

Acupuncture for patients with insomnia disorder protocol for a resting-state functional magnetic resonance imaging study

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Study protocol

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Abstract

Background

Insomnia is among the most prevalent sleep-related disorders. Previous researches suggest insomnia disorder is associated with brain hyperarousal state manifested as abnormal regional brain activity and resting-state functional connectivity (rs-FC). Acupuncture is considered to be beneficial to improve sleep quality and modulate hyperarousal state. Its underlying neurobiological bases remain poorly understood. The purpose of the trial is to investigate the effectiveness and potential neural mechanism in acupuncture treatment for insomnia disorder using neuropsychological measurements and resting-state functional magnetic resonance imaging (rs-fMRI).

Methods /Design

This study is a randomized, patient-assessor-blinded trial. A total of 60 eligible patients with insomnia disorder will be randomized in a ratio of 1:1 to the real acupuncture group and sham acupuncture group. Acupuncture intervention will be administered to all patients three times a week for 4 weeks, followed up for 8 weeks. 30 age- and sex-matched healthy good sleepers will be recruited as healthy control group without any treatment intervention.

All participants will undergo neuropsychological and rs-fMRI evaluations. The primary outcome includes the change of Pittsburgh Sleep Quality Index (PSQI) scores. The secondary outcome includes Hyperarousal scale (HAS),rs-fMRI measurements, Fatigue scale-14 (FS-14), Hamilton depression scale (HAMD), Hamilton anxiety scale (HAMA), a sleep diary, and actigraph test.

All outcomes will be evaluated at baseline, post-treatment period and follow-up. The main analyses will be carried out on the basis of the intention-to-treat principle.

Discussion

The results of the trial will contribute to the efficacy and central mechanism of acupuncture treating insomnia disorder.

Background

Insomnia, which affects 10 to 15% of the population [1], is characterized by problems falling asleep, remaining asleep, or obtaining refreshing sleep, and is accompanied by impairments of daytime functioning [2]. However, the pathophysiology of insomnia is still under investigation. The most compelling hypotheses for insomnia is the hyperarousal model [3], which states that somatic, cognitive, and brain activation are increased in patients with insomnia [4].

The first-line therapies for insomnia are pharmacologic intervention with hypnotic medications and cognitive-behavioral therapy. However, many patients are troubled by the side effects of medications,

including lingering daytime sedation, cognitive impairment, and medication dependence. Psychotherapy is time-consuming and depends on the availability of trained therapists [5]. These factors lead to a low compliance rate for insomnia therapy [6]. Therefore, some patients have sought alternative treatments. Acupuncture, a critical component of Traditional Chinese Medicine, may relieve the symptoms of insomnia [7–10]. Nevertheless, the underlying neural basis for the effects of acupuncture remains largely unknown.

Recently, neuroimaging investigators have become interested in the spontaneous low-frequency fluctuations in brain activity when at rest. Studying these low-frequency fluctuations may help in elucidating the brain's intrinsic functional organization to aid in understanding the neurobiological mechanisms of insomnia and its treatment [11]. For instance, enhanced functional connectivity between the amygdala and the premotor and sensorimotor cortex occurs in insomnia disorder patients. The amygdala is closely related to fears, depression, and anxieties. Therefore, insomnia disorder may be related to increased negative emotional memory activity [12]. The insula is connected to other parts of the emotional circle [13], and anterior insula interactions with salient networks have been detected [14]. IN a study by Dong, increased whole brain positive connectivity,

detected in insomnia disorder patients was associated with a hyperarousal state [15]. Furthermore, Regional Homogeneity (ReHo) increased in the left insula of insomnia disorder patients that positively correlates with Self-Rating Anxiety Scale scores [16]. Taken together, research using resting-state functional magnetic resonance imaging (rs-fMRI) data suggest a brain hyperarousal state, especially in the emotion-related areas. Thus, patients with insomnia may benefit from modulation of this excessive brain activity. A recent fMRI study indicates that acupuncture can modulate the activity of the cerebro-cerebellar and limbic systems [17].

