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The Effects of Tai Chi on Insomnia Based on Multi-modal Brain Functional Connection and Signal Extraction: A Protocol for Randomized Controlled Trial

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Abstract

Background: Insomnia is a prevalent and costly disorder that poses a significant health burden and may be associated with abnormal brain functional connectivity. Tai Chi has shown promise as a non-pharmacological therapy in improving sleep quality in insomnia patients, but the underlying brain network mechanisms remain unclear. This study utilized advanced multimodal brain function analysis techniques, including resting-state functional magnetic resonance imaging (rs-fMRI) and functional near-infrared spectroscopy (fNIRS), to investigate how Tai Chi affects brain networks in individuals with insomnia. The research aims to assess the therapeutic effects of Tai Chi in different intervention cycles and to explore the potential for Tai Chi to become the preferred non-pharmacological treatment for insomnia.
Methods: This study is designed as a parallel, single-blind, randomized controlled clinical trial (RCT) involving 36 participants. Eligible patients will be divided into three groups: Tai Chi group, Cognitive behavioral therapy for insomnia (CBTI) group and Health education group, in a 1:1:1 ratio with 12 subjects in each subgroup. The primary outcomes will be LC resting-state functional magnetic resonance imaging (rs-fMRI); Hemoglobin (HbO) and deoxyhemoglobin (HbR) of the prefrontal cortex (PFC) will be measured by functional near-infrared spectroscopy (fNIRS). The secondary outcomes will be pittsburgh sleep quality index (PSQI), insomnia severity index (ISI), and hamilton anxiety scale (HAMA). Outcomes will be evaluated at baseline, 4, 8, and 12-week post treatment, as well as at 4-week follow-up.
Discussion: This study is the first randomized controlled trial to investigate the effects of Tai Chi on insomnia by incorporating multimodal information such as brain functional connectivity signals and cerebral oxygenation signals, aiming to assess the therapeutic efficacy of Tai Chi on insomnia and to clarify its intervention mechanism. This study has the potential to significantly impact the field of insomnia treatment and sleep disorder research by providing valuable insights into the therapeutic effects of Tai Chi.
Trial Registration: The study protocol has been registered in the China Clinical Trial Registry (ChiCTR2300077348).

Attachments

Figure 1.pdf
3.8MB

Figure2.pdf
2.4MB

Supplementary Materi...
266KB

Materials

Supple entary Material 1 SPIRIT 2013
Supplementary Material 2 Informed consent

Introduction

1 Insomnia is a prevalent clinical condition that is characterized by difficulties in either initiating or maintaining sleep, often leading to symptoms during waking hours, including fatigue, decreased attention span, impaired cognitive functioning, irritability, anxiety, and depressed mood.[1] The prevalence of insomnia is increasing worldwide, approximately 10-20% of adults in the United States suffer from insomnia.[2] In addition, the prevalence of insomnia in the Chinese population is as high as 45.4%.[3] Meanwhile, Insomnia can lead to changes in brain function, affecting mood regulation and even doubling the risk of future depression.[4,5] It can have a significant impact on an individual's overall well-being and quality of life, but this problem has not been effectively solved.

A recently updated review suggests that the vulnerability to insomnia may exist in the brain circuits regulating emotion and arousal and speculated that in people with insomnia, the locus coeruleus (LC) is more sensitive to or receives more inputs from the salience network and related circuits.[6] Neuroimaging studies using functional magnetic resonance imaging (fMRI) indicate that insomnia amplifies activity within the “fear network”, which includes the salience network and the limbic system.[7-9] Furthermore, the anxiogenic impact of insomnia relates to impaired medial prefrontal cortex (PFC).[10] These findings collectively underscore the intricate interplay between brain regions involved in arousal, attention, emotional processing, and cognitive control, shedding light on how insomnia may impact these systems. Therefore, the abnormal functional state of brain connectivity signals can be used as a research target for insomnia. It is a breakthrough point to supplement and explain the neurobiological mechanism of insomnia.[11]

The treatment of insomnia is divided into pharmacological and non-pharmacological therapy. However, prolonged medication usage may lead to drug resistance and dependency, while escalating doses and adverse effects can further impact the patient's health.[12] In addition, medication is not suitable for special populations (e.g., the elderly, pregnant women, and children). Cognitive behavioral therapy for insomnia (CBTI) is considered to be the gold standard in treating insomnia, which is expensive, labor intensive, and beyond the reach of many.[13] Novel non-invasive methods, such as transcranial direct current stimulation, transcranial magnetic stimulation, or auditory stimulation, lack sufficient evidence for clinical use in treating insomnia.[4] As a traditional non-pharmacological therapy in China, Tai Chi achieves co-regulation of emotion and arousal, improves high tonic LC discharge rates with high levels of arousal, and increases cognitive resources through

bilateral activation of the PFC under dual-tasking.[14,15] A recent study found that 3 months of Tai Chi was no worse than CBTI in improving sleep.[16] Importantly, Tai Chi enhances and activates functional brain connectivity, which can improve the quality of sleep in

patients.[17,18] Thus, Tai Chi is a clinical option that is widely applicable, cost-effective, easy to perform, and has additional health benefits.

