ORIGINAL RESEARCH

Electroacupuncture Activated Impaired Brain Areas and Improved Mental Status and Sleep Quality in Primary Insomnia Patients

Ganbin Qiu, MS; Liang Wang, MS;, Weixiong Liao, MS; Yonghui Liu, MS; Zhongyan Wen, MS; Guangcheng Zou, MS; Ting Wu, MS; Jincan Chen, MS

ABSTRACT

Objective • This study aimed to investigate the specific neurological mechanisms underlying the effects of electroacupuncture at Shenmen (Heart 7) with Neiguan (Pericardium 6) acupoints in patients with primary insomnia (PI). We sought to understand these mechanisms by comparing changes in areaal homogeneity (ReHo) before and after treatment in PI patients and healthy controls (HC).

Methods • Between November 2019 and November 2021, we recruited 17 primary insomnia patients (PI group) and 20 matched healthy controls (HC group) as study subjects from Zhaoqing First People's Hospital. Before electroacupuncture treatment, all participants completed the Pittsburgh Sleep Quality Index (PSQI), Hamilton Depression Rating Scale (HAMD), and Hamilton Anxiety Rating Scale (HAMA) assessments. Resting-state magnetic resonance imaging (MRI) scans were conducted before and after two sessions of electroacupuncture at Shenmen and Neiguan acupoints.

Results • Before treatment, primary insomnia patients showed higher PSQI (χ^2=1.964; *P* = .017), HAMA (χ^2=2.016; *P* = .027), and HAMD scores (χ^2=2.367; *P* = .013) compared to healthy controls, and increased ReHo values were observed in the left amygdala, bilateral middle temporal gyrus, and left posterior cingulate gyrus in PI patients, while decreased ReHo values were found in the left posterior cingulate gyrus, right middle frontal gyrus, and right precuneus. After treatment, ReHo values increased in the left superior frontal gyrus, right parahippocampal gyrus, and right cingulate gyrus, while they decreased in the left amygdala and right angular gyrus. Primary insomnia disrupts brain areas in the default network, salience network, and parts of the affective cognitive network.

Conclusion • Electroacupuncture at Shenmen and Neiguan acupoints partially activated impaired brain areas in patients with primary insomnia, leading to improvements in mental status and sleep quality. This offers a novel perspective for the clinical treatment of primary insomnia. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

With the accelerating pace of life, the mental and psychological stress of modern people has increased dramatically, which may lead to physical or psychological disorders such as insomnia. Primary insomnia (PI) is a group of neuropsychiatric syndromes characterized by persistent (more than 1 month) sleep deprivation, difficulty falling asleep, or lack of deep sleep, excluding other factors (disease, alcohol, or drug effects).[1] Studies have shown that chronic sleep deprivation is associated with multiple system dysfunctions such as obesity, diabetes, immune system dysfunction, cognitive dysfunction, affective disorders, and memory deficits.[2]

Currently, approximately 30% of the world's population has a sleep disorder, with primary insomnia being the most common diagnosis. The prevalence of insomnia is approximately 56% in the United States,[30] 31% in Europe,[31] 23% in Japan,[32] and 38.2% in China.[33] Primary insomnia, the most common form of sleep disorder, affects around 6% of adults globally,[34] with increasing incidence among young and middle-aged individuals,[35,36] often triggered by emotional factors such as depression[37] and psychological stress caused by life, work, study pressure,[38] unfulfilled aspirations,[39] and changes in living conditions.[40] The clinical manifestations of insomnia include self-conscious fatigue and lethargy, varying degrees of loss of concentration and memory, lack of social functioning, and irritability, which seriously affect the normal study, work, and life of insomnia patients. Insomnia predisposes to hypertension, dizziness, headaches, neurasthenia, and other cardiovascular and cerebrovascular diseases, which can seriously affect the social activities of patients and may even cause sudden death in serious cases. Primary insomnia severely impairs patients' daytime functioning, often leading to symptoms such as drowsiness and impaired cognitive function, which greatly increases the risk of accidents. The economic impact of insomnia is enormous, with direct economic losses due to insomnia in the United States alone reaching tens of billions of dollars in the 1990s. Insomnia has a negative impact and a serious burden on individuals, families, and society, and is a global problem that needs to be addressed urgently.[29]

In the previous, the treatment of PI was mainly controlled by drugs, the most common of which were anti-anxiety drugs and hypnotic sedatives, which could quickly put patients into a sleep state, effectively prolonging light sleep time and making it less likely that they would wake up during sleep. However, such drugs are prone to drug dependence and drug resistance. Medication is effective in the early stages of the disease, however, long-term use can have certain side effects, such as drug dependence and insomnia rebounding after stopping medication, which can cause negative psychological effects in patients; Although psychotherapy is a common mode of treatment both nationally and internationally, its effectiveness varies from person to person, while the mechanisms involved in physiotherapy are not well described and scientific research is still lacking; traditional Chinese medicine has been widely used in clinical practice to treat insomnia in a variety of ways. Acupuncture has become a specialty of TCM because of its unique advantages of simplicity, few side effects, and stable efficacy. In recent years, the efficacy of traditional Chinese medicine acupuncture in the treatment of insomnia has received widespread academic attention. However, research into the treatment mechanism of electroacupuncture for Shenmen and Neiguan acupoints for PI is still in its early stages, with a lack of precise, objective, and scientific data to determine its success.[3]

