

Neurological and psychological mechanisms of the specific and nonspecific effects of acupuncture on knee osteoarthritis: study protocol for a randomized, controlled, crossover trial

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Study protocol

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Abstract

Background Acupuncture, as one of the promising non-pharmacological interventions, has been proved to be beneficial for patients. However, the magnitude of acupuncture's specific and nonspecific effects, as well as their neurological and psychological determinants, remain unclear. Therefore, this study is designed to examine the acupuncture efficacy, investigate whether the brain mechanisms between the specific and nonspecific effects of acupuncture are different, and to evaluate how psychological factors affect the acupuncture effects.

Methods This is a randomized, controlled, crossover clinical trial. A total of 60 patients with knee osteoarthritis will receive 4 weeks of acupuncture treatment and 4 weeks of sham acupuncture treatment in a random order separated by a washout period of 2 weeks. The changes in clinical characteristics based on pain-related scales will be assessed to investigate the clinical efficacy of acupuncture. Resting state functional magnetic resonance imaging (fMRI) scans will be used to identify the brain activity changes related to the specific and nonspecific effects of acupuncture. The questionnaires of psychological factors will be used to evaluate patients' psychological properties. Correlation and mediation analyses will be conducted among psychological factors, brain activity changes and symptoms improvement to explore the neurological and psychological correlates of the acupuncture effects.

Discussion This study will concentrate on distinguishing and clarifying the specific and nonspecific effects of acupuncture. The results of this study may contribute to rationally optimize the acupuncture therapies by flexible application of the specific and nonspecific effects of acupuncture.

Background

The total effects of an intervention (e.g., acupuncture) comprise specific and nonspecific effects [1, 2]. The specific effect is generated by characteristic and inherent components, while the nonspecific effect is generated by incidental elements [3, 4]. Acupuncture, as one of the promising non-pharmacological interventions, has been proved to be beneficial for patients in the application of evidence-based approaches [5, 6]. But the specific effect of acupuncture has been criticized. Several recent randomized trials have found that acupuncture can benefit patients while its total effect is slightly or even no better than sham acupuncture [7–9]. Some researchers attribute the effect of acupuncture to a powerful placebo effect or a nonspecific effect [10]. In addition, the greater effect has been generally observed when compared acupuncture with no treatment rather than with sham acupuncture, also suggesting that nonspecific effect can contribute to acupuncture's benefits [11]. Therefore, the recognition of specific and nonspecific effects may be important for the selection, conduction and optimization of acupuncture to improve clinical efficacy [12]. However, the magnitude of acupuncture's specific and nonspecific effects, as well as their determinants, remains unclear.

Many studies have shown that the size of placebo or nonspecific effect can be influenced by psychological factors, such as expectation, emotion, awareness and personality [13–15]. And it is worth noting that positive expectation and good doctor-patients communication are both important psychological factors on acupuncture treatment, and can enhance efficacy of acupuncture [16, 17]. For instance, Kong found that expectancy could modulate the pain experience on KOA patients in both acupuncture and sham acupuncture [18]. Moreover, cumulative evidence suggests that acupuncture may be accompanied by strong psychobiological responses [4]. Therefore, in our study, an emphasis will be placed on exploring the influence of psychological factors on specific and nonspecific effects of acupuncture.

Functional magnetic resonance imaging (fMRI) can reveal the functional changes of the brain, and improve our understanding about the central neurological mechanisms of acupuncture [19]. In recent years, fMRI has been applied to investigate the central regulation mechanisms of the acupuncture's effects [20–22]. Acupuncture and sham acupuncture have relatively different brain responses in the medial frontal cortex, periaqueductal gray and rostral ventromedial medulla during analgesia [23, 24]. Most clinical trials focus on evaluating abnormal brain activity triggered by the specific effect (acupuncture – sham acupuncture), while ignoring the modulation of nonspecific effect (sham acupuncture) on brain. Interestingly, an fMRI study found that pre-treatment functional connectivity could predict symptom changes for acupuncture and sham acupuncture, respectively, and the functional connectivity characteristics that were differed [25]. There are differences in central regulation mechanisms between specific and nonspecific effects, and fMRI is an appropriate method to distinguish them. However, there are insufficient evidences on differentiating the neurological mechanisms triggered by specific and nonspecific effects of acupuncture.