The following are the aims of this clinical trial: 1) to determine the effectiveness of acupuncture on sleep quality in patients with insomnia disorder using neuropsychological and rs-fMRI methods and 2) to elucidate the neurological mechanism by which acupuncture improves sleep quality. In addition to resting state fMRI, actigraphy will also be used to monitor sleep quality, by assaying time in bed, sleep latency, waking after sleep onset, sleep time, and sleep efficiency. Patients will be asked to complete sleep diaries and self-report questionnaires, such as Pittsburgh Sleep Quality Index (PSQI), Hyperarousal scale (HAS), Hamilton Depression Scale (HAMD), Hamilton anxiety scale (HAMA), and Fatigue scale–14(FS–14).

Methods And Design

Objectives

The objectives are: 1) determine the efficacy of acupuncture for the treatment of insomnia disorder and 2) elucidate the neural mechanisms for the effects of acupuncture on insomnia disorder.

Hypothesis

- We hypothesize that sleep quality will be significantly improved in the group receiving acupuncture treatment versus the sham group, as assessed by both subjective (PSQI) and objective (actigraphy) measurements.
- The hyperarousal state, measured by HAS, will be decreased more in the group receiving acupuncture versus the sham group.
- Based on fMRI examination, functional connectivity and ReHo, in the emotion-related areas, will be altered in the group receiving acupuncture versus the sham group.

Setting

The trial site will be the Acupuncture and Moxibustion Department, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, China. Sixty patients with insomnia disorder will be assigned to either a real acupuncture group or a sham group, using a digital randomization table in a 1:1 ratio.

Trial design

This study will be conducted as a single-center, prospective parallel-group, patient-assessor-blinded, randomized controlled trial (RCT). The trial will be conducted in accordance with the CONSORT (Consolidated Standards of Reporting Trials) [18] and STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture) principles [19], to fulfill adequate reporting standards for RCTs. Sixty patients, with insomnia disorder, will be assigned to either a real acupuncture group or a sham acupuncture group, using a digital randomization table in a 1:1 ratio. Participants will keep a sleep diary at baseline, during the 4th week of treatment, and during the 8th week of follow-up period. Both the neuropsychological measurements and fMRI scans will be performed at baseline, after completion of the acupuncture treatments, and at the conclusion of the follow-up period. Thirty age- and sex-matched healthy good sleepers will be recruited as controls for the fMRI data analysis. All outcome measures will be performed once for the healthy control patients. (Fig. 1)

Participants and recruitment

Posted notices in the hospital and recruitment information on the website of the Beijing Hospital of Traditional Chinese Medicine will be used to recruit study participants.

Participants will be informed about the benefits, as well as possible risks, of participation in the study, including poor clinical outcome and adverse events associated with acupuncture therapy. Completion of consent forms will be compulsory before trial participation and randomization. A neurologist will determine the PSQI, HAS, HAMD, HAMA scores to decide whether the participants meet the inclusion

criteria. Patients who satisfy the inclusion criteria will be randomized (1:1) into either a real acupuncture group or a sham acupuncture group. All participants will complete the baseline rs-fMRI, a 3-day actigraphy test, and the 1-week sleep diary. Participants will receive acupuncture treatment for 4 weeks. In addition, thirty age- and sex-matched Healthy good sleepers will be recruited as healthy controls for the fMRI data analysis. All personal information about the participants will be maintained confidentially by the research investigators and used for research purposes only.

Inclusion criteria

Compliance with the criteria listed below will be required for participation in the study.

- Age between 20 and 60 years.
- Meet the diagnostic criteria for insomnia disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V).
- A PSQI score >8 points; HAMD score <7; HAMA score <14; and HAS score >32.
- Signed informed consent form specific for this trial.
- Have not received medications for anxiety, depression, or insomnia within 1 month prior to enrollment in the study.

Exclusion criteria

Patients will be excluded from enrollment in the trial if they meet one or more of the following:

- Diagnosis of anxiety, depression, or schizophrenia.
- Diagnosis of severe medical disorders, including cardiac, cerebral, renal, hepatic, or metabolic diseases, or benign prostatic hyperplasia.
- Diagnosis of other sleep disorders, such as sleep apnea and restless leg syndrome
- Women who are pregnant or breastfeeding.
- Difficulty completing the inspection and treatment.
- Contraindication for MRI including claustrophobia. Abnormal signal or obvious asymmetrical head structure by MRI.
- Acupuncture therapy for insomnia treatment in the past month.
- Addiction to drugs or alcohol.

Inclusion criteria for healthy good sleepers

- No complaints of sleep quality and quantity.
- Patients between 20 and 60 years of age.
- Signed informed consent form specific for this trial.
- Have not received medications for anxiety, depression, or insomnia within 1 month prior to enrollment in the study.

