 515041, Guangdong, China. ORCID: https://orcid.org/0000-0002-1750-4999. Tel: +86-754-88915717, Fax: +86-754-8346543, E-mail: hwenb@126.com

How to cite this article: Zhang G, Kong L, Wu B, Wang X, Wang J, Chen Y, *et al*. Magnetic Resonance Study on Restoration of the Glymphatic System and Brain Network in Insomnia Patients with TCM Physiotherapy: A Case Report. *Future Integr Med* 2024;000(000):000–000. doi: 10.14218/FIM.2023.00090.

© 2024 The Author(s). This article has been published under the terms of Creative Commons Attribution-Noncommercial 4.0 International License (CC BY-NC 4.0), which permits noncommercial unrestricted use, distribution, and reproduction in any medium, provided that the following statement is provided. "This article has been published in *Future Integrative Medicine* at https://doi.org/10.14218/FIM.2023.00090 and can also be viewed on the Journal's website at https://www.xiahepublishing.com/journal/fim".

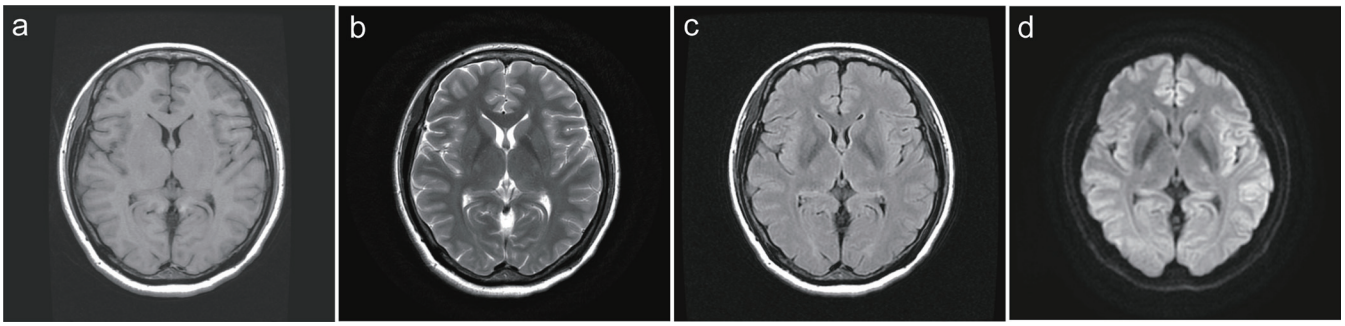

Fig. 1. Cranial magnetic resonance routine scan images. (a) T1-weighted image, (b) T2-weighted image, (c) T2-weighted-fluid-attenuated inversion recovery image, (d) diffusion-weighted image.

insomnia.

Meridian sinew therapy is an important branch of physical therapy in traditional Chinese medicine (TCM) that employs mechanical stimulation (massage, acupuncture, *etc*.) to eliminate lesions; stimulate fascia, periosteum, muscles, and other tissues; and activate nerve fibers, blood vessels, lymphatic vessels, and connective tissues in the state of activity in the treatment of insomnia, with good efficacy and few side effects.[5,6] Our team previously used magnetic resonance imaging (MRI) technology to discover that meridian sinew therapy can regulate the metabolic state of volunteers' brains and improve neural network scheduling,[7,8] but the effect and mechanism of its action on the glymphatic system are still unknown.

Magnetic resonance diffusion tensor imaging (DTI) has been shown to have utility in observing neurological microstructural alterations in patients with insomnia.[4] DTI analysis along the perivascular space (DTI-ALPS) and structural brain network graph theory analysis are the only current methods that can show the glymphatic system's function and the operating efficiency of the neurofibrillary network in a noninvasive and quantitative manner; these methods also have been used in insomnia research.[9,10] DTI-ALPS uses the diffusion tensor method to assess the movement of water molecules in the direction of the perivascular space, which is combined with the formula proposed by Taoka *et al*.[11] to calculate the ALPS index to indirectly characterize the function of the glymphatic system, while the graph theory analysis method characterizes the operational efficiency of the neural network by calculating its topological parameters including the small-worldness. We present the ALPS index and small-worldness modifications in a 35-year-old female with chronic insomnia before and after meridian sinew therapy. The results showed that the patient's glymphatic system function and neural network operation efficiency were increased, and her sleep quality improved after treatment, demonstrating the potential of the corresponding techniques in the study of insomnia and TCM mechanisms as well as providing a new way of thinking about insomnia treatment and monitoring efficacy.