It should be mentioned that pain is one of the most important conditions for acupuncture recommended by the World Health Organization, and it is a subjective sensory condition that is sensitive to a placebo response. Knee osteoarthritis (KOA), which is a common disease with chronic pain as the main symptom, is a suitable model for investigating the specific and nonspecific effects of acupuncture. Therefore, we design a randomized, controlled, crossover trial to clarify the specific and nonspecific effects of acupuncture. In this study, the first objective is to evaluate the magnitude of acupuncture's specific and nonspecific effects on treating KOA. The second objective is to assess the central neurological mechanism of acupuncture's specific and nonspecific effects. The third objective is to explore how psychological factors affect the efficacy of acupuncture.

Methods

Study design

This is a randomized, controlled, crossover clinical trial (Fig. 1). In order to accurately clarify the specific and nonspecific effects of acupuncture, a controlled, crossover trial is designed to control the interference of individual difference (e.g. demographic characteristics, brain metrics and psychological factors) on the

results. This trial has been approved by the ethical committees of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine (NO: DZMEC-KY-2017-53-02) and registered in Chinese Clinical Trial Registry (NO: ChiCTR1900025807). The protocol will be reported following Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (Additional file 1). A total of 60 patients diagnosed with KOA according to American College of Rheumatology clinical criteria will be recruited [26]. After informed consent acquisition, all patients will be randomly assigned to group A and group B based on the ratio of 1:1. The patients in group A will receive acupuncture 3 sessions per week for 4 weeks. After a 2-week washout period, the patients in group A will receive sham acupuncture 3 sessions per week for 4 weeks. The patients in group B will receive the reverse intervention process.

Study setting and recruitment

The study will be carried out at the Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine. Sixty patients with KOA will be recruited via hospital outpatient clinics, advertisements in hospital social media (WeChat), flyer displays at community service centers. Informed consent will be acquired prior to randomization.

Inclusion criteria

The inclusion criteria include: (1) Age 45–65 years (male or female); (2) Duration of chronic knee pain \geq 6 months; (3) Radiologic confirmation of knee osteoarthritis (Kellgren-Lawrence grade II or III) [27] within 12 months; (4) Numerical rating scale (NRS) \geq 4 with in the past week; (5) Right-handed; (6) Written informed consent.

Exclusion criteria

The exclusion criteria include: (1) History of knee surgery or waiting for knee surgery (e.g. knee replacement or arthroscopy); (2) History of knee injection in the past 6 months or arthroscopy in the past 12 months; (3) Knee pain caused by other diseases (e.g. trauma, fracture, gouty arthritis, infection, malignant tumor, etc.); (4) Psychiatric or neurological disorders (e.g. traumatic brain injury, stroke, Parkinson's disease); (5) Coagulation disorders, severe acute or chronic organic disease; (6) MRI contraindications (e.g. claustrophobia, cardiac pacemaker or other metallic agents embedded within body); (7) Severe skull anatomical asymmetry or definite lesions found on magnetic resonance scanning; (8) Alcohol or drug abuse; (9) Pregnant or lactating or planning a pregnancy; (10) Recent acupuncture in 1 months.

Randomization and blinding

Eligible patients will be randomly assigned to one of two groups in a 1:1 ratio. The randomization sequence and grouping will be generated and stored by a specific statistician who will not participate directly in this study using the software SAS 9.3 (SAS Institute, Cary, NC, USA). Acupuncturists cannot be blinded to treatment allocation, and they will not be allowed to discuss with patients the type of

intervention. The outcome evaluators, fMRI scanners, statisticians and all patients will be blinded to group assignment until completion of the study.