Sample size

This pilot study aims to determine the efficacy and central mechanism by which acupuncture affects insomnia disorder. Based on our previous pilot study [20], the PSQI score significantly decreased by 4.43 ± 3.60 in the group treated with acupuncture compared to 1.30 ± 2.58 in the control group. Based on a power analysis, 26 patients per group were required to detect a significant difference (power = 0.9, $\alpha = 0.05$, two-sided). Thus, we plan on recruiting 30 patients per group, to compensate for a 15% drop out rate. There is no known sample size calculation for fMRI research [21]. However, for exploratory and pilot studies, 10 to 30 patients are adequate to test the null hypothesis [22].

Ethics

Protocol approval was obtained by the Medical Ethical Committee of Beijing Hospital of Traditional Chinese Medicine on 12 March 2018 (2018BL-002-02). Written informed consent will be attained from each participant. This trial is funded by the National Natural Science Foundation of China (81774391, 81871507).

Randomization, allocation concealment, and blinding

After meeting the eligibility requirements, participants will be randomly assigned (1:1 ratio) to the real or the sham acupuncture group. The random allocation sequence will be generated by an independent statistician using Statistical Analysis Software (version 9.3, SAS Institute Inc., Cary, NC, USA). The randomization list will be closed in computer-made opaque envelopes with sequence numbers printed on the outside of the envelopes. After the patient has been screened, determined to be eligible, and has given informed consent, the envelopes will be opened by the researchers.

The acupuncturists cannot be blinded, and, therefore, will be excluded from assessments and data processing. In the trial, the participants, data analysts, and outcome assessors will be blinded. Assessors will not perform data analysis.

In addition, sterile steel needles of the same size and number for each treatment session will be used in both groups. Participants will be required to write down if they have received real acupuncture at the final

treatment. The answer 'Y' or 'N' will be assessed to determine the confidence in the treatment.

Interventions

Real Acupuncture group (*shown in table 1 and table 2*)

The acupoints selection is based on the experience of experts and our previous clinical research [23]. All acupuncturists will receive training to assure consistent acupuncture technique in all participants. Acupoints on the vertex, including Baihui (GV-20), Shenting (GV-24), Benshen (GB-13), and Sishencong (EX-HN1), will be inserted horizontally for 10mm. Sanyinjiao (SP-6) will be inserted for 10 mm straight in, while Neiguan (PC-6) and Shenmen (HT-7) will be inserted perpendicularly for 5 mm. Needle manipulation, such as needling rotation, lifting, and inserting, will be employed to attain the 'De Qi' sensation (swelling, pain, numbness, distention, and heaviness). Needles will be kept in position for 30 min. Stainless steel needles used in the trial will be 0.32 mm×40 mm. The real acupuncture therapy will be performed three times per day at 2-day intervals for 4 weeks. The localization of the acupoints will be in accordance with the WHO Standard Acupuncture Locations [24].

Sham Acupuncture group (*shown in table 1 and table 2*)

The sham acupuncture group will be given the sham therapy with the same treatment duration and frequency of sessions as the real acupuncture group. Based on previous clinical experience, we chose acupoints that are ineffective in treating insomnia for the sham acupuncture group. The following acupoints will be punctured in the sham group: Binao (LI-14), Shousanli (LI-10), Yangchi (TE-4), Waiguan (TE-5), Fengshi (GB-31), Liangqiu (ST-34), and Futu (ST-32). The same needle size as in the real acupuncture group will be used. Unlike the real acupuncture application, needles will be inserted superficially 1 mm without manual stimulation. The needles will be kept in place for 30 min. Meanwhile, creation of the De qi sensation will be prevented by not manipulating the needles.

Healthy Control group

No acupuncture intervention will be conducted in the healthy control group.

Functional MRI scanning procedure

The rs-fMRI data will be obtained with a Siemens TRio 3.0 Tesla MRI scanner in Beijing Hospital of Traditional Chinese Medicine. All rs-fMRI images will be taken from a contiguous echo planar imaging (EPI) template under the following conditions: 33 axial slices, repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, thickness/gap = 3.5/0.6 mm, field of view (FOV) = 220×220 mm², flip angle (FA) = 90°, and matrix size 64mm x 64mm with 240 volumes. All participants will receive the following instructions: stay

awake, do not move, close your eyes, and do not to think about anything. For an anatomic reference, T1 images will be obtained before resting state scans.

