

The Cerebral Mechanism of Acupuncture for Chronic Insomnia with Gastrointestinal Disorder: Protocol for a Randomized Controlled Trial

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Study protocol

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Abstract

Background

Many patients with chronic insomnia disorder (CID) have gastrointestinal (GI) symptoms. First-line insomnia medications do not treat GI problems. Acupuncture has a comprehensive regulative action on both CID and GI disorder and is receiving increasing attention. Recent studies indicate that both CID and GI diseases may cause abnormal brain activity. However, the neurological mechanism underlying the effect of acupuncture on such diseases is still unclear. The aim of this study is to explore the pathological mechanisms of CID with GI discomfort, as well as the main response characteristics of acupuncture treatment from multiple perspectives using multimodal magnetic resonance imaging (MRI).

Methods

A total of 60 participants with CID and GI disorders will be randomly divided into two groups (real acupuncture group and sham acupuncture group; ratio of 1:1). Patients will receive 20 sessions (five sessions per week) of real acupuncture treatment or sham acupuncture treatment. The primary outcome is the aggregate score on the Pittsburgh Sleep Quality Index. Secondary outcomes are scores on the Gastrointestinal Symptom Rating Scale, Self-Rating Anxiety Scale, and Self-Rating Depression Scale. Multimodal MRI scans and clinical assessments will be performed both at baseline and post-treatment. Another 30 age-, sex-, and education-matched healthy subjects will be recruited as controls and will receive MRI scans and clinical evaluations.

Discussion

This study aims to provide scientific evidence for the mechanism of acupuncture in treating CID with GI disorder using multimodal MRI imaging data on brain structure, function, and metabolism.

Trial registration

The study was registered in the Chinese Clinical Trial Registry on July 11, 2018. (ChiCTR1800017092)

Background

Chronic insomnia disorder (CID) is defined as difficulty initiating or maintaining sleep that is associated with daytime consequences and occurs at least three times per week for more than 3 months; CID has a prevalence rate of 5% to 10%.^[1] Typical nighttime symptoms include difficulty falling asleep, difficulty maintaining sleep, and waking early.^[2-3] Additional symptoms include fatigue, memory decline, cognitive deficits, and mood disorder.^[4-5] Recent studies have identified a correlation between sleep disturbances and gastrointestinal (GI) diseases.^[6] According to a previous survey,^[3] about 27.5%–33.4% of insomnia patients have concomitant GI symptoms, such as dyspepsia, diarrhea, and constipation. Interestingly, patients with multiple GI symptoms are more likely to have sleep problems.^[7-9] It has recently been

suggested that GI function plays a vital role in sleep.^[10] These findings provide new insights into the pathological features and treatment of CID associated with GI.

Pharmacotherapy is the primary recommended treatment for CID, according to the American Academy of Sleep Medicine clinical practice guideline.^[1] Although there is evidence for the short-term efficacy of insomnia medications,^[11-12] long-term use is associated with the risk of addiction and adverse drug reactions, particularly GI side effects.^[13] Therefore, treatments with fewer side effects are needed for this population. Acupuncture is a possible alternative therapy. Multiple studies have shown that acupuncture effectively improves sleep quality^[14-15] and regulates GI function.^[16-17] Moreover, acupuncture is more effective than drug therapy in treating insomnia with GI disorder.^[18-19] However, the mechanism underlying the effect of acupuncture on CID with GI symptoms remains to be elucidated.

In recent years, magnetic resonance imaging (MRI) techniques, such as functional magnetic resonance imaging (fMRI), structural magnetic resonance imaging (sMRI), diffusion tensor imaging (DTI), and magnetic resonance spectroscopy (MRS), have been widely used to study the pathophysiological mechanisms of insomnia. Using fMRI, we previously confirmed that the core pathological features of patients with CID are evident in the structural and functional plasticity of the brain.^[20-21] Some DTI research indicates that the white matter tracts in the anterior internal capsule, right arcuate fasciculus, and superior longitudinal fasciculus of patients with insomnia are abnormal.^[22-23] MRS is the only non-invasive method that can quantify biochemical substances in the brain,^[24] and MRS studies have identified abnormal brain metabolic activity in insomnia patients.^[25-26] Such studies have helped to clarify the pathology and treatment mechanisms of CID with GI disorder.