Sample size

Currently, there is no clear standard for the sample size of fMRI studies. A sample size of 20 subjects are sufficient to detect a significant difference with a type I error of 5%, and about 25 subjects are required when $\alpha = 0.000002$, to achieve a stable statistical power [28–30]. Considering a 20% attrition rate and possible excessive head motions occur in the fMRI scanning, we plan to recruit 30 subjects in each group.

Interventions

Each type of acupuncture treatment will include 12 sessions of 30-min duration over 4 weeks (3 sessions per week). The date of each patient's treatment will be recorded, and the number of treatment received by each patient at intervention phase I and intervention phase II will be counted for monitoring adherence. The licensed acupuncturists with more than 5 years of experience with acupuncture will be trained for a standard intervention procedure before this study. Patients will be given paracetamol sustained-release tablets (Tylenol; Shanghai Johnson Pharmaceutical Co., Ltd.) as a rescue medication when they have excessive pain, and the administration of rescue medication will be recorded in detail.

Acupuncture treatment

The acupoints for the acupuncture intervention will include Dubi (ST 35), Neixiyan (EX-LE4), Ququan (LR8), Xiyangguan (GB33), Xuehai (SP10), Sanyinjiao (SP6), Taixi (KI3) and an ashi point (the point where the patient feels most pain). An adhesive pad will be placed on the skin above the acupoints according to WHO Standard Acupuncture Locations, and then a single-use sterile needle (0.25 * 40 mm or 0.25 * 25 mm, Hwato, Suzhou, China) will be used to penetrate into the skin 5–20 mm through the adhesive pad (Fig. 2). Acupuncturists will manually stimulate the needles to achieve de qi (mainly including the sensations of numbness, distention, soreness and heaviness), and then the needles will be left in place for 30 minutes. Table 1 and Fig. 2 show the location of acupoints for acupuncture.

Table 1
Locations of acupoints for acupuncture.

| Acupoints | Locations |
|--|---|
| Dubi (ST 35) | On the anterior aspect of the knee, in the depression lateral to the patellar Ligament |
| Neixiyan (EX-LE4) | On the anterior aspect of the knee, in the depression medial to the patellar Ligament |
| Ququan (LR8) | On the medial aspect of the knee, in the depression medial to the tendons of the semitendinosus and the semimembranosus muscles, at the medial end of the popliteal crease |
| Xiyangguan (GB33) | On the lateral aspect of the knee, in the depression between the biceps femoris tendon and the iliotibial band, posterior and proximal to the lateral epicondyle of the femur |
| Xuehai (SP10), | On the anteromedial aspect of the thigh, on the bulge of the vastus medialis muscle, 2 cun superior to the medial end of the base of the patella |
| Sanyinjiao (SP6), | On the anteromedial aspect of the thigh, on the bulge of the vastus medialis muscle, 2 cun superior to the medial end of the base of the patella |
| Taixi (KI3) | On the posteromedial aspect of the ankle, in the depression between the prominence of the medial malleolus and the calcaneal tendon |
| ^a 1 cun (\approx 20 mm) is defined as the width of the interphalangeal joint of patient's thumb. | |

Sham acupuncture treatment

Non-acupoints will be used for the sham acupuncture intervention, and the locations of the non-acupoints are shown in Table 2 and Fig. 2. An adhesive pad will be placed on the skin of non-acupoints, and then a blunt single-use sterile needle (0.25 * 40 mm or 0.25 * 25 mm, Hwato, Suzhou, China.) will be used to penetrate into the adhesive pad, but not penetrate into the skin (Fig. 2). The needles will be left in place for 30 minutes. Table 2 and Fig. 2 show the location of non-acupoints for sham acupuncture.