The real acupuncture and sham acupuncture groups will be examined three times (before treatment, after treatment, and in the follow-up period.) and the healthy controls will be examined only once.

Follow-up procedure

Eight weeks after the end of treatment, the PSQI, fMRI, FS-14, HAS, HAMD, actigraphy, and sleep diary records will be collected.

Outcome measurements

Table 1 and Figure 1 show all outcome parameters.

Primary outcome

The PSQI, a self-assessment to evaluate sleep quality, will be the primary outcome measurement [25]. The PSQI contains 19 items consisting of 7 component scores, including sleep quality, sleep latency, sleep duration, daytime dysfunction, sleep efficiency, sleep disturbances, and sleeping medication. Higher global scores reflect worse sleep quality [26].

Secondary Outcomes

Sleep diaries

Sleep diaries will be assessed for sleep quality [27]. Participants with insomnia disorder will be required to record bedtime, sleep time, wake-up time, sleep latency, the state after morning awakening, and related factors in their sleep diaries. Recording of sleep diaries will be performed at baseline and at 4 and 12 weeks following entrance into the study.

Hyperarousal scale (HAS)

The HAS is a self-evaluation questionnaire containing 26 items. The questionnaire will be employed to evaluate the behaviors of cortical arousal, including information processing, strong response to unexpected stimuli, and introspective tendencies [28]. The scores correlate positively with a heightened arousal state. This questionnaire is usually applied to measure the change of cognitive and physical hyperarousal state [29].

Fatigue scale-14 (FS-14)

Fatigue is a dominant effect of insomnia [30]. The FS-14 is a self-rating scale to measure the severity of physical and mental fatigue. The FS-14 scores correlate positively with fatigue severity.

Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA)

Assessment of depressive status will be achieved with the HAMD. The HAMD is comprised of 17 variables with five- or three-point scales. Scores will be interpreted as follows: normal, less than 7; 8 to 17, mild depression; 17 to 24, moderate depression; and 24 or over, severe depression [31].

The 14-item HAMA will be used to determine anxiety. The HAMA is comprised of a 14 point self-assessment questionnaire, with a five-point scale for each item. A normal score is less than 7, scores between 7 and 14 suggest mild anxiety, scores between 14 and 20 indicate moderate anxiety, scores between 21 and 28 indicate severe anxiety, and a score greater than or equal to 29 indicates extremely severe anxiety [32].

For insomnia disorder participants, the scores for HAMD and HAMA will be collected at baseline, week 4, and at the 8 week follow-up. The HAMD and HAMA will be collected only once at baseline for the healthy control group. Collection of the week long sleep diaries will be at baseline, at 4 weeks after treatment, and at the end of the 8 week follow-up.

Actigraph

To obtain objective data on sleep and activity, we will request that participants wear an actigraph (MTI Health Services Company, Pensacola, Florida, USA) on their non-dominant wrist for three one week periods before the intervention, at the end of the intervention period, and at the end of the follow-up period [33].

Safety monitoring

Potential acupuncture adverse events include fainting, needle sticking, infections at the puncture site, and subcutaneous hematoma. Participants will be asked to report adverse events and practitioners will report any adverse events at each patient visit. Vital signs and adverse events will be chronicled in the Case Report Form (CRF) at each visit.

Quality control

To ensure a standard operation procedure, acupuncturists will consistently apply acupuncture with the correct acupoints and manipulation. Investigators will attend training to properly apply the randomization number table, to make the diagnoses, to understand the inclusion and exclusion criteria, and to complete

the case report forms. In addition, the fMRI scan will be performed with the same scanner and operator. Patients will be asked to close their eyes during the entire scanning procedure and stay still but do not sleep.

Additionally, the Scientific Research Supervision group of Beijing Hospital of Traditional Chinese Medicine trial will monitor the study regularly to ensure adequate recruitment rate, data accuracy, and data validity.

Statistical Analysis

Clinical data analysis

Statistical analyses will be performed with Statistical Package for the Social Sciences (SPSS, version 19.0). Two-sided tests will be considered significant at 5%. We will investigate the reasons for any missing data and, if necessary, multiple imputations will be applied. Data will be evaluated in agreement with the intention-to-treat principle. Sociodemographic information will be shown as the mean \pm standard deviation or the frequency (%) when appropriate. The baseline continuous, dependent variable data will be compared using independent-sample t-tests and chi-square tests will be performed for categorical data. Differences between group means will be analyzed with a repeated-measures analysis of variance (ANOVA). Multivariate analysis of variance (MANOVA) will be performed and Bonferroni correction will be applied for pairwise comparisons of changes in questionnaire scores with repeated measurement times for each group.