With advances in neuroimaging technology, it is helping to reveal how insomnia affects brain function, thus providing a basis for the development of more effective therapeutic strategies. Using multimodal brain function analysis techniques such as resting-state functional magnetic resonance imaging (rs-fMRI) and functional near-infrared spectroscopy (fNIRS), this study provides an innovative approach to investigate how Tai Chi affects brain networks in insomnia, its therapeutic effects in different intervention cycles, and to clarify whether Tai Chi can replace CBTI as the preferred non-pharmacological therapy for insomnia.

Methods

2 **Study design**

This study is designed as a parallel, single-blind, randomized controlled clinical trial (RCT). The protocol for the RCT follows the Recommendations for Interventional Trials 2013 Statement (SPIRIT 2013) (Supplementary Material 1) and follows the principles of the Declaration of Helsinki.[19] This study has been approved by the Ethics Committee of Chengdu Sport University (2023153). and registered with the China Clinical Trial Registry (ChiCTR2300077348). A flow diagram of the trial is presented in Figure 1.

3 Participants

The trial will be conducted at the Institute of Sports Medicine and Health at Chengdu Sport University, Affiliated Sport Hospital of Chengdu Sport University. The recruitment site is at the Sleep Medicine Center of West China Hospital Sichuan University, Sichuan, China. The main source of the subjects will be the outpatients who meet our criteria. In addition, we will also recruit participants through newspapers, social media, and advertising. The researchers will obtain written informed consent from all participants (Supplementary Material 2). Participants will have the right to withdraw from the study at any time.

4 Sample size calculation

Sample size calculations are performed using G*Power Software, the effect size is 0.25, type 1 error (α)=5% (two-tailed), power (1−β) 95%, and the allocation ratio between the groups is 1:1:1.[20] According to the G*Power calculation, the total sample size should be 33. With consideration of the dropout rate, increase this by 10%. Therefore a total of 36 subjects were included in this study, 12 in each group.

5 Eligibility criteria

5.1 Exclusion criteria

1. Pregnant and lactating women.
2. Patients currently diagnosed with other mental disorders.
3. Patients currently diagnosed with severe sleep apnea, heart failure, myocardial infarction, stroke, tumor, severe lung disease, neurodegenerative disease, epilepsy, restless leg syndrome, etc.
4. Alcoholics and pill-popper.
5. Night shift work, shift workers, and frequent cross-time zone fliers.
6. Those who are using any other insomnia treatment and cannot stop that treatment.
7. Those who received any psychotropic drugs or drugs known to affect sleep in the month before enrollment.
8. Participants who had participated in or were participating in other clinical trials within 1 month before enrollment.
9. Other situations judged by the researcher not suitable for inclusion.

5.2 Inclusion criteria

1. Meet DSM-5 criteria for insomnia disorder.[2]
2.Regardless of gender, aged 18-59 years old.
3. ISI >= 8 points and <= 21 points
4. No disturbance of consciousness, no intellectual impairment, did not affect the scale score
5.Patients voluntarily participate in this study and sign a written informed consent.

6 Randomization and Blinding

The randomization sequence of subjects in this research will be generated by the random numbers generated by the SPSS 26.0 statistical software program by the research members who will have nothing to do with the experiment operation and evaluation. Randomly assigned sequences will be placed in consecutively numbered (1-36) sealed opaque envelopes in a 1:1:1 ratio. The envelopes will be kept by others not involved in this study (third parties). Researchers, which include statisticians, outcome assessors, and data analysts, will all be blinded to patients' group assignments. In addition, all researchers will undergo training for specific procedures before the trial begins.

7 Intervention

7.1 **Tai Chi**

Participants will practice Tai Chi at a set time, with each set of movements under the guidance of the same Chengdu Martial Arts College teacher, assisted by two professional assistants. Tai Chi will adopt the 24-style simplified standard movements of Yang's Tai Chi issued by the General Administration of Sport of

China.[18] The intervention will be prescribed as a 3-month program with two 1-h sessions weekly (including 10 min of warm-up, 45 min of Tai Chi, and 5min of finishing activities). Introductory skills and focussed teaching will take place in the week before the formal intervention. The professional teacher will introduce and demonstrate the movements, explain the precautions of 24-style simplified Yang's Tai Chi, and answer questions about the subjects. During the intervention period, all course materials, including videos of breathing exercises, relaxation exercises, and 24-style Tai Chi, will be sent to the subjects via WeChat for follow-up.