Case presentation

Patient information

A 35-year-old female patient presented to the clinic with trouble going to asleep, easy awakening, and early waking for one year, and worsening symptoms in the last three months, including headache and memory loss. The patient has been taking Stilnox as a sleep aid for six months, one pill each night, and says that she can fall asleep and sleep longer after using the drug, but her insomnia symptoms return after ceasing the drug. The earlier physical examination of the patient indicated an unclosed patent foramen ovale of the heart, which was not treated further, and she denied any other relevant past medical history.

Clinical findings

The patient had a score of 26 on the Insomnia Severity Index (ISI), indicating severe clinical insomnia, and a score of 19 on the Pittsburgh Sleep Quality Index (PSQI), indicating poor sleep quality. There were no anomalies discovered during the physical checkup. No abnormalities were found in routine blood and urine tests, or liver and renal function tests. No abnormalities were found on a chest X-ray, electrocardiogram, ultrasonogram (abdomen, thyroid, and breast), or cranial MRI (Fig. 1).

Diagnostic assessment

The patient, a 35-year-old female, complained of difficulty falling and staying asleep as well as impaired daytime functioning, with symptoms lasting more than three months and occurring more than three times per week. She was diagnosed with chronic insomnia disorder using the International Classification of Sleep Disorders, Third Edition.

Therapeutic intervention

The patient agreed to TCM physiotherapy after extensive discussion. A two-week drug elution program was first carried out under the supervision of a neurologist. In March 2022, the patient officially began the meridian sinew treatment, which used "Wu Jinghua's Jingjin (meridian sinew) Therapy" with the overall conditioning of untying the sinew nodules and dredging the qi of the meridians as the core,[7,8] along with a variety of professional massage techniques and acupuncture treatment to condition the patient's whole body meridian sinew system as well as to guide and encourage neural network remodeling and nervous system metabolic function restoration. For massage, a skilled meridian sinew therapist utilized manual exploration to discover sinew nodules and abnormal soft tissues along the patient's meridians and then released the fascia of the diseased area using the "somatic twisting daoyin (dao yin an qiao)" technique. The "Muscle Region Needling Method (jing jin ci fa)" was used to apply acupuncture, with the needles left in place for about an hour each time. There were two treatment courses, each of which was repeated 12 times (for a total of 24 times), the gap between treatments was roughly two days, and each treatment lasted about 1–2 h. During the treatment period, the patient received no medi-

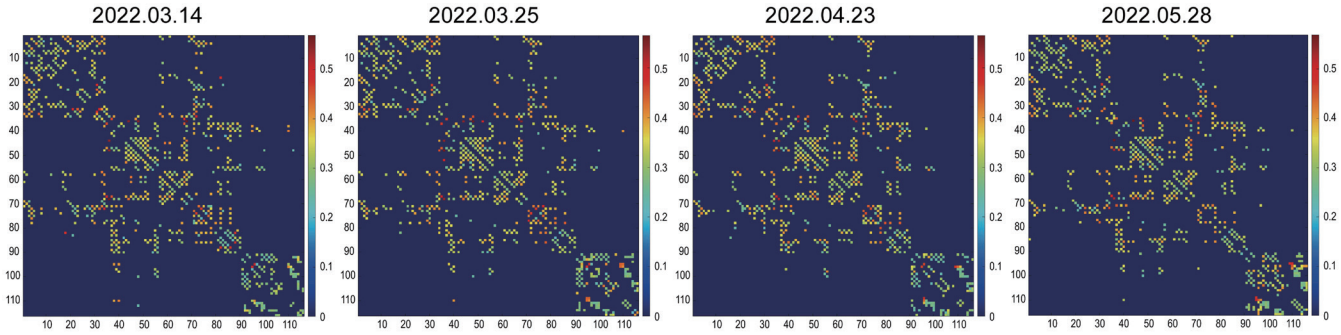

Fig. 2. Neurofiber network matrices at different time points. The horizontal and vertical coordinates of the respective brain regions as well as the colors of the little squares inside the matrix indicate the strength of connections between intersecting brain regions. The dates are indicated above the panels.

cation or other therapies for insomnia.