Shenmen and Neiguan are the original points of the Heart channel, the entrance and exit gateway for the heart *Qi*, which could calm the heart and tranquilize the mind. In recent years, functional magnetic resonance imaging (fMRI) has been extensively used in the field of acupuncture, which provides new means and research horizons to study the mechanisms of acupuncture in treating patients with insomnia.[4-6] Areaal homogeneity (ReHo) is a functional magnetic resonance data analysis method[7] that predicts the synchronization between brain areas in a time series by calculating the Kendall coefficient concordance (KCC) of adjacent brain areas. In this study, we utilized the fMRI technique and analyzed ReHo to explore the potential neurological mechanisms underlying the treatment of insomnia with electroacupuncture at Shenmen and Neiguan acupoints. By focusing on these specific acupoints, our research aims to shed light on how their stimulation may impact sleep and mental well-being, aligning with the traditional Chinese medicine concepts associated with these acupoints.

MATERIALS AND METHODS

Baseline data

From November 2019 to November 2021, 17 eligible PI patients (5 males and 12 females, aged 23 to 47 years, with a mean age of [32.17±5.50] years) were recruited as the experimental group and 20 eligible healthy individuals (7 males and 13 females, aged 24 to 46 years, with a mean age of [32.40±5.59] years) matched for age, gender and education level, were recruited as the control group from the Department of Neurology, Zhaoqing First People's Hospital. All eligible participants were informed of the process of the study process and provided written informed consent. All participants underwent clinical Pittsburgh Sleep Quality Index (PSQI),[8] Hamilton Depression Rating Scale (HAMD),[9] and Hamilton Anxiety Rating Scale (HAMA)[10] tests.

The original sample size calculation estimated that 30 patients in each group would be needed to detect a 3-point difference between groups in a 2-sided significance test with a power of 0.8 and an alpha error level of 0.05.

The trial was conducted by the standards of Good Clinical Practice and the Declaration of Helsink*i*. The trial protocol and all amendments were approved by the appropriate ethics body at each participating institution (Aprroval NO. NT-SD201901127). All patients provided written informed consent before enrolment. The trial protocol has been published online and is available with the full text of this article.

Inclusion and exclusion criteria

Inclusion criteria: (1)(1)Patients were diagnosed with insomnia as per the diagnostic criteria for PI in the US DSM-IV.[11] (2) Patients without significant organic diseases in the brains of all participants. (3) Patients without the use of anti-anxiety or antidepressant drugs in the last week. (4) healthy controls with a regular daily schedule in the last month, without alcohol abuse.

Exclusion criteria: (1) Patients with psychiatric or other organic diseases. (2) Patients with severe heart, cerebrovascular disease, hepatic or renal insufficiency. (3) Patients who are pregnant, breastfeeding, or preparing for pregnancy. (4) Patients with secondary insomnia caused by physical illness, various psychiatric disorders, or medication. (5) People who are unable to undergo acupuncture treatment, have coagulation disorders, and suffer from acupuncture sickness. (6) Patients who have recently received other related treatments. (7) Patients with family genetic diseases. All participants were right-handed. This study was reviewed and approved by the Ethics Review Committee of our hospital.

Methods

All participants first completed the PSQI, HAMD, and HAMA tests, underwent resting-state magnetic resonance imaging (MRI) scan, and then received two sessions of electroacupuncture 30 minutes each at the Shenmen and Neiguan acupoints for 1 day, followed by another resting-state MRI scan. The resting-state functional MRI data was acquired using a GE HDx 3.0T device and a dedicated 16-channel head coil with an echo-planar imaging (EPI) BOLD sequence with the following acquisition parameters: Repetition time (TR) of 1800 ms, echo time (TE) of 50 ms, field of view (FOV) of 240 mm×240 mm, the layer thickness of 3 mm, layer spacing of 1 mm, flip angle FA of 90 degrees, acquisition matrix of 64×64, number of layers of 35 (scan positioning line was parallel to the anterior-posterior joint line), and total 230-time points acquired. T1 anatomical images were acquired using a high-resolution BRAVO sequence with the following parameters: TR of 8.208 s, TE of 3.22 ms, TI of 450 ms flip angle FA12 degree, FOV of 240 mm × 240 mm, and axial position of 118 layers. To minimize the effect of noise on data collection, all participants wore rubber noise-canceling earplugs, closed their eyes during the scanning process, kept their heads as still as possible, and avoided emotionally volatile and stressful thinking.

We acquired resting-state functional MRI data both before and after electroacupuncture treatment to assess the impact of the intervention on brain activity and connectivity. This approach allows us to investigate any changes in brain function associated with electroacupuncture. The pre-electroacupuncture resting-state MRI scan serves as a baseline measurement of the participant's brain activity and connectivity in their original state. It helps us establish the initial neural patterns and connectivity, which we can later compare to the post-electroacupuncture scan. The post-electroacupuncture resting-state MRI scan enables us to examine how electroacupuncture may have influenced the participants' brain function. By comparing the two sets of data, we can identify any significant alterations in neural activity or connectivity that may be attributed to the electroacupuncture treatment. Therefore, this before-and-after approach allows us to gain insights into the immediate effects of electroacupuncture on the brain and helps us better understand the neural mechanisms underlying the therapeutic benefits of this intervention. It also provides a more comprehensive view of the treatment's impact on brain function and connectivity in the context of our study.