Table 2
Locations of non-acupoints for sham acupuncture.

| Non-Acupoints | Locations |
|--|--|
| Non-Acupoint 1 | On the anterior aspect of the thigh, 6 cun above the upper edge of the patella (between the spleen and stomach meridian) |
| Non-Acupoint 2 | On the anterior aspect of the thigh, 5 cun above the upper edge of the patella (between the spleen and stomach meridian) |
| Non-Acupoint 3 | On the anterior aspect of the thigh, 4 cun above the upper edge of the patella (between the spleen and stomach meridian) |
| Non-Acupoint 4 | In the middle of GB34 and ST36 (between the gallbladder and bladder meridian). |
| Non-Acupoint 5 | 3 cun below GB34 (between the gallbladder and bladder meridian) |
| Non-Acupoint 6 | 2 cun above the medial malleolus (between the liver and spleen meridian) |
| Non-Acupoint 7 | In the middle of GB40 and ST41 (between the gallbladder and bladder meridian). |
| ^a 1 cun (\approx 20 mm) is defined as the width of the interphalangeal joint of patient's thumb. | |

Clinical outcomes evaluation

The pain-related scales will be used to evaluate the magnitude of acupuncture's specific and nonspecific effects in treating KOA. We will use the changes of pain on the Numerical Rating Scale (NRS) as our primary clinical outcome. And the minimal clinically important improvement (MCII) will be defined as at least 2-point reduction on the NRS, and patients who attain the MCII will be defined as responders [9, 31]. The secondary clinical outcomes will include the change of short-form of the McGill Pain Questionnaire (SF-MPQ) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The SF-MPQ, which includes sensation and affection of pain [32], will be used to assess the pain quality. The WOMAC consists of three subscales with five-point Likert scale: pain, stiffness and physical function [33]. Adverse events and blinding assessment during the study will be recorded (Fig. 3).

Neuroimaging data evaluation

Many functional systems of the brain are involved in pain modulation, such as descending pain, affective, cognitive processing systems. Resting state fMRI data will be measured to identify the neurological mechanisms of the specific and nonspecific effects of acupuncture. Functional MRI scanning will be carried out using a Siemens 3.0 T scanner (Skyra, Siemens, Erlangen, Germany) equipped with a standard head coil at the Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University. During the resting state fMRI acquisition, patients will be in a supine position with their eyes closed, and be instructed to remain awake, avoid thinking. The resting state fMRI data will be obtained using a gradient echo planar imaging (EPI) sequence with the following parameters: whole brain, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, field of view (FOV) = 224 mm × 224 mm, flip angle (FA) = 90°, slice thickness/gap = 3.5/0.6 mm, voxel size = 3.5 mm × 3.5 mm × 3.5 mm, axial slices = 32, in-plane resolution = 64 × 64, and 240 volumes. Foam pads will be used to minimize head motion and earplugs will be used to reduce noise interference. The fMRI scans will be performed at baseline and the end of 4-week treatment in each phase (Fig. 3).

Psychological factors evaluation

Psychological factors assessment will include the Mindful Attention Awareness Scale (MAAS), Trait Meta-Mood Scale (TMMS), Big Five Personality (BFP), and Stanford Expectations of Treatment Scale (SETS). MAAS will be used to assess the variations in awareness and attention to present experience [34, 35]. TMMS will be used to assess the capacity to identify emotional states and regulate them [36]. BFP is a widely used personality factors scale, which including openness, conscientiousness, extraversion, agreeableness, neuroticism [37, 38]. SETS is a suitable scale to assess individual expectation for upcoming interventions [39]. These psychological factors are relatively stable and not easily modifiable, so they will be only assessed at baseline (Fig. 3). Correlation analyses will be performed to determine the relationships among the brain activity changes, psychological factors and symptom improvement (Fig. 4).