Follow-up and outcomes

The patient began treatment in March 2022, and the DTI and three-dimensional T1-weighted data as well as ISI and PSQI scores were collected at various time points after treatment. The DTI data were processed and the ALPS index was calculated using DTI Studio software (https://www.mristudio.org/),[12] structural brain networks (Fig. 2) were constructed using Panda software (https://www.nitrc.org/projects/panda/), and the small-worldness values were computed using Gretna software (http://www.nitrc.org/projects/gretna/).[13] The ALPS index can indicate the function of the glymphatic system, whereas the small-worldness shows the neural network's operating state and information transmission efficiency.

A GE 3.0T MRI scanner (3.0T HDxt, GE) with an 8-channel standard head coil was used to acquire the data. To limit the impact of MRI noise, the patient was immobilized with sponge pads around the head and wore earplugs. To exclude the impact of scanning discrepancies and timing disparities on the data, all data were collected by the same experienced radiologist within the same time period (2:00 pm to 2:30 pm). The patient was asked at the end of the scan if there had been any coughing, trunk movement, or other abnormalities during the scan. If the result was positive, a second scan was scheduled after adjusting the status, and the images were visually inspected before preprocessing to ensure that there were no severe artifacts or significant head movements. The MRI scanning parameters and post-processing procedures are detailed in Supplementary Material 1.

After 11 days of treatment, the patient's small-worldness and ALPS index were mildly elevated compared to before treatment, with an ISI score of 21 and a PSQI score of 13, indicating that neural network patterning and glymphatic system function had improved and that insomnia symptoms had decreased. At the end of treatment, the patient's small-worldness and ALPS index were significantly elevated, with an ISI score of 14 and a PSQI score of 10, indicating that neural network patterning, glymphatic system function, and insomnia symptoms had improved. We collected the same data one month after the therapy ended to investigate the treatment's long-term efficacy, when the patient was not taking medication or receiving insomnia-related care. With an ISI score of 7 and a PSQI score of 4, the patient had a tiny decrease in the ALPS index but a slight increase in the small-worldness compared to before. Despite the fact that her neural network patterning and glymphatic system function had stabilized, the patient's sleep quality continued to improve (Table 1, Fig. 3).

Discussion

Insomnia treatment comprises medication, cognitive behavioral therapy, and alternative therapies (acupuncture, tuina, music therapy, and so on). Drug therapy and cognitive behavioral therapy are perhaps the most well-known; however, drug therapy may cause bad responses and addiction, while cognitive-behavioral therapy

Table 1. Various parameters before and after meridian sinew therapy

Index	14 March 2022 (Before treatment)	25 March 2022 (After treatment)	23 April 2022 (After treatment)	28 May 2022 (After stopping treatment)
Dxproj	0.682	0.712	0.672	0.678
Dxassoc	0.668	0.691	0.745	0.79
Dyproj	0.398	0.426	0.387	0.395
Dzassoc	0.412	0.405	0.388	0.421
ALPS index	1.667	1.692	1.830	1.800
Small-worldness	5.094	5.098	5.447	5.529
ISI	26	21	14	7
PSQI	19	13	10	4

Dxproj, diffusivity along the x-axis in the projection fiber area; Dxassoc, diffusivity along the x-axis in the association fiber area; Dyproj, diffusivity along the y-axis in the projection fiber area; Dzassoc, diffusivity along the z-axis in the association fiber area; Diffusivity was measured with apparent diffusion coefficient values ($\times 10^{-3}$ mm^2/s). ALPS, analysis along the perivascular space; ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index.