Electroacupuncture: We used sterile, non-magnetic copper alloy acupuncture needles (0.35mm × 35mm, Huatuo, Suzhou Medical Equipment Supplies Factory) and the SDZ-II multifunctional electronic acupuncture instrument. The selection of acupuncture points, Shenmen and Neiguan on both sides, was based on the national standard 'Name and Positioning of Acupoints' (GB/T123456-2006) published in 2006. All electroacupuncture procedures were performed by the same experienced acupuncturist. The needles were inserted vertically into the skin to a depth of approximately 10-15 mm, and participants were asked about their sensations during insertion, which were scored using the MASS scale to determine the appropriateness of insertion. The copper wire of the electrotherapy apparatus was attached to the needle and energized for 30 minutes, with an output current frequency of 50Hz, a continuous waveform, and an intensity set to the subject's maximum perceptual threshold, ensuring no tingling sensation in the muscle but frequent twitching sensation. A second fMRI scan was conducted immediately after needle removal.

Data pre-processing

All data were imported into MRIcro software (1.40 bulid 1 version; www.MRIcro.com) for processing. Data with excessive or incomplete image artifacts were first screened out and the rest of the data pre-processing based on the MATLAB2013b (Mathworks, Natick, MA, USA) platform using the DPARSFA software (http://rfmri.org/DPARSF), including (1) DICOM format conversion: Temporal calibration was performed to ensure the consistency and accuracy of the data over time; (2) Removal of the first 10 time points of onset: The first 10 time points in the dataset were removed to account for potential magnetization stabilization and allow for more stable resting-state measurements; (3) Temporal calibration: Temporal calibration was performed to ensure the consistency and accuracy of the data over time; (4) Head motion calibration: Any head motion during the MRI scans was addressed, as excessive motion can introduce artifacts. This step is crucial for maintaining data quality; (5) Spatial normalization (using EPI templates): Spatial normalization was conducted using EPI (Echo Planar Imaging) templates. This step aligns the data to a common reference space, facilitating group-level analyses; (6) Anomalous data rejection: Data containing anomalies or outliers were identified and rejected to further enhance data quality and reliability; (7) spatial smoothing (using a 6 mm × 6 mm × 6 mm half-height full-width Gaussian kernel): This step helps reduce noise and enhances the signal-to-noise ratio for subsequent analyses.

Statistical analysis

In the statistical analysis, we employed a variety of tests to analyze the data, depending on the nature of the variables and the specific objectives of the analysis.

For normally distributed variables, we used the student's *t* test to compare the mean differences between the two groups. For non-normally distributed variables, we applied the Mann-Whitney U test to assess the differences between the groups. The choice between these tests was based on the normality assumption of the data.

Data were analyzed using SPPS version 22.0 statistical software. To compare the age and literacy level between the two groups of participants, we used the Mann-Whitney U test. This non-parametric test is suitable for comparing non-normally distributed demographic data. Gender distribution

Table 1. Demographics and clinical characteristics of all participants

Groups	PI group (n = 17)	HC group (n = 20)	χ2/ *t* value	*P* value
Male/female	5/12	7/13	1.614	.178
Age (years)	32.1±5.50	32.4±5.59	0.935	.337
Education level (years)	13.47±3.03	13.35±2.89	0.771	.295
PQSI score	13.2±2.68	5.61±1.72	1.964	.017
HAMD score	8.47±3.49	2.58±2.95	2.016	.027
HAMA score	11.9±2.81	3.65±1.75	2.367	.013

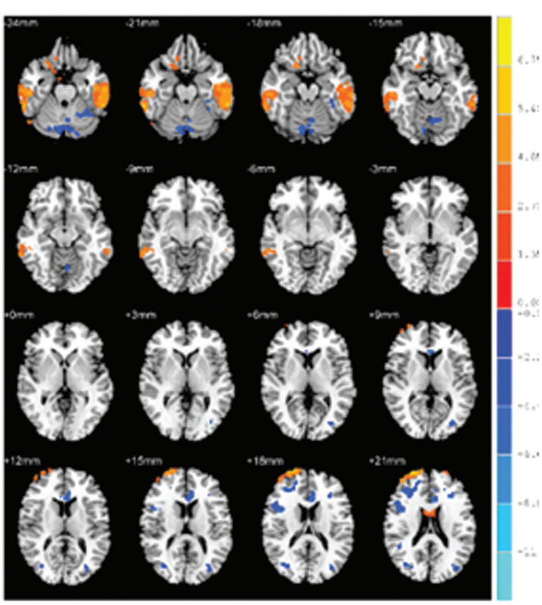
Abbreviations: PI, primary insomnia; PQSI, Pittsburgh Sleep Index; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale

Table 2. Areas showing different ReHo values between the two groups before acupuncture treatment

Brain area	R/L	Volume (mm^3)	Peak MNI coordinates (mm) X	Y	Z	*t* value
Brain areas with increased ReHo						
Amygdala	L	312	-26	3	-18	3.816
Superior frontal gyrus	L	174	-3	49	31	5.147
Middle temporal gyrus	R	685	66	-42	-3	4.386
Middle temporal gyrus	L	813	-57	-34	5	4.532
Brain areas with decreased ReHo						
Posterior cingulate gyrus	L	251	-6	-43	28	-4.352
Middle frontal gyrus	R	268	8	51	30	-5.271
Precuneus	R	351	10	56	48	-3.178

Note: paired *t* test, clusters $P < .05$ (FDR multiple calibrations); MNI, Montreal Neurological Institute-Hospital; MNI coordinates correspond to the maximum activating voxel in each activation cluster; R, right side; L, left side.