Functional MRI data analysis

The fMRI data will be analyzed with SPM12 software (SPM12, Wellcome Department of Imaging Neuroscience, London, UK), MATLAB_R2018a (Mathworks, Inc., Natick, MA, USA), DPARSF_V2.2 (<http://www.rfmri.org/DPABI>), and Freesurfer (<http://surfer.nmr.mgh.harvard.edu/>) software. Original data will be corrected; slice timing, affine head motion, and nonbrain extraction, spatial smoothing and temporal filtering will be applied.

Baseline ReHo and Amplitude of Low-Frequency Fluctuations (ALFF) values and FC maps from the real and sham acupuncture groups and the HC group will be compared using independent t- tests. Independent t-tests will be used for comparison of ReHo or ALFF values from the two groups after acupuncture. Paired t-tests will be utilized to compare the pre-acupuncture and post-acupuncture data within each group. Average time series data from significant areas will be extracted to test regional relationship with the rest of the brain utilizing voxel-based general linear modeling (GLM). Fisher's R-to-Z transformation will be applied to compare rs-FC using independent sample t-tests between groups [34].

Pearson's correlation analyses will be performed to evaluate the relationship of clinical symptoms with ReHo or ALFF values in regions demonstrating significant differences between groups.

Discussion

The purposes of the trial are to determine the effectiveness of acupuncture for the treatment of insomnia disorder and explore the potential neural mechanisms by which acupuncture affects sleep quality using neuropsychological measurements and rs-fMRI methods.

The influence of acupuncture on spontaneous regional brain activity and functional connectivity in insomnia disorder patients will be explored using ALFF, ReHo, and FC analyses. ALFF [35] and ReHo analyses are simple, easily implemented methods which exhibit favorable test-retest reliability and have been successfully applied to insomnia research. Increased information processing in the emotion-related regions, manifested as higher ReHo and ALFF scores suggest an association with the hyperarousal state of insomnia disorder [13–16]. In recent studies, acupuncture therapy decreased hyperarousal level and improved sleep quality in insomnia disorder patients [36]. We speculate that this effect may have relevance to the modulation of regional brain activity and functional connectivity, especially in emotion-related areas. If our hypothesis is correct, ALFF and ReHo values and FC maps of the emotional regions will be modulated more in the group receiving acupuncture compared to the sham group. These results will provide insight into the potential intrinsic mechanism of acupuncture for treating insomnia disorder.

Actigraphy will be applied in our trial to assess the changes in sleep quality. Although actigraphy may not be as accurate as polysomnography, this method can provide an accurate estimate of typical sleep duration. Actigraphy is more accepted and well tolerated by insomnia disorder patients. Furthermore, actigraphy can record sleep in the patients' natural environment and decreases the interference of factors that change a patient's characteristic sleep patterns [37]. Meanwhile, sleep diaries and questionnaires will be recorded at the same time as the actigraphy. At follow-up, rs-fMRI and actigraphy analyses will be performed to provide objective measures related to the long-term alterations of sleep quality and brain function in insomnia disorder.

The design of an appropriate control group for a clinical trial is critical. However, it is difficult to use placebo needles for controls. Thus, we will use acupoints in the sham acupuncture group that are considered ineffective for insomnia according to our clinical experience. The possible non-specific physiological reactions induced by needle pricking will be minimized by superficial puncturing and no manipulation to avoid the De qi sensation, which is believed to be fundamental to the efficacy of acupuncture.

The acupuncturists will receive training for consistent practices, including acupuncture point location and manipulation, to achieve effective quality control.