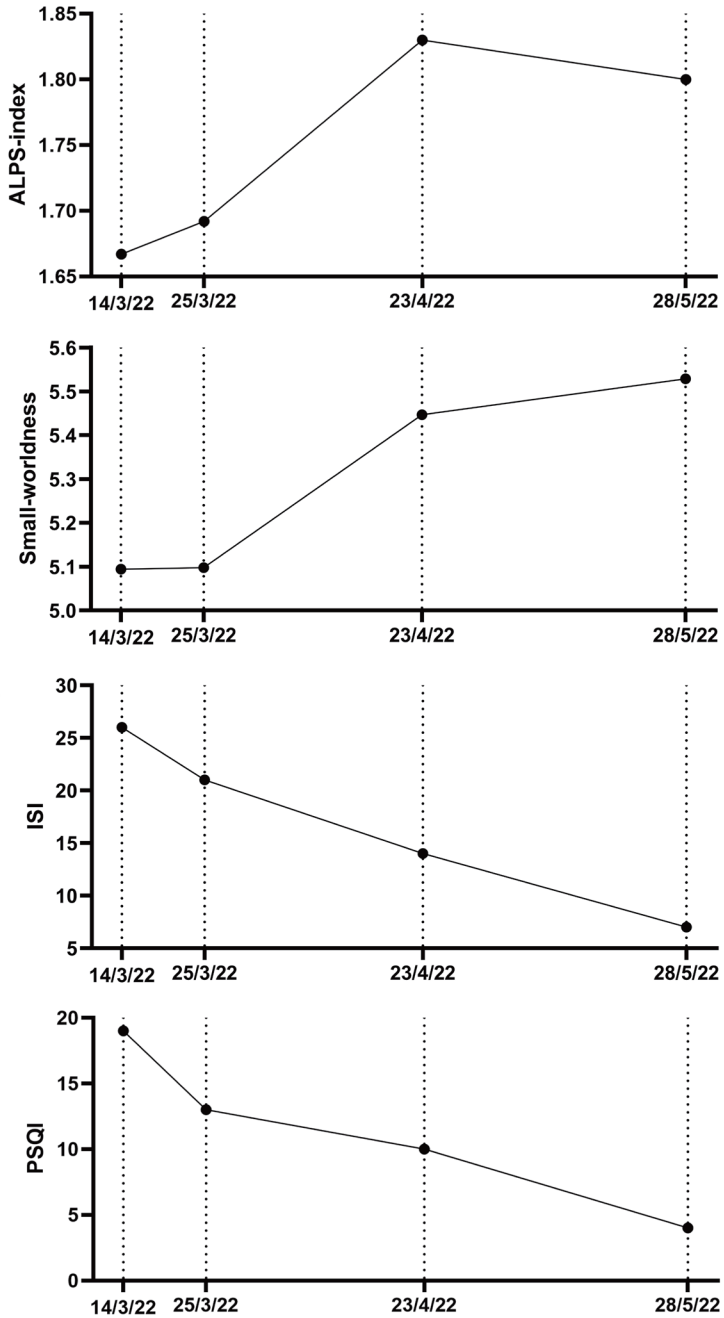

Fig. 3. Trends in various parameters before and after meridian therapy. The horizontal coordinate is the date of the patient's imaging examination. ALPS, analysis along the perivascular space; ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index.

has limitations such as difficulties in follow-up and high demands for doctors' expertise. Meridian sinew therapy not only has good efficacy and few side effects in the treatment of insomnia,[5,6] but it also has targeted treatment based on the sinew nodules on the meridian route and the principle of dialectical treatment as well as physical stimulation of acupuncture points on the pathway while clearing up the sinew nodules of the meridian sinew,[14,15] which is more advantageous in the individualization of the treatment of insomnia patients. In this case study, we also noticed high effectiveness and a favorable prognosis.

According to TCM, the root cause of insomnia is the meridian obstruction that blocks blood and qi, depriving the mind and spirit of nourishment.[5] We hypothesized that the aberrant neural network and glymphatic system function observed in insomnia patients in earlier research may be the externalized expression of the brain's deficiency in blood and qi.[2–4] To understand the therapeutic effect of meridian sinew therapy on insomnia, it can be summarized as the obstruction of qi and blood operation leading to abnormalities of meridian sinew and the occurrence of sinew nodules as well as the lifting of the pressure of sinew nodules

playing a role in regulating qi and blood and balancing yin and yang, which indirectly improves the blood supply to the brain and provides material conditions for the repair of glymphatic system function and the remodeling of the neural network. In this case report, we discovered that the patient's ALPS index and small-worldness improved over time with meridian sinew therapy, implying that the glymphatic system's function and the operational status of the neural network were healed, which was commensurate with improved sleep quality. Previous research by our team has shown that meridian sinew therapy has an optimizing influence on the blood supply and neuronal network arrangement in the brain.[7,8] Moreover, Lu *et al*.[16] and Sung *et al*.[17] have reported that interventions like acupuncture can promote restorative remodeling of brain neuronal networks across numerous pathways, supporting the corresponding theory.