Figure 1. Differential brain areas with ReHo values in the PI group relative to the HC group before acupuncture.



Note: Warm tones represent brain areas with increased ReHo values and cool tones represent brain areas with decreased ReHo values.

between the groups was compared using the Chi-squared (χ^2) test, which is a standard method for assessing the association between categorical variables. To compare the PSQI, HAMA, and HAMD scores between the two groups, we applied the two-sample *t* test. This parametric test is used for comparing means when the data exhibit a normal distribution.

Furthermore, the resting-state fMRI data from the two groups of participants were analyzed using the xjView software (http://www.alivelearn.net/). Specifically, the Regional Homogeneity (ReHo) values were analyzed. To assess the statistical significance of the ReHo values, we employed the REST software. A two-sample *t* test was performed, and the threshold level was set at $P < .01$, with False Discovery Rate (FDR) multiple calibration. Additionally, a minimum cluster size of > 113 voxels was applied.

These statistical methods were chosen based on the type and distribution of the data. The selection of parametric or non-parametric tests depended on the normality assumption. The analysis of fMRI data incorporated specific software and thresholds to ensure robust and statistically meaningful results. Correcting for multiple comparisons was achieved through the application of the FDR method, enhancing the reliability of the findings. All differences were considered statistically significant when $P < .05$. These analytical approaches were utilized to rigorously examine and interpret the results of our study.

RESULTS

Demographics and clinical characteristics

There was no statistically significant difference between the two groups in terms of age, gender, and education level ($P > .05$). PI patients showed significantly higher scores of PSQI, HAMA, and HAMD versus HC ($P < .05$). (Table 1)

ReHo values

The resting-state MRI data of the patients in both groups before electroacupuncture therapy are shown in Table 2 and Figure 1. Before treatment, patients with primary insomnia (PI) displayed increased ReHo values in brain regions, including the left amygdala, bilateral middle temporal gyrus, and left posterior cingulate gyrus. These brain regions play a crucial role in emotional regulation and cognitive processing, potentially related to the emotional and cognitive components of insomnia. Simultaneously, before treatment, brain areas with decreased ReHo values in PI patients included the left posterior cingulate gyrus, right middle frontal gyrus, and right precuneus. These regions are associated with the autonomic nervous system and attention control, potentially linked to insomnia symptoms and cognitive function decline.

The Reho values for both groups after electroacupuncture treatment are demonstrated in Table 3 and Figure 2. Following treatment, brain regions with significantly increased ReHo values in PI patients included the left superior frontal gyrus, right parahippocampal gyrus, and right cingulate gyrus, reflecting statistically significant changes ($P < .05$) with moderate to large effect sizes. These regions are associated with emotional regulation and cognitive function, suggesting a positive impact of electroacupuncture on these aspects. Conversely, after treatment, brain regions with significantly decreased ReHo values in PI patients were the left amygdala and right angular gyrus, with corresponding moderate to large effect sizes, highlighting their role in emotional processing and cognitive function, and their modulation by the treatment.

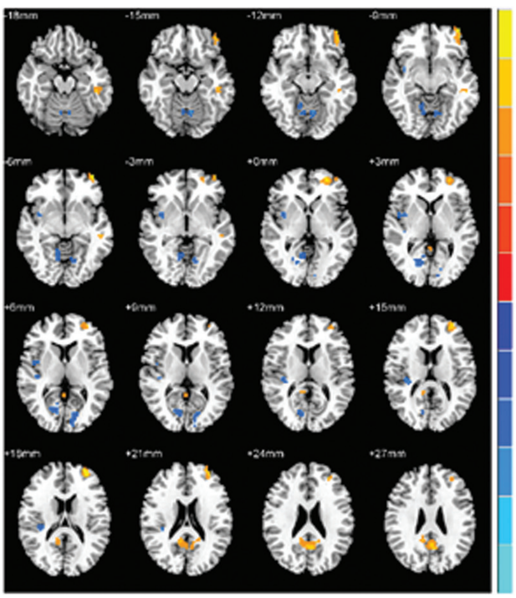
DISCUSSION

Table 3. Areas showing different ReHo values between the PI and HC groups after acupuncture treatment

Brain Area	R/L	Volume (Mm^3)	Peak Mni Coordinates (Mm)			*t* value
			X	Y	Z	
Brain Areas With Increased Reho						
Upper Frontal Gyrus	L	516	-16	35	42	4.063
Hippocampal Side Gyrus	R	297	28	-16	-28	5.337
Posterior Cingulate Gyrus	R	253	6	-42	22	4.253
Brain Areas With Decreased Reho						
Amygdala	L	247	-3	49	31	-4.352
Angular Gyrus	R	183	30	15	6	-5.271

Note: paired *t*-test, clusters $P < .05$ (FDR multiple calibrations); MNI, Montreal Neurological Institute-Hospital; MNI coordinates correspond to the maximum activating voxel in each activation cluster; R, right side; L, left side.