Oxytocin and genetics evaluation

Although valid scales will be adopted to assess the individual psychological factors, these scales are subjective. Oxytocin is a neurotransmitter associated with psychological factors, and it could be used as an objective indicator for further estimating how psychological factors affect the specific and nonspecific effects of acupuncture [40]. Neurophysiological study indicated that genetic variations in neurotransmitter pathways mediating placebo effects provided the possibility of identifying placebo responders through genetic screening [41]. Based on recent studies, catechol-o-methyltransferase (COMT) and opioid receptor (OPRM1) participated in mediating the regulation of psychological process and pain process [42–45]. These genes will be selected as candidate genes for objectively assessing and predicting the specific and nonspecific effects of acupuncture, estimating correlations among gene polymorphisms, psychological factors and brain activity.

At baseline, KOA patients will be asked to fasting at least 8 hours prior to the sample collection and blood will be obtained in the morning from a vein in upper arm. The blood samples will be centrifuged

immediately. Then, plasma and blood cells will be separated into two refrigerating tubes and stored at -80°C . Subsequent, samples will be sent to technical laboratory to be processed by standard means.

Data management and monitoring

Data associated with this study will be recorded in the case report form (CRF), and a special assistant will be responsible for reviewing data integrity, accuracy and consistency. Patients will be assigned in a quiet room for psychological factors assessments. In order to ensure the consistency of source data, all the scales will be assessed by the same researcher during the study. The research data will be input into EpiData electronic database. For ensuring the accuracy in data entry, data will be entered independently by two researchers, and then the discordances will be resolved by tracing source data. MRI scans will be performed in the same scanner, and a professional technician will check the quality of imaging data after each scan. Blood samples will be collected in the morning.

Statistical analysis

Clinical data analysis

The continuous variables will be described as the mean (standard deviation) or the median. The categorical variables will be described as the percentage. The comparisons between the two groups will be analyzed by independent sample t-test, Wilcoxon rank-sum or χ^2 test in demographic, psychological factors and other indicators. The comparison between the acupuncture and sham acupuncture will be analyzed using general liner model. Intention-to-treat analysis (ITT) will be performed to analyze all randomized data, and last observation carried forward (LOCF) will be adopted to impute the missing values. Per protocol analysis will be used and per protocol population will be defined that patients who complete at least 10-session acupuncture during each phase and finish 4 fMRI scans. The specific effect of acupuncture will be calculated by subtracting the sham acupuncture from the acupuncture. The nonspecific effect of acupuncture will be calculated by subtracting the pre-acupuncture from the post-acupuncture. The data will be statistically analyzed by SPSS software (SPSS V.22.0 KO for Windows).

Neuroimaging data analysis

The resting state fMRI data will be preprocessed using the Data Processing Assistant and Resting-State fMRI (DPARSF) toolbox [46]. The preprocessing will consist of removing the first 10 volumes, slice timing, head motion correction, spatial normalization (re-sampled to 3 mm x 3 mm x 3 mm), spatial smoothing (with a 6 mm full-width half-maximum Gaussian kernel), filter (0.01–0.1 Hz), removing linear trend and the nuisance signals (white matter signals, cerebral spinal fluid signal, and Friston 24 head motion).

After preprocessing, neuroimaging data will be evaluated by using the methods of amplitude of low frequency fluctuation (ALFF), regional homogeneity (ReHo) or functional connectivity (FC) to identify the brain responses significantly associated with the specific and nonspecific effects of acupuncture. Pearson's correlation analysis will be used to assess the association between the brain activity and clinical variables.

Psychological factors data analysis

In order to determine whether psychological factors can affect acupuncture efficacy, Pearson's correlation analysis will be performed to assess the relationship between psychological factors and clinical symptom improvement.

Mediation analysis

Besides, we will investigate whether the relation between psychological factors and clinical effects of acupuncture are mediated by brain activity by using a method of mediation analysis. In the above analyses, age, gender and education years will be taken as covariates. The detailed statistical analysis is shown in Fig. 4.