7.2 CBTI

Participants will practice CBTI at a set time, with each intervention under the guidance of a CBTI-trained therapist, assisted by two professional assistants. CBTI includes stimulation control (such as going to bed only when sleepy), sleep restriction (such as initially limiting the amount of time spent in bed to increase sleep efficiency), sleep hygiene (such as removing stimulators from the bedroom, such as TV/radio/clock), relaxation (such as diaphragmatic breathing, guided images), cognitive restructuring (e.g., thought diaries, behavioral experiments) and relapse prevention (e.g., summaries of effective skills, maintenance of progress).[16] The intervention will be prescribed as a 3-month program with two 1-h sessions weekly. A weekly CBTI supervisory meeting is also held to discuss cases, resolve issues, and listen to and provide feedback on the recorded treatment process. During the intervention period, all course materials will be sent to the subjects via WeChat for follow-up.

7.3 Health education

Health education served as the control group, which received no interventions other than verbal health education and recording of sleep twice a week for a total of 3 months.

8 Outcome measures

8.1 Resting-state functional connectivity (rs-FC) feature extraction of locus coeruleus (LC) based on resting-state functional magnetic resonance imaging (rs-fMRI).

The brain regions with abnormal rs-FC were obtained through the analysis of the LC and other voxels, and rs-fMRI will be collected from the following brain regions under different interventions: right precuneus, right posterior cingulate cortex (PCC), left middle temporal gyrus (MTG), left calcarine cortex, and right superior orbitofrontal cortex (OFC).[22] Then, based on seed analysis, the changes of abnormal rs-FC signals between LC and various brain areas under different interventions were compared to compare the correlation between improved rs-FC values and clinical scale scores.

FMRI data acquisition

The FMRI scan will be completed on a 3.0 T whole-body MRI scanner (MAGNETOM-Skyra-SIEMENS) with a volume transmit head coil and 32-channel receive coil. The MRI sequences included the following: (1) T1-weighted MRI: data were acquired using a magnetization-

prepared rapid gradient-echo sequence with TR/TE at 700 ms/11 ms, FOV at 256 × 256 × 192, and a voxel size of 1 × 1 × 0.9; (2) rs-fMRI: data were acquired using an echo planar imaging (EPI) sequence sensitive to BOLD with TR/TE/FA at 2020 ms/30 ms/90°, and FOV at 106 × 106 × 46, and a voxel size of 2.4 × 2.4 × 3.75. The rs-fMRI scan duration lasted 200 TR.[23] After the scan, all of the subjects will be asked if they were asleep during the scan. Those who have fallen asleep will be excluded.

Rs-fMRI preprocessing and data analysis

This preprocessing will be performed using the Data Processing Assistant for rs-fMRI (DPARSF) package (http://www.restfmri.net) based on statistical parametric mapping (SPM8, Welcome Department of Imaging Neuroscience, Institute of Neurology, London; http://www.fil.ion.ucl.ac.uk/spm), which will run on MATLAB (MathWorks, Natick, MA, USA).[24]

The main steps include the following: The first of 10 images points for each participant will be removed to eliminate the effect of magnetic field inhomogeneity at the beginning of the test on image quality and results. Subsequently, the rs-fMRI data will be regulated for the existence of temporal differences between slice timing and realignment. All participants will have a maximum displacement of no more than 2.0 mm in any direction and a maximum rotation of no more than 2.0. The fMRI data will be spatially normalized according to a standard template (Montreal Neurological Institute, MNI) and re-sampled to 3 mm^3. Spatial smoothing will be carried out using a 4-mm half-maximum full-width Gaussian kernel, removing the linear trend, and will be filtered with a 0.01-0.1 Hz bandwidth for filtering. Finally, regressions will be performed on interfering variables including the Friston 24 head movement model, white matter, CSF signal, and overall signal.

The seed region of the LC location will be defined as a sphere with a radius of 3 mm to ascertain spatial specificity to very small anatomical structures centered on the MNI coordinate (x = −14; y = −34; z = −28).[25] A voxel-wise FC map of the LC will be calculated using the correlations between the mean time series of the seed region and the remaining voxels within the brain.[22]

8.2 Functional near-infrared spectroscopy (fNIRS)-based feature extraction of prefrontal cortex (PFC) activation in a dual task.