Figure 2. Differential brain areas with ReHo values in the PI group relative to the HC group after acupuncture.



Note: Warm tones represent brain areas with increased ReHo values and cool tones represent brain areas with decreased ReHo values.

Insomnia can occur alone or as a result of other illnesses, and its main clinical manifestation is difficulty falling asleep. Chinese Guidelines for the Diagnosis and Treatment of Adult Insomnia (2012) states that there are two types of insomnia, primary and secondary insomnia.[42] PI is characterized by simple insomnia and can be divided into three types according to its nature, including subjective, idiopathic, and psychophysiological insomnia. Insomnia is a common clinical condition with a high prevalence. The results of the survey found that the incidence of insomnia in Western countries is about 35.29%, and ours reaches 1%-20%. According to current data, it is predicted that the number of insomniacs worldwide could reach 700 million in ten years.[43] Chronic sleep deprivation is a major hazard, affecting daily work and study, distracting attention, and causing unexpected events to occur; in addition, insomnia can lead to irritability and anxiety, causing unnecessary family conflicts and affecting family harmony. Insomnia disorder is linked to reduced health-related quality of life, greater healthcare resource utilization, increased costs, and diminished productivity. Patients with insomnia experience impaired overall health, quality of life, and social functioning when compared to those without the condition. They also tend to have more frequent outpatient and emergency department visits, along with higher use of prescription and over-the-counter medications.[26-28] As a result, sleep problems are becoming a major health problem that requires active treatment.

There is a considerable amount of spontaneous and continuous neuronal activity in the human brain during the awake and quiet state. Raichle et al. (2015)[12] found that certain functional areas of the brain remain activated at rest and in the absence of a specific cognitive task, while they were negatively activated in the presence of a task. They called the network with these features as the 'Default Mode Network (DMN)', comprising mainly the posterior cingulate/precuneus, medial prefrontal, bilateral inferior parietal lobule, and bilateral hippocampus functional areas. This network is activated positively during internal mental activities such as moral judgment, contextual memory, and introspection, moreover, negatively activated during external specific tasks. Based on these biological properties, Prof. Zang et al. (2020)[7] pioneered the ReHo analysis, a new method for analyzing resting-state brain functional data. It measures trends in the tendency of temporal homogeneity of neuronal activity in local brain areas; a high ReHo value indicates temporal homogeneity of local neuronal activity, whereas a low ReHo value indicates temporal disorder of local neuronal activity. The ReHo analysis approach is extensively employed in neuropsychiatric disorders such as Parkinson's disease, Alzheimer's disease, bipolar disorder, and autism,[13-16] and has yielded considerable promising results.

In our study, we found that patients with PI exhibited distinct changes in ReHo values in specific brain regions before and after electroacupuncture treatment. These changes were particularly notable in areas associated with emotional regulation, cognitive processing, and the autonomic nervous system. The increased ReHo values in brain regions related to emotional regulation and cognitive function suggest that electroacupuncture can partially activate these impaired areas, potentially contributing to improvements in mental status. Additionally, the decrease in ReHo values in areas such as the amygdala and angular gyrus may reflect improved sleep quality in PI patients. Therefore, the observed changes in ReHo values appear to be directly linked to the clinical improvements in mental status and sleep quality in PI patients after electroacupuncture treatment. These findings provide valuable insights into the neurological mechanisms underlying the therapeutic effects of electroacupuncture on insomnia.

Medication is effective in the early stages of the disease, however, long-term use can produce certain side effects, such as drug dependence and insomnia rebound after stopping the medication, which can lead to negative psychology; although psychotherapy is a common mode of treatment at home and abroad, the effectiveness of treatment varies from person to person; The mechanisms of physiotherapy are not well described and scientific research is lacking. Chinese medicine classifies primary insomnia as 'sleeplessness' based on the clinical characteristics of the patient, a type of illness characterized by frequent failure to obtain normal sleep, with symptoms such as difficulty falling asleep or waking up at times, or difficulty regaining sleep after waking; In severe cases, the person may not be able to sleep through the night. Insomnia in traditional Chinese medicine encompasses insomnia in modern medicine, and the symptoms of both are similar, with sleep disorders being the main cause. Through the exploration of generations of medical practitioners, Chinese medicine has a unique perspective on the treatment of insomnia. It can grasp the characteristics of the organism from a holistic perspective and can carry out theoretical analysis in terms of *Yin* and *Yang*, *Ying* and *Wei,* and other related doctrines to regulate the functions of the internal organs to achieve the purpose of holistic treatment. The treatment of insomnia in traditional Chinese medicine has been widely used clinically and in a variety of ways.