Ethics and dissemination

The protocol has been approved by the local ethical committees of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine (reference: DZMEC-KY-2017-53-02) and registered in Chinese Clinical Trial Registry (reference: ChiCTR1900025807). We will conduct the study according to the principles of the Declaration of Helsinki. Written informed consent will be obtained before randomization from all patients. The results will be published in the peer-reviewed journal and presented at conference presentations.

Discussion

To the best of our knowledge, this is the first study to evaluate the neurological and psychological mechanisms of specific and nonspecific effects of acupuncture. A crossover trial is an ideal design for clinical, psychological and neuroimaging studies, because higher effect accuracy will be achieved on account of assessing the effects developed by different interventions for each patient. In our study, alternation in cerebral activities and differences in psychological factors are observed through the acupuncture intervention for patients with KOA for further understand and identify the specific and nonspecific effects of acupuncture. By combing clinical and psychological measurements and neuroimaging analysis, acupuncture effects-associated neural changes and psychological affections can be tracked longitudinally.

Indeed, the clinical efficacy of acupuncture depends on comprehensive functions of physiology and psychology [47]. Psychological factors play an important modulatory role during acupuncture intervention [48]. The specific effect is the biological effect produced by its nature [3], while the nonspecific effect may be mainly mediated by such psychological factors as expectation, personality, awareness and emotion. Both could contribute to the effects of acupuncture [16, 17]. However, plenty of previous studies focused on capturing the total or specific effects of acupuncture, whereas ignoring the nonspecific effect. Consequently, few studies tended to evaluate and differentiate the specific and nonspecific effects. And our study could exactly fill the vacancy regarding the mechanism of the specific and nonspecific effects of acupuncture.

Moreover, although there has been major contention which is whether clinically relevant effect of acupuncture is equivalent to placebo acupuncture, it can't be denied that the nonspecific effect of acupuncture is a crucial part of the clinical effects [49]. In fact, clinical practice desires to explicitly understand the maximum potential of an intervention. And there is an interest in optimizing nonspecific effect of acupuncture to enhance existing clinical effects. Hence, a better comprehending of the neurological and psychological mechanisms of specific and nonspecific effects of acupuncture is essential to achieve these aims. Our study will contribute to explore the maximum potential of acupuncture.

Trial Status

The Ethical Committee of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine approved the study protocol on 29 August 2019 (version 2.0, 25 June 2019). This trial is currently recruiting patients and the first patient was included in 30 October 2019. We predict that recruitment will be completed by December 2021.

Abbreviations

NRS: Numerical Rating Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; SF-MPQ: short form McGill pain questionnaire; BFP: Big Five Personality; MAAS: Mindful Attention Awareness Scale; TMMS: Trait Meta-Mood Scale; SETS: Stanford Expectations of Treatment Scale; fMRI: functional Magnetic Resonance Imaging; NA: Non-Acupoint; KOA: Knee Osteoarthritis; CRF: Case Report Form; ITT: Intention-to-treat analysis; LOCF: Last observation carried forward.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

Study design was conducted by XW, C-ZL and C-QY. Study supervision is conducted by C-ZL. Data collection is done by J-HL and Y-SQ. Neuroimaging and statistical analyses are done by J-LL, WX and L-QW. Study protocol was drafted by J-LL and NZ. The manuscript was modified by XW and J-FT. C-ZL sought funding and ethical approval. All authors contribute to the manuscript writing and approve the final draft.

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Availability of data and materials

Not applicable as this is a study protocol and does not contain data or results.

Ethics approval and consent to participate

The protocol has been approved by the local ethical committees of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine (reference: DZMEC-KY-2017-53-02). We will conduct the study according to the principles of the Declaration of Helsinki. Written informed consent will be obtained before randomization from all patients.

Consent for publication

Not applicable.

Competing interests

All authors have no conflicts of interest to declare.