There is growing evidence from MRI studies that acupuncture can restore abnormal brain structure, connections, and metabolism in pathological states.^[27-29] For example, in a study of carpal tunnel syndrome, researchers using DTI therapy found that acupuncture can increase the plasticity of the primary somatosensory cortex to improve median nerve function.^[30] An acupuncture study of migraine demonstrated an increase in N-acetylaspartate/creatine levels in the brain after acupuncture.^[31] Both insomnia^[32] and GI disease^[33] studies have shown that acupuncture can repair abnormal connections in the brain. However, no studies have focused on the mechanism underlying the effect of acupuncture on CID with GI disorder. Therefore, a multimodal MRI approach combining fMRI, sMRI, DTI, and MRS is needed to explore the main mechanisms by which acupuncture affects CID with GI disorders.

For these reasons, we designed this multimodal neuroimaging trial. The study aims are as follows: (1) to confirm the efficacy of acupuncture for patients with insomnia and GI discomfort by comparing it with sham acupuncture; (2) to explore the central response mechanism underlying the effect of acupuncture on CID with GI disorders, focusing on cerebral structure, function, and metabolism; (3) to explore a possible correlation between brain activity changes and symptom improvement caused by different acupuncture modes.

Methods/design

The protocol was developed in accordance with Standard Protocol Items for Clinical Trials with Traditional Chinese Medicine 2018^[34] and Standards for Reporting Interventions in Clinical Trials of Acupuncture.^[35]

Table 1 Study protocol schedule of enrollment, intervention, and assessment

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
TIMEPOINT(week)	-1	0	1	2	3	4	5
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Demographics	X						
Allocation		X					
INTERVENTIONS:							
Real acupuncture Group							
Sham acupuncture Group							
Healthy Group							
ASSESSMENTS:							
MRI scans		X					X
PSQI		X					X
GSRS		X					X
SAS		X					X
SDS		X					X
Adverse events		X	X	X	X	X	X

Legend: MRI Magnetic resonance imaging, PSQI Pittsburgh sleep quality index, GSRS Gastrointestinal symptom rating scale, SAS Self-rating anxiety scale, SDS Self-rating depression scale

Study design

This randomized, single-blind, sham-controlled neuroimaging study will be conducted at the affiliated hospital of Chengdu University of Traditional Chinese Medicine (CDUTCM), China. A total of 60 CID patients with GI disorder will be recruited using advertisements on posters and hospital networks. All patients meeting the inclusion criteria will randomly receive either 20 sessions of real acupuncture treatment or 20 sessions of sham acupuncture treatment. A multimodal MRI examination and evaluation will be performed at both baseline and the end of treatment. Additionally, 30 healthy controls (HCs) matched for age, sex, and education level will receive one multimodal MRI scan and a clinical assessment. A flowchart of the trial design is shown in **Figure 1**, and the assessment schedule is shown in **Table 1**.

Inclusion criteria

Patients diagnosed with CID are eligible to participate in the study. Inclusion criteria are (1) aged between 18 and 65 years, right-handed, any gender; (2) meets the CID diagnostic criteria in the International Classification of Sleep Disorders-Third Edition (ICSD-3),^[36] and meets the criteria for spleen and stomach disharmony syndrome in the Clinical Terminology of Traditional Chinese Medical Diagnosis and Treatment—Syndromes (GB/T 16751.2-1997);^[37] (2) Pittsburgh Sleep Quality Index score above 7 (PSQI score >7); (3) not taking any medication or health care products to improve sleep quality and experienced GI diseases at least 2 weeks before study enrollment; (5) has not participated in other clinical trials within the last month; (6) agrees to voluntarily participate in the study and signs an informed consent form.