Acupuncture therapy is favored by the majority of patients for its unique advantages of simplicity, few side effects, and stable efficacy, thus becoming a characteristic therapy of Chinese medicine. From the historical development of the disease's TCM name, various expressions existed in different historical periods, including 'not being able to lie down', 'unable to lie down', 'restlessness', 'eyes not closing', 'not being able to sleep' and 'sleeplessness'. Acupuncture therapy is an integral part of traditional Chinese medicine, and the experience of acupuncture and moxibustion in treating various diseases and pains is recorded in the *Yellow Emperor's Classic of Internal Medicine*, a masterpiece of traditional medicine in China, which laid the theoretical foundation for the establishment and development of the meridian theory. Acupuncture could be applied to a variety of disorders such as surgical analgesia, drug addiction, hypertension, and sleep disorders, moreover, shows benefits in improving sleep quality, as evidenced by a wealth of evidence-based medicine.[17-18]

However, this study represents a pioneering effort, as it is the first to employ the ReHo analysis method to examine changes in brain function in patients with PI following electroacupuncture at Shenmen and Neiguan acupoints. The clinical implications of our findings are noteworthy. They suggest that electroacupuncture at Shenmen and Neiguan acupoints could serve as a promising avenue for the treatment of primary insomnia. By modulating brain function, especially in areas associated with emotional regulation and cognitive processing, acupuncture may contribute to alleviating the emotional and cognitive components of insomnia. This novel approach offers potential benefits in improving sleep quality. In practice, the integration of electroacupuncture at Shenmen and Neiguan acupoints into insomnia treatment regimens can be explored further. Acupuncturists and healthcare providers can consider incorporating this modality alongside other therapeutic approaches to offer a more comprehensive and holistic treatment strategy for individuals with primary insomnia. Additional research is needed to further refine and optimize the application of acupuncture in the clinical management of sleep disorders, with the ultimate goal of enhancing patients' well-being.

According to the findings of this study, the brain areas with increased ReHo values in PI patients before treatment included the left amygdala, bilateral middle temporal gyrus, and left posterior cingulate gyrus, while the brain areas with decreased ReHo values included the left posterior cingulate gyrus, right middle frontal gyrus, and right precuneus, indicating adaptive changes in certain functional areas of the brain in chronic insomnia patients. The brain areas with elevated ReHo values primarily involved the brain areas responsible for maintaining the organism's arousal state and the emotion-processing center, while brain areas responsible for cognitive functions such as memory and decision-making behavior showed decreased ReHo values, in line with the previous research results.[19,20] Abnormalities in these critical brain areas may provide a theoretical foundation for the cognitive-behavioral changes in PI patients such as recurrent depression, memory loss, and irritability. The electroacupuncture results of resting-state brain function in the Shenmen and Neiguan acupoints in the PI group revealed that the brain areas with increased ReHo values in the PI patients included the left superior frontal gyrus, the right parahippocampal gyrus, the right cingulate gyrus and the brain areas with decreased ReHo values included the left amygdala and the right angular gyrus. The DMN is one of the most critical subnetworks of the resting-state neural network, a vital skeleton for the activity of the entire central brain network, and one of the most essential functional networks that maintain the brain's perception of external information in the resting state, which is closely related to high-level cognitive functions such as episode processing and learning memory.[21]

The posterior cingulate gyrus in the DMN is a key component of the neurofunctional anatomical system of learning memory. It has been demonstrated[22] that a complete closed neural loop exists between the hippocampus and the cingulate gyrus: hippocampus-hypothalamus-anterior thalamic nucleus-cingulate gyrus-hippocampus, which contributes significantly to the regulation of learning and memory abilities, suggesting that electroacupuncture at Shenmen and Neiguan acupoints facilitates the enhancement of the functional connections in the hippocampal-cingulate gyrus loop, which further improves the activity of brain areas responsible for cognition and control tasks and the higher cognitive functions of the body. The amygdala is the primary brain area responsible for emotion regulation, and irritability and irregular mood in CPSD patients may be attributed to reduced functional connectivity between the prefrontal brain areas in charge of emotion control.[23-25]

Electroacupuncture at the Shenmen and the Neiguan acupoints in CPSD patients could effectively reduce abnormal activation of the amygdala and suppress negative mood episodes by enhancing connections with executive control-related brain areas, indicating the feasibility of electroacupuncture at Shenmen and Neiguan acupoints for treating mental disorders (depression, anxiety, mania, etc.) or eliminating tension in individuals.

However, this study has several shortcomings due to several constraints. In terms of the study sample, the sample size collected in this trial was relatively small, which did not allow for a more comprehensive and objective evaluation of the significant differences in efficacy between the two treatment groups from the perspective of a large sample size. In terms of observational indicators and efficacy determination, this study used more subjective efficacy assessment criteria, and it was difficult to give an objective and accurate description of the assessment on the scale due to the wide variation in subjective feelings between individuals, their different levels of education, and differences in their understanding of the questions on the scale. In terms of follow-up time, the follow-up period after treatment in this trial was relatively short, and the long-term treatment effects were not well observed.

CONCLUSION

Patients with PI have damaged brain areas in the default network, salience network, and part of the affective cognitive network. Electroacupuncture at Shenmen and Neiguan acupoints can partially activate the impaired brain areas of PI patients, thereby improving the mental status and sleep quality, which provides a new perspective for the clinical treatment of the PI population.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article

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AUTHOR CONTRIBUTIONS

Ganbin Qiu and Liang Wang contributed equally to the manuscript.