Experimental tasks

The dual-task test includes two single-task tests, the Verbal Fluency Task (VFT) and the Emotional Sound Task (EST). VFT: mainly assesses executive function and cognitive function, which are related to neurocognitive functions such as memory, motivation, and attention.[26]

EST: Provides better information for emotion recognition and higher specificity for different types of emotions.[27]

Each trial will consist of a 30s break before the task, a 40s break during the task, and a 60s break following the task. Under the guidance of a specialized practitioner, during the 30s baseline period, subjects will sit motionless in a chair and repeat counting from one to five until the task begins. The 120 s task cycle is divided into four 30 s blocks. The single block consists of a 20 s double task, followed by a 10 s break. During the task, subjects will be asked to form

as many words as possible within 20 s of hearing a specific Chinese word (e.g., "time," "home," "fire," "name").[28] This will be accompanied by sound stimulation (e.g., “happy,” “calm,” “fear,” “white noise”). At the end of
the task, subjects will be asked to repeat the counting from one to five until the end of the task, which will take 60 s. The total duration of the experiment will be approximately 3.5 min. subjects will be asked to limit their physical movements as much as possible during the experiment.[29] As shown in Figure 2.
The dual-task combines two single tasks, VFT and EST. Specifically, subjects will perform a simultaneous task of constructing phrases in response to different types of sound stimulation. Subjects will be told to give equal attention to both VFT and EST to minimize the effect of task priority.

fNIRS data acquisition

Subjects were informed that the test was designed to monitor relevant brain oxygen data during the dual tasks described above. The fNIRS signal of PFC was obtained using the multi-channel continuous wave (CW) NIRScout fNIRS system (NIRx Medical Technologies, LLC) to observe the changes in Brain Hemoglobin (HbO) and deoxyhemoglobin (HbR).
By the modified Beer-Lambert law, Twenty-six multichannel fNIRS instruments (Wuhan Union Medical Technology Co., Wuhan, China) were used. The concentration changes of HbO and HbR in the brains of participants were measured by wavelengths of 670/830 nm and a sampling frequency of 20Hz. The probe is a cap based on a standard human brain with 16 light sources and 7 light detectors. The space between each pair of light sources and detectors is fixed at 3 cm. A channel is a region between a pair of source probes and a pair of detector probes where measurements are made. So, when we placed the probe set in the participant's prefrontal region via the International 10–20 EEG electrode placement system, all 26 channels in the PFC could therefore display different waveforms for HbO andHbR.
By the international 10–20 system, 26 channels are available: The following channels were available: According to Brodmann's area, channels 1–3, 24–26 are located in the ventrolateral PFC (VLPFC; BA44, 45, and 47), channels 10–12, 14, 15, 20, and 21 are located in the frontopolar PFC (FPPFC; BA 10). and channels 4–9, 13,16–19, 22–23 are located in the dorsolateral PFC (DLPFC; BA 9 and 46), based on Brodmann’s area.[30]

fNIRS preprocessing and data analysis

FNIRS data can be analyzed with the toolbox homer2, which offers a graphical user interface based on MATLAB. A band-pass filter operating between 0.01 and 0.1 Hz was used to remove high-frequency noise from the raw data. Following band-pass filtering, a threshold of 30 dB was used to locate the noise in the detection channel and eliminate slowly drifting noise from the body and environment.[31] Motion artifacts were then removed using a processing technique based on moving standard deviations and cubic spline interpolation.[32] The sliding window's standard deviation over a predetermined threshold was used to locate artifacts. After that, cubic spline interpolation was used to eliminate them. Based on the filtered optical data, HbO and HbR concentrations were calculated using an improved version of the beer Lambert Law.[33] As the baseline, we took the last ten seconds of the pre-task break. Each channel contains the average HbO and HbR levels for each participant during the task period and at baseline. By

deducting the baseline mean HbO and HbR value from the task period mean HbO and HbR value, HbO and HbR value during the task was calculated. Through this, we were able to determine the mean difference between the baseline and task periods for HbO and HbR.