Despite the measures taken to assure a well-controlled trial, there are several methodologic limitations to this study. First, the treatment intervention duration of 4 weeks may be insufficient to achieve a measurable response, and a prolonged treatment period may result in a better effect. Second, there is no insomnia subgroup design. According to the definition of psychophysiological insomnia, this subtype has more relevance to the hyperarousal state. The description in the International Classification of Sleep

Disorders (ICSD–2) states that the “heightened arousal and learned sleep-preventing associations that result in a complaint of insomnia and associated decreased function during wakefulness” [38]. Other subtypes such as paradoxical insomnia and adjustment insomnia may have lower levels of hyperarousal. In our study, the insomnia disorder inclusion criteria of a “score above 32 on the HAS” will ensure the degree of hyperarousal. In further research, subgroup design and prolonged treatment periods should be considered when investigating the efficacy of acupuncture in treating insomnia. With the improvements in fMRI techniques, further advances can be made to clarify the neural substrates underlying the effects of acupuncture in insomnia disorder. In spite of its limitations, we hope our trial will help to provide new insights into the central neurological bases of acupuncture for treating insomnia disorder.

Declarations

Trial status

The Medical Ethical Committee of the Beijing TCM Hospital approved the study protocol on 12 March 2018 (permission 2018BL–002–02 for protocol 20180209). This trial is registered since March 2018 (Registration Number ChiCTR1800015282). The trial started at the beginning of 2018. The first participant was included in January 2019, and 6 participants have been recruited as of the date of this submission. The trial is currently recruiting participants. We predict that recruitment will be completed by November 2020.

Additional file

SPIRIT 2013 checklist.

Abbreviations

rs-FC: resting-state functional connectivity; rs-fMRI: resting-state functional magnetic resonance imaging; PSQI: the Pittsburgh Sleep Quality Index; HAS: Hyperarousal scale; FS–14: Fatigue scale–14; HAMD: Hamilton depression scale; HAMA: Hamilton anxiety scale; ReHo: Regional Homogeneity; CONSORT: Consolidated Standards of Reporting Trials; STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture; DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CRF: Case Report Form; Beijing TCM Hospital: Beijing Hospital of Traditional Chinese Medicine; SPSS: Statistical Package for the Social Sciences; ANOVA: analysis of variance; MANOVA: Multivariate analysis of variance; ALFF: Amplitude of Low Frequency Fluctuations

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Availability of data and materials

Not applicable.

Author Contributions

JG and CHL designed the study. JG and SY Y wrote the first manuscript for this trial. GLW and BL will conduct the acupuncture operation. All authors read and approved the final manuscript. All authors approved the final manuscript.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The study protocol was approved by the Medical Ethical Committee of the Beijing TCM Hospital approved on 12 March 2018 (permission number 2018BL-002-02). The trial is registered in the Chinese Clinical Trial Registry on 20 March 2018, ChiCTR1800015282.

Informed consent will be required for study participation. In addition, all researchers will be required to sign a pledge to protect the confidentiality of study participants.

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Tables

Due to technical limitations, Tables 1 & 2 are only available for download from the Supplementary Files section.

Figures

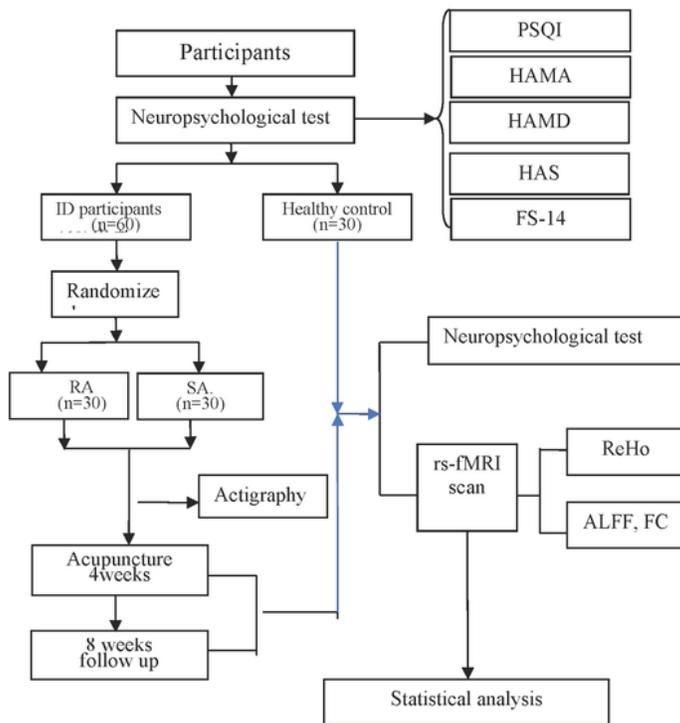


Figure 1

Flow chart of study.

Supplementary Files

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