CONFLICT OF INTEREST

All authors declared that they have no financial conflict of interest.

REFERENCES

1. Shekleton JA, Flynn-Evans EE, Miller B, et al. Neurobehavioral performance impairment in insomnia: relationships with self-reported sleep and daytime functioning. *Sleep*. 2014;37(1):107-116. doi:10.5665/sleep.3318
2. Kay DB, Buysse DJ. Hyperarousal and Beyond: New Insights to the Pathophysiology of Insomnia Disorder through Functional Neuroimaging Studies. *Brain Sci*. 2017;7(3):23. doi:10.3390/brainsci7030023
3. Han KH, Kim SY, Chung SY. Effect of acupuncture on patients with insomnia: study protocol for a randomized controlled trial. *Trials*. 2014;15(1):403. doi:10.1186/1745-6215-15-403
4. Zhu Y, Zhao X, Yin H, Zhang M. Functional connectivity density abnormalities and anxiety in primary insomnia patients. *Brain Imaging Behav*. 2021;15(1):114-121. doi:10.1007/s11682-019-00238-w
5. Yao L, Li M, Cao J, et al. Study on acupuncture improving insomnia comorbid with depression and anxiety based on rs-fMRI: A protocol for systematic review and meta-analysis. *Medicine (Baltimore)*. 2021;100(20):e25988. doi:10.1097/MD.0000000000025988
6. Peng W, Hong X, Huangfu Y, et al. The cerebral mechanism of acupuncture for chronic insomnia with gastrointestinal disorder: protocol for a randomized controlled trial. *Trials*. 2021;22(1):386. doi:10.1186/s13063-021-05332-3
7. Zhao B, Yang B, Tan Z, et al. Intrinsic brain activity changes in temporal lobe epilepsy patients revealed by regional homogeneity analysis. *Seizure*. 2020;81:117-122. doi:10.1016/j.seizure.2020.07.030
8. Sedov ID, Cameron EE, Madigan S, Tomfohr-Madsen LM. Sleep quality during pregnancy: A meta-analysis. *Sleep Med Rev*. 2018;38:168-176. doi:10.1016/j.smrv.2017.06.005
9. Fenton C, McLoughlin DM. Usefulness of Hamilton rating scale for depression subset scales and full versions for electroconvulsive therapy. *PLoS One*. 2021;16(11):e0259861. doi:10.1371/journal.pone.0259861
10. Thompson E. Hamilton Rating Scale for Anxiety (HAM-A). *Occup Med (Lond)*. 2015;65(7):601-601. doi:10.1093/occmed/kqv054
11. Davies J. How Voting and Consensus Created the Diagnostic and Statistical Manual of Mental Disorders (DSM-III). *Anthropol Med*. 2017;24(1):32-46. doi:10.1080/13648470.2016.1226684
12. Raichle ME. The brain's default mode network. *Annu Rev Neurosci*. 2015;38(1):433-447. doi:10.1146/annurev-neuro-071013-014030
13. Xing Y, Fu S, Li M, et al. Regional Neural Activity Changes in Parkinson's Disease-Associated Mild Cognitive Impairment and Cognitively Normal Patients. *Neuropsychiatr Dis Treat*. 2021;17:2697-2706. doi:10.2147/NDT.S323127
14. Wang SM, Kim NY, Kang DW, et al. A Comparative Study on the Predictive Value of Different Resting-State Functional Magnetic Resonance Imaging Parameters in Preclinical Alzheimer's Disease. *Front Psychiatry*. 2021;12:626332. doi:10.3389/fpsyt.2021.626332
15. Chrobak AA, Bohaterewicz B, Sobczak AM, et al. Time-Frequency Characterization of Resting Brain in Bipolar Disorder during Euthymia-A Preliminary Study. *Brain Sci*. 2021;11(5):599. doi:10.3390/brainsci11050599
16. Lan Z, Xu S, Wu Y, et al. Alterations of Regional Homogeneity in Preschool Boys With Autism Spectrum Disorders. *Front Neurosci*. 2021;15:644543. doi:10.3389/fnins.2021.644543
17. Yn J, Jh G, Ql W, Yz J, Xy G, Xz D. [Effect of Scalp Acupuncture Stimulation on Mood and Sleep in Children with Autism Spectrum Disorder]. *Zhen ci yan jiu = Acupuncture research*. 2021;46(11). doi:10.13702/j.1000-0607.20210276
18. Cao HJ, Yu ML, Wang LQ, Fei YT, Xu H, Liu JP. Acupuncture for Primary Insomnia: An Updated Systematic Review of Randomized Controlled Trials. *J Altern Complement Med*. 2019;25(5):451-474. doi:10.1089/acm.2018.0046
19. Wang T, Li S, Jiang G, et al. Regional homogeneity changes in patients with primary insomnia. *Eur Radiol*. 2016;26(5):1292-1300. doi:10.1007/s00330-015-3960-4
20. Zhang Y, Zhang Z, Wang Y, et al. Dysfunctional beliefs and attitudes about sleep are associated with regional homogeneity of left inferior occidental gyrus in primary insomnia patients: a preliminary resting state functional magnetic resonance imaging study. *Sleep Med*. 2021;81:188-193. doi:10.1016/j.sleep.2021.02.039