8.3 Assessment of sleep-related indicators

Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a widely used questionnaire to assess one's sleep quality for the past month. The questionnaire assesses seven domains including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleep-related medication use, and daytime dysfunction, which are quantified into a global score (range: 0–21). Lower scores indicate better sleep quality.[34]

Insomnia Severity Index (ISI)

The Insomnia Severity Index (ISI) is a 7-item scale that has been used as both a screening and outcome measure in insomnia treatment research.49 It assesses the severity of both nighttime and daytime symptoms of insomnia over the past week and has been validated as a clinical endpoint for minimally important treatment response (ISI total score reduction > 7 points) and remission (ISI total score < 8).[35]

Hamilton Anxiety Scale (HAMA)

A total score of ≥ 29 indicates severe anxiety, a score of ≥ 21 indicates severe anxiety and a score of ≥ 14 indicates anxiety. A score below 7 indicates no symptoms of anxiety. In addition to the total score, subscales of " physical anxiety " and " psychological anxiety " can also be calculated. A higher score indicates a more serious condition.[36]

9 Safety assessments

Previous studies have indicated that Tai Chi is rather safe and did not report any adverse outcomes. Participant's insomnia severity will be monitored by subjective measurements during treatment and at 3-month follow-up. Additionally, in the event of any moderate-to-severe side effects occurring in the participants, such as headaches, insomnia, or acute mood changes, the experimental session will be immediately suspended.

10 Statistical analysis

SPSS26.0 statistical software was used for data analysis. The statistics and analysis of all data will be performed by an analytical researcher independent of the trial. Intention to treat (ITT) will be used for the main efficacy analysis and per protocol (PP) for the consistency test. The multiple imputation method will be the primary method for processing the missing data. Measurement data as mean ± standard deviation, using T-test, repeated measurement ANOVA, and non-parametric test methods such as Friedman analysis, The significance test was conducted by Mann-Whitney U test. All statistical tests will be performed on a two-sided test, and $p \leq 0.05$ will be considered statistically significant.

Discussion

11 This study utilized an innovative approach to investigate the therapeutic effects of Tai Chi on insomnia. The integration of multidisciplinary cutting-edge technology to explore the

mechanisms of Tai Chi's impact on insomnia, including its effects on emotion and arousal brain circuits, and neurocognitive function. This comprehensive approach has the potential to provide valuable insights into the treatment of insomnia and related mood disorders.

By incorporating multi-modal information such as brain functional connection signals and brain oxygen signals, the study aims to clarify new mechanisms of regulating emotion and arousal brain circuits in insomnia. This approach has the potential to advance understanding of the neurobiological underpinnings of insomnia and its relationship to neurocognitive dysfunction.

The inclusion of 4, 8, and 12-week therapeutic interventions, as well as a follow-up 4 weeks after the intervention, will allow for a comprehensive assessment of the therapeutic effects of Tai Chi on insomnia. This multi-angle assessment will provide valuable data on the short-term and potential longer-term effects of Tai Chi on sleep function and related symptoms.

The emphasis on traditional Chinese sports therapy, specifically Tai Chi, aligns with the rich cultural and historical context of this practice. Comparing characteristic differences in symptoms and sleep function before and after the intervention will help clarify the specific effects of Tai Chi and contribute to the understanding and development of traditional Chinese sports therapy.

The potential implications of this study are far-reaching, and the results could provide evidence for a more effective, affordable, and widely available treatment for insomnia, with the potential to shed light on the therapeutic benefits of Tai Chi for insomnia and contribute to the broader field of understanding and treating sleep disorders.

Strengths and limitations

12 Brain function was assessed by rs-fMRI and fNIRS, which will provide valuable insights into the clinical effects of Tai Chi in insomnia patients; Establishing the brain mechanism of Tai Chi in insomnia from the perspective of multimodal information such as brain functional connectivity signals and brain oxygen signals; Future perspectives could delve deeper into cross-diagnostic mechanisms from insomnia to mental disorders to further address the primary prevention of mental disorders.

Data management and monitoring

13 Participant data will be stored in password-protected files on a designated computer, with limited access granted only to the principal investigator and data analysts. This ensures that sensitive information is kept secure and confidential. An independent data monitoring committee, comprising individuals free from competing interests, will oversee the study. This committee will include the principal investigator, statisticians, outcome assessors, and data analysts, ensuring a comprehensive and unbiased review of the study's progress and outcomes.

Data Sharing Statement

14 Datasets obtained during this study can be provided by the corresponding author upon reasonable request.

Adverse Events Report

15 Participants will be encouraged to report any adverse events experienced during the trial, such as unfavorable or unintended signs or symptoms of diseases. Psychiatrists within the research team will evaluate these events to determine if they are associated with the intervention. Depending on the assessment, participants may be advised to continue in the study or withdraw and seek alternative healthcare support if necessary.

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Author Contributions

17 JL, JY, YL, NL, and YL conceived the concept of the manuscript and design of the work. JL and JY drafted the manuscript. All authors discussed, read, and revised the manuscript, and approved its final version.

Disclosure

18 The authors report no conflicts of interest in this work.

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