The HCs must meet the following inclusion criteria: (1) passes the neuropsychological tests and reports good sleep quality; (2) no GI symptoms; (3) all physiological indexes within the normal range following a physical examination, and no previous functional or organic disease or head injury; (4) agrees to voluntarily participate in the study and signs an informed consent form.

Exclusion criteria

Patients with any one of the following criteria will be excluded: (1) any severe conditions of the cardiovascular, cerebrovascular, liver, kidney, and hematopoietic systems; (2) secondary insomnia caused by drugs, cervical spondylosis, or other diseases; (3) history of psychiatric and neurological disorders or head trauma with loss of consciousness; (4) abuse of psychotropic drugs for anxiety and depression or sedative and hypnotic drugs; (5) pregnant, preparing for pregnancy, or lactating; (6) MRI contraindications such as claustrophobia, cardiac pacemaker, defibrillator, heart stenting, metal dentures, or intrauterine device.

The exclusion criteria for the HC are the same as for the patients.

Withdrawal criteria

Participants with any of the following conditions will be withdrawn: (1) complications that affect safety; (2) serious adverse events; (2) unwilling to follow the study protocol for examination and treatment.

Sample size

This is a trial to investigate the mechanism of acupuncture and is based on neuroimaging technologies. The requirements of imaging studies^[38] and previous similar studies^[39-40] suggest that 12–26 individuals in each group is a reasonable sample size for brain image data analysis. To allow for potential problems such as subject dropout and invalid imaging data owing to head movements, a sample of 30 patients in each group is considered reasonable.

Randomization

The randomization will be conducted using random number lists created by SAS 9.2 (SAS Institute Inc., Cary, NC, USA). Sixty CID patients will be randomly divided into two groups of 30 cases each. A third researcher, who will not participate in the subsequent research process, will place serial numbers, group numbers, and random numbers in opaque envelopes. Each sealed envelope will be renumbered. If participants meet the inclusion criteria, envelopes with the same serial number will be opened in the order of enrollment and the randomized results will be forwarded to the acupuncturists.

Blinding

The blinding of acupuncturists is quite difficult to achieve.^[41] Therefore, only patients, outcome assessors, and statisticians will be fully blind in this study.

Interventions

Treatments will be performed by certified acupuncturists with at least 3 years of acupuncture experience. Disposable sterile filiform needles (XingLin acupuncture needle, $\Phi 0.25 \times 25$ mm/ $\Phi 0.25 \times 40$ mm, Tianjin Yi Peng Medical Instrument Co., Ltd., China) will be used. Both the acupuncture and sham acupuncture treatments will comprise 20 sessions over 4 weeks (five sessions per week).

Real acupuncture group

Patients in the real acupuncture group will receive acupuncture treatment on the acupoints *Baihui* (DU20), *Zhongwan* (RN12) and *Zusanli* (ST36) with disposable sterile filiform needles. All acupoints will be located according to the World Health Organization Standard Acupuncture Locations and are shown in **Table 2** and **Figure 2**. Needles in DU20 will be inserted 0.5–1 cun (a unit of measurement in acupuncture,

1 cun = 25 mm) using horizontal needling. Needles in RN12 and ST36 will be inserted 0.5–1.5 cun using perpendicular needling after skin disinfection. After the needle enters into the skin, needles will be manipulated by twirling, lifting, and thrusting to generate the sensation of de qi in the local tissue. The experience of de qi is characterized by sensations of numbness, heaviness, or distension felt by the patient. All needles will be retained for 30 minutes.

Sham acupuncture group

The sham acupuncture group will receive a superficial skin penetration treatment at sham acupoints (SA). These SA are located near real acupoints (2 cm lateral from DU20, RN12, and ST36) but do not belong to any known meridian and are not conventional acupoints. The SA locations are shown in **Table 3** and **Figure 2**.

Superficial skin penetration at SA, without needle manipulation for de qi, is a common sham acupuncture method used in many acupuncture randomized controlled trials.^[42] Patients in this group will undergo an acupuncture procedure similar to the one received by patients in the real acupuncture group.

Table 2 Acupoint locations for the real acupuncture group

Acupoints	Locations
<i>Baihui</i> (DU20)	The intersection of the crown midline and the apex of the ears
<i>Zhongwan</i> (RN12)	On the upper abdomen, anterior median line, four cun* above the navel
<i>Zusanli</i> (ST36)	On the outside of the calf, three cun below <i>Dubi</i> (ST35)**

Legend: * According to the theory of traditional Chinese medicine, the navel is 8 cun below the xiphoid process; **ST35 is located on the lateral depression of the patellar ligament

Table 3 Sham acupoints locations for the sham acupuncture group

Sham acupoints (SA)	Locations
SA 1	2cm to the right of DU20
SA 2	2cm to the right of RN12
SA 3	2cm outside of ST36

Legend: cm Centimeter

Concomitant medication

Patients will be advised to avoid medication as much as possible during the study. Following medical ethical principles, if patients' insomnia symptoms do not significantly improve and they cannot tolerate their insomnia, they may temporarily take sleeping drugs. Researchers will record the name, dosage, and time of the drugs taken in detail in the Case Report Form (CRF).

Multimodal MRI data acquisition

MRI examinations will be performed at the MRI Center at the University of Electronic Science and Technology of China using a 3.0T MRI scanner (GE Discovery MR750, USA) equipped with a standard 8-channel head coil. MRI scans will be assessed at baseline and after 4 weeks. Subjects will be told to eat light food; avoid drinking strong tea, coffee, and wine; and avoid strenuous exercise the day before the scan. To prevent head movements affecting the image, foam pads and towels will be used to hold the head. During the MRI examination, all subjects will wear earplugs and be instructed to relax with their eyes closed and keep their heads clear. The scanning procedure produces a three-dimensional T1 image (3D-T1), a blood oxygenation level-dependent fMRI (BOLD-fMRI), a DTI sequence, and a proton ^1H -MRS. The 3D-T1 scanning parameters will be as follows: repetition time (TR)/echo time (TE) = 5.988/1.972 ms, slice thickness = 1 mm, slice number = 154, field of view (FOV) = 256×256 mm. The BOLD-fMRI scanning parameters will be as follows: TR/TE = 2000/30 ms, flip angle = 90° , slice number = 35, matrix size = 3.75×3.75 , FOV = 64×64 mm, slice thickness = 4 mm. The DTI data will be obtained using the following parameters: FOV = 240×240 mm, TR/TE = 6800/93 ms, matrix size = 128×128 , and slice thickness = 3 mm with no gap. The proton ^1H -MRS asymmetric PRESS sequence includes TE1 = 25 ms, TE2 = 85 ms, TR=2 s, and a $2 \times 2 \times 2$ cm area of interest on the anterior cingulate gyrus will be selected.^[26]

Outcome measures

The outcome assessments will be performed at baseline and after 20 treatment sessions. All outcome assessors will be trained in conducting interviews and performing measurements before the study begins and will follow a standard protocol. An overview of the outcome measurement at different time points is shown in **Table 1**.

Primary outcome

The primary outcome is the PSQI scale score. The PSQI comprises 19 self-evaluation items, among which 18 items generate 7 components. Each component is graded from 0 to 3, and the cumulative score of each component is the total score of PSQI, which ranges from 0 to 21. The PSQI is the most widely used sleep quality rating scale.^[43]

Secondary outcomes

The Gastrointestinal Symptom Rating Scale (GSRS)^[44] will be used to measure GI symptoms.

The Self-Rating Anxiety Scale (SAS) and the Self-Rating Depression Scale (SDS)^[45] will be used to assess subjects' emotional state.

Data management

Clinical data will be managed using printed and electronic CRF accessible only by the research team. The CRF is the original record and cannot be changed at will. It will be kept by a researcher of the research team. At the end of the trial, two researchers will enter data from the case report form into a computer. The Evidence-based Medicine Center of the CDUTCM will regularly monitor the trial data.

Data analysis

Clinical data analysis

Statistical analyses of the clinical data will be performed using SPSS 20.0 statistical software (IBM Corporation, Armonk, NY, USA) and supervised by a skilled statistician blinded to group allocation. The Kolmogorov–Smirnov test will be used to test the normal distribution of continuous variables. Continuous normally distributed data will be reported as means and standard deviations; continuous non-normally distributed data will be expressed as medians with interquartile ranges. Categorical data will be presented as frequencies or percentages.

For the demographic and clinical information at baseline, the chi-squared test or Fisher's exact test will be used for comparison of dichotomous data. The two-sample t-test will be used for normally distributed continuous data or the Mann-Whitney U-test for non-normally distributed data. To compare baseline and post-treatment changes in the same group, we will use the paired t-test. Covariance analysis using baseline data as covariates will be used to compare the effects of different interventions on continuous data. A p-value <0.05 will be considered statistically significant.

Imaging data analysis

The fMRI data will be preprocessed and analyzed using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/>) and CONN toolbox 18b (<https://web.conn-toolbox.org/>) with MATLAB 2014b (MathWorks, Inc., Natick, MA, USA). The sMRI data will be analyzed using the VBM toolbox within SPM12. DTI data will be processed using FSL Software on Linux. MRS data will be preprocessed using the commercially available software LCModel spectral-fitting package (version 6.3-1N; Stephen Provencher, Inc., Oakville, ON, Canada). After

standard preprocessing of each imaging modality, the following brain activity information will be calculated to examine the neural response to different treatments: the amplitude of low-frequency fluctuation, group independent component analyses, seed-based functional connectivity, cortical thickness, tract-based spatial statistics, and glutamate. Finally, Pearson correlation analysis will be used to assess the association between changes in multimodal neuroimaging features and improvements in clinical outcomes in each group.

Patient safety

During treatment, any adverse events (AEs) will be monitored and recorded in the CRFs throughout the trial. Important AEs in this study would be needle-related AEs, such as bleeding, hematoma, dizziness, infection, neurological symptoms, and fainting. Patients with mild and moderate AEs will receive symptomatic treatment. Severe AEs will be reported to the research ethics committee within 48 hours.

Patients and public involvement

Patients and the public were not involved in the design and implementation of the study. They were also not asked to advise on the reporting and dissemination of the results.

Discussion

Multimodal MRI will be used to explore the pathological mechanism of CID with GI disorder and the main response characteristics of acupuncture therapy for this type of insomnia. There will be several study strengths and limitations.

In the theoretical system of traditional Chinese medicine, insomnia accompanied by GI disorder is a common syndrome. According to the Yellow Emperor's Canon of Internal Medicine, a famous Chinese medical text, Chinese doctors discovered a link between GI illness and sleep more than 2,000 years ago, and developed the principle of "harmonizing the stomach and mind".^[46] Our acupoint selection protocol is based on this treatment principle, and the selected points DU20, RN12, and ST36 are commonly used acupoints for insomnia associated with GI disorder in acupuncture clinical trials.^[47] DU20 improves sleep, and RN12 and ST36 harmonize GI functions. Evidence from clinical trials using the "harmonizing the stomach and mind" principle has confirmed the effectiveness and safety of acupuncture for CID with GI disorder.^[18,48-49]

Multimodal MRI will provide technological data to examine the neuropathological mechanism underlying the effect of acupuncture on CID with GI disorder. We first want to explore neuropathological changes in patients with CID and GI disorder from the perspectives of brain structure, function, and metabolism. Our previous study was a preliminary exploration of the pathogenesis of insomnia (rather than CID with GI disorder) in terms of brain function and structure.^[20-21,50] Other research teams have confirmed that

insomnia patients have abnormal brain metabolism using MRS technology.^[24-26] At present, there are no brain imaging studies on patients with CID with GI. Most studies on insomnia have identified the abnormal brain regions in CID patients as the anterior cingulate gyrus, hippocampus, thalamus, and other regions,^[51-52] these brain regions also feature in GI imaging studies.^[53] It remains to be determined whether the structure, function, and metabolism of these brain regions are also changed in CID with GI disorder. Second, we wish to explore the central response mechanism of acupuncture. There is evidence that acupuncture can regulate the neuroplasticity and functional connectivity of abnormal brain regions in other diseases,^[28,30] but most studies have used only a single neuroimaging pattern, and cannot fully explain the mechanism of acupuncture. Multimodal MRI provides a new way of exploring the mechanism underlying acupuncture. It can examine the mechanism of action in detail from multiple perspectives, which is a more comprehensive approach than the use of single-mode magnetic resonance technology. At present, multimodal MRI has been used to investigate the effect of acupuncture on depression, chronic fatigue syndrome, and other diseases.^[54-56] In this study, we will use multimodal MRI combined with sMRI, fMRI, DTI, and MRS. Of these techniques, sMRI and DTI can detect structural changes in different brain regions, fMRI can explore changes in functional connections between different brain regions, and MRS can detect changes in different brain metabolites.

To improve the reliability of results and reduce bias, we will incorporate the following quality control measures. First, the inclusion and exclusion criteria will be strictly applied and the subject groups will be matched on age, gender, height, weight, and other variables. Second, a project workshop manual will be developed. All the members of our team will be trained to use related diagnostic standards, methods, and evaluation forms. Acupuncture will be performed by two equally qualified acupuncture physicians who will only perform acupuncture after passing a training trial agreed by the research group. Finally, all the imaging will be performed by the same experienced imaging professionals.

Some study limitations must be noted. First, during the study, subjects will be allowed to take sleeping medications if they cannot tolerate their insomnia. We cannot ethically limit patients' choices, and therefore can only ask patients to follow the study treatment regimen as closely as they can, and to record the name and dose of any medication they take on the CRF. Therefore, medication use may be a confounding factor that affects the results. However, as this is a randomized controlled trial, we believe that any noise caused by other treatments will mostly be controlled. Second, the study will be performed in only one center. The bias inherent in the collection and analysis of magnetic resonance data may be increased if the study were to be conducted in multiple locations. Therefore, given the existing technical conditions, we can only conduct a single-center study.

In summary, this study will investigate the effectiveness of acupuncture therapy for CID with GI disorder. We seek to provide scientific evidence for the mechanism of acupuncture in treating CID with GI disorder using multimodal MRI imaging data on brain structure, function, and metabolism.

Trial status

Study approval was obtained from the Sichuan Traditional Chinese Medicine Regional Ethics Review Committee, China on May 24, 2018 (protocol version number: 20180425). Clinical registration was completed on July 11, 2018 (Chinese Clinical Trial Registry, ChiCTR1800017092). The trial is still ongoing at the time of manuscript submission. The scheduled start of recruitment was 1 August 2018. The anticipated end of recruitment is August 1, 2020.

Abbreviations

AEs: Adverse events; BOLD-fMRI: Blood oxygenation level-dependent functional magnetic resonance imaging; CID: Chronic insomnia disorder; CRF: Case report form; DTI: Diffusion tensor imaging; FOV: Field of view; GI: Gastrointestinal; GSRS: Gastrointestinal symptom rating scale; HCs: Healthy controls; ICSD-3: International classification of sleep disorders-third edition; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; PSQI: Pittsburgh sleep quality index; SA: Sham acupoints; SAS: Self-rating anxiety scale; SDS: Self-rating depression scale; TR: Repetition time; TE: Echo time

Declarations

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Authors' contributions

YPH and SSY conceived the study and acquired the funding in China. WP, XJH, YRHF, ZS, FF, ZFS, BJG, and LXZ helped to improve the study design. WS and LG developed the data analysis plan. WP drafted the manuscript of this protocol. XJH, YNW, YZ, TMZ, SSY, and YPH critically revised the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

Not applicable; no data have yet been generated.

Ethics approval and consent to participate

This study has been approved by the Sichuan Traditional Chinese Medicine Regional Ethics Review Committee (No.2018kl-041) in China. This study determined the informed consent in accordance with the relevant requirements of the declaration of Helsinki. The participant or his or her agent shall have the right to know the purpose, method and implementation of the study. All subjects are required to sign informed consent before the start of the clinical trial. The participants' personal data will be kept confidential throughout the study and only available to the research team. The aggregated research findings will be published in a peer-reviewed publication.

Consent for publication

The informed consent for publication of individuals' details will be obtained from the trial participants. It can be obtained from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Dissemination policy

The authors will report the final data to the Sichuan Provincial Science and Technology Department of China. Results will be disseminated in peer-reviewed publications and published in international journals.

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Figures

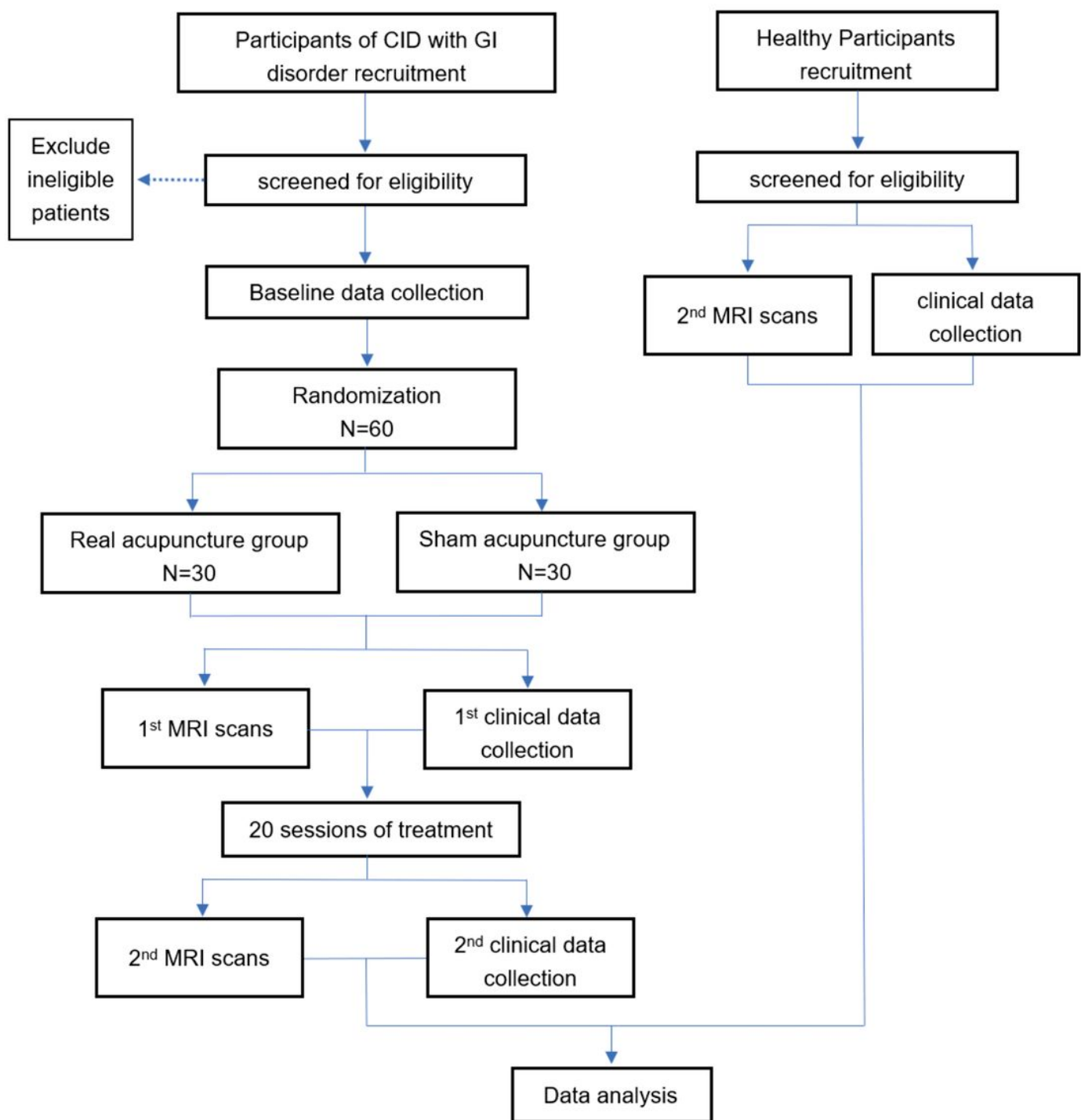


Figure 1

Flowchart of the trial Legend: CID Chronic insomnia disorder, GI Gastrointestinal, MRI Magnetic resonance imaging

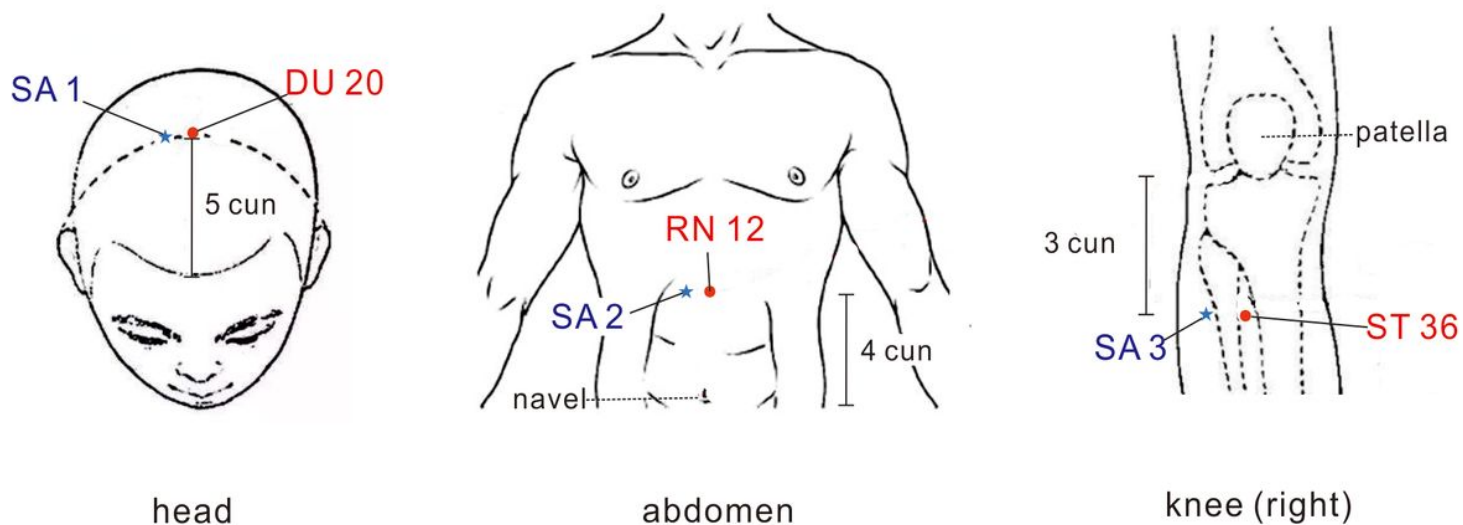


Figure 2

Location of acupoints and sham acupoints Legend SA Sham acupoint

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