21. Chen WH, Chen J, Lin X, et al. Dissociable effects of sleep deprivation on functional connectivity in the dorsal and ventral default mode networks. *Sleep Med*. 2018;50:137-144. doi:10.1016/j.sleep.2018.05.040
22. Dinkelacker V, Valabregue R, Thivard L, et al. Hippocampal-thalamic wiring in medial temporal lobe epilepsy: enhanced connectivity per hippocampal voxel. *Epilepsia*. 2015;56(8):1217-1226. doi:10.1111/epi.13051
23. Simon EB, Oren N, Sharon H, et al. Losing Neutrality: The Neural Basis of Impaired Emotional Control without Sleep. *J Neurosci*. 2015;35(38):13194-13205. doi:10.1523/JNEUROSCI.1314-15.2015
24. Motomura Y, Kitamura S, Oba K, et al. Sleepiness induced by sleep-debt enhanced amygdala activity for subliminal signals of fear. *BMC Neurosci*. 2014;15(1):97. doi:10.1186/1471-2202-15-97
25. Liu HR, Fang XY, Wu HG, et al. Effects of electroacupuncture on corticotropin-releasing hormone in rats with chronic visceral hypersensitivity. *World J Gastroenterol*. 2015;21(23):7181-7190. doi:10.3748/wjg.v21.i23.7181
26. Harvey AG, Tang NKY. (Mis)perception of sleep in insomnia: a puzzle and a resolution. *Psychol Bull*. 2012;138(1):77-101. doi:10.1037/a0025730
27. Jungwirth S, Fischer P, Weissgram S, Kirchmeyr W, Bauer P, Tragl KH. Subjective memory complaints and objective memory impairment in the Vienna-Transdanube aging community. *J Am Geriatr Soc*. 2004;52(2):263-268. doi:10.1111/j.1532-5415.2004.52066.x
28. Tsapanou A, Vlachos GS, Cosentino S, et al. Sleep and subjective cognitive decline in cognitively healthy elderly: results from two cohorts. *J Sleep Res*. 2019;28(5):e12759. doi:10.1111/jsr.12759
29. Taddei-Allen P. Economic burden and managed care considerations for the treatment of insomnia. *Am J Manag Care*. 2020;26(4)(suppl):S91-S96. doi:10.37765/ajmc.2020.43008
30. National Sleep Foundation. (2021). Sleep in America Poll.
31. Riemann D, Baglioni C, Bassetti C, et al. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res*. 2017;26(6):675-700. doi:10.1111/jsr.12594
32. Kaneita Y, Ohida T, Osaki Y, et al. Association of insomnia with job stress and work hours: cross-sectional study of 1300 workers in Japan. *J Sleep Res*. 2006;15(1):41-45.
33. Li Y, Zhang X, Winkelman JW, et al. The association between insomnia symptoms and mortality: a prospective study of US men. *Circulation*. 2018;138(6):551-553.
34. Morin CM, LeBlanc M, Daley M, Gregoire JP, Mérette C. Epidemiology of insomnia: prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. *Sleep Med*. 2006;7(2):123-130. doi:10.1016/j.sleep.2005.08.008
35. Chung KF, Yeung WF, Ho FY, Yung KP, Yu YM, Kwok CW. Cross-cultural and comparative epidemiology of insomnia: the Diagnostic and statistical manual (DSM), International classification of diseases (ICD) and International classification of sleep disorders (ICSD). *Sleep Med*. 2015;16(4):477-482. doi:10.1016/j.sleep.2014.10.018
36. Pallesen S, Sivertsen B, Nordhus IH, Bjorvatn B. A 10-year trend of insomnia prevalence in the adult Norwegian population. *Sleep Med*. 2014;15(2):173-179. doi:10.1016/j.sleep.2013.10.009
37. Buysse DJ. Insomnia. *JAMA*. 2013;309(7):706-716. doi:10.1001/jama.2013.193
38. Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord*. 2011;135(1-3):10-19. doi:10.1016/j.jad.2011.01.011
39. Nofzinger EA. Functional neuroimaging of sleep. *Semin Neurol*. 2005;25(1):9-18. doi:10.1055/s-2005-867070
40. Gao L, Hou Y, Wang H. Public health impact of insomnia and obstructive sleep apnea syndrome. *Sleep (Basel)*. 2014;37(12):1901-1909.
41. Rorden C, Karnath HO, Bonilha L. Improving lesion-symptom mapping. *J Cogn Neurosci*. 2007;19(7):1081-1088. PMID:17583985 doi:10.1162/jocn.2007.19.7.1081
42. ZHANG. P; Zhong-xin, Z. Interpretation of "Guidelines for the diagnosis and treatment of adult insomnia in China. Chinese Journal of Contemporary Neurology & Neurosurgery. *Tianjin Shi*. 2013;13(5):363-367.
43. Feng M. Dr. Feng Meiyin "Guqin moxibustion" combined with psychological intervention to treat heart and kidney insomnia test case [J]. *Asia-Pacific Traditional Medicine*. 2018;14(05):130-132.