On the other hand, despite a minor decline in the glymphatic system's functionality and a leveling off of small-worldness a month after the patient stopped receiving treatment, her sleep quality steadily improved. This might be because the patient's capacity for self-healing was stimulated by meridian sinew therapy. One of the fundamental ideas of TCM is the "holistic concept," which advocates using a holistic perspective to grasp the human body and strive for the harmony, unity, and completeness of all physiological functions in both clinical treatment and thought.[18] Therefore, TCM places a greater emphasis on treating the ailment through encouraging the patient's capacity for self-healing.[19] According to Yang *et al*.,[14] meridian sinew therapy may treat "spirit" to maintain the organism's unity and coordination, which will improve the therapeutic impact and control the operation of the entire body. Other researchers also have discussed the function of meridian sinew therapy in releasing sinew nodule compression, clearing qi and blood blockages, and yin and yang balancing to enhance the immune system and self-healing capacity of insomnia patients.[5] Of course, the mechanism underlying this improvement needs more research.

Despite the positive efficacy and data trends shown in the present case, this research has limitations. First, further research with more samples is needed to confirm the therapeutic effect of meridian sinew therapy on brain glymphatic system function. Second, analyzing the relationship between glymphatic system function, neurofibrillary network arrangement status, and sleep quality using a wide sample of data could assist in understanding the pathophysiology of insomnia.

Clinical perspectives

The mechanism of action of TCM physiotherapy on the glymphatic system and neurofibrillary network of insomnia patients has not been investigated, and quantifying its efficacy on insomnia is also a problematic challenge. This report opens up new avenues for investigating the mechanism of TCM treatment of insomnia as well as quantitatively demonstrating the therapeutic impact of TCM physiotherapy.

Conclusion

TCM physiotherapy can improve insomnia symptoms, and this report suggests that the corresponding mechanism of action may be achieved by repairing the glymphatic system's function and optimizing the state of neurofibrillary network arrangement, providing a new perspective for the study of the TCM therapeutic mechanism of insomnia.

Acknowledgments

None.

Funding

This study was supported by the Joint Research Fund for Enterprise and Basic and Applied Basic Research Programs of Guangdong Province of China (No. 2021A1515 220112), the Provincial Science and Technology Innovation Strategy Special Project Funding Program (No. STKJ2023042), the Guangdong Province "New Medical" Construction Steering Committee 2023 Teaching Reform Program (No. 129), and the Shantou University Medical College 2023 Teaching Quality Provincial Project.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study design (WBZ), patient treatment (JHW), data collection (JW, YC, XHS), data analysis (BXW, XWW), manuscript writing (GBZ), manuscript revision (LMK, JHW), and manuscript finalization (WBZ). All authors revised the manuscript critically and approved the version to be published.

Ethical statement

This study received ethical approval from the Ethics Committee of the Second Affiliated Hospital of Shantou University Medical College (No. 2022-120) and was performed in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report.

References

[1] Duncan C, Sheppard K. Implications and recommendations for addressing insomnia disorder. Nurse Pract 2019;44(1):19–25. doi:10.1097/01.NPR.0000550249.19773.87, PMID:30570533.

[2] Siow TY, Toh CH, Hsu JL, Liu GH, Lee SH, Chen NH, *et al*. Association of Sleep, Neuropsychological Performance, and Gray Matter Volume With Glymphatic Function in Community-Dwelling Older Adults. Neurology 2022;98(8):e829–e838. doi:10.1212/WNL.0000000000013215, PMID:34906982.

[3] Wang XX, Cao QC, Teng JF, Wang RF, Yang ZT, Wang MG, *et al*. MRI-visible enlarged perivascular spaces: imaging marker to predict cognitive impairment in older chronic insomnia patients. Eur Radiol 2022;32(8):5446–5457. doi:10.1007/s00330-022-08649-y, PMID:35286409.

[4] Sanjari Moghaddam H, Mohammadi E, Dolatshahi M, Mohebi F, Ashrafi A, Khazaie H, *et al*. White matter microstructural abnormalities in primary insomnia: A systematic review of diffusion tensor imaging studies. Prog Neuropsychopharmacol Biol Psychiatry 2021;105:110132. doi:10.1016/j.pnpbp.2020.110132, PMID:33049323.

[5] Ye L, Wang Y, Jiang P, Lin Y, Hong M, *et al*. Clinical, Interleukin-6 and Tumor Necrosis Factor-α Responses to Needling Posterior Neck Meridian Sinews Nodes and Herbal Ointment Externally Applied to Yongquan Acupoint in Patients with Post-ischemic Stroke Insomnia. Chin Gen Pract 2022;25(27):3422-3428+3442. doi:10.12114/j.issn.1007-9572.2022.0117.

[6] Li Y, Xu X, Zuo C. Evaluation of the efficacy of Zuo's "regulating qi, regulating blood, and regulating meridian sinew" acupuncture method in the treatment of primary insomnia. Journal of Sichuan of Traditional Chinese Medicine 2015;33(07):168–170.

[7] Gao Q, Zhang G, Liu H, Zheng H, Zhang L, Wu J, *et al*. Meridian Sinew Therapy for Cerebral Blood Flow and Brain Function in Sub-Healthy Individuals: A Study of ASL and rsfMRI. In: Casalino G, Nayyar A (eds). Computer Methods in Medicine and Health Care. Amsterdam: IOS Press; 2022:1–12. doi:10.3233/ATDE220538.
[8] Gao Q, Wu J, Lin Q, Zheng W, *et al*. A study of the effect of channel tendon therapy on the cerebral blood in healthy human brain by arterial spin labeling. Chinese Imaging Journal of Integrated Traditional and Western Medicine 2021;19(06):519–523. doi:10.3969/j.issn.1672-0512.2021.06.004.
[9] Lu FM, Dai J, Couto TA, Liu CH, Chen H, Lu SL, *et al*. Diffusion Tensor Imaging Tractography Reveals Disrupted White Matter Structural Connectivity Network in Healthy Adults with Insomnia Symptoms. Front Hum Neurosci 2017;11:583. doi:10.3389/fnhum.2017.00583, PMID:29249951.
[10] Okada I, Iwamoto K, Miyata S, Fujimoto A, Tanaka M, Amano M, *et al*. FLUID study: study protocol for an open-label, single-centre pilot study to investigate the efFect of Lemborexant on sleep management in Japanese sUbjects aged 50 years and older with Insomnia Disorder. BMJ Open 2021;11(11):e054885. doi:10.1136/bmjopen-2021-054885, PMID:34836909.
[11] Taoka T, Masutani Y, Kawai H, Nakane T, Matsuoka K, Yasuno F, *et al*. Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease cases. Jpn J Radiol 2017;35(4):172–178. doi:10.1007/s11604-017-0617-z, PMID:28197821.
[12] Xu J, Su Y, Fu J, Wang X, Nguchu BA, Qiu B, *et al*. Glymphatic dysfunction correlates with severity of small vessel disease and cognitive impairment in cerebral amyloid angiopathy. Eur J Neurol 2022;29(10):2895–2904. doi:10.1111/ene.15450, PMID:35712978.
[13] Humphries MD, Gurney K. Network 'small-world-ness': a quantitative method for determining canonical network equivalence. PLoS One 2008;3(4):e0002051. doi:10.1371/journal.pone.0002051, PMID:18446219.
[14] Mo Q, Huang Y, Yang S. Discussion on diagnosis and treatment of insomnia with acupuncture and moxibustion from perspective of “spirit” and meridian-tendon theory. Shanghai J Tradit Chin Med 2022;56(01):39–42. doi:10.16305/j.1007-1334.2022.2007135.
[15] Chen YM, Zhao Y, Xue XL, Zhang QC, Wu XY, Li H, *et al*. Distribution characteristics of meridian sinew (jingjin) syndrome in 313 cases of whiplash-associated disorders. Chin J Integr Med 2015;21(3):234–240. doi:10.1007/s11655-014-1955-7, PMID:25533512.
[16] Lu Y, Zhuang L. Theoretical discussion of musculature therapy on treating spastic hemiplgia induced by stroke. Journal of Clinical Acupuncture and Moxibustion 2007;23(08):1–4. doi:10.3969/j.issn.1005-0779.2007.08.001.
[17] Ahn SM, Kim YR, Kim HN, Shin YI, Shin HK, Choi BT. Electroacupuncture ameliorates memory impairments by enhancing oligodendrocyte regeneration in a mouse model of prolonged cerebral hypoperfusion. Sci Rep 2016;6:28646. doi:10.1038/srep28646, PMID:27350403.
[18] Huang J, Zhang G. Origin and innovative development of holism of traditional Chinese medicine. China Journal of Traditional Chinese Medicine and Pharmacy 2020;35(01):35–38.
[19] Sun J. A mathematic equation derived from host-pathogen interactions elucidates the significance of integrating modern medicine with traditional Chinese medicine to treat infectious diseases. J Integr Med 2023;21(4):324–331. doi:10.1016/j.joim.2023.06.004, PMID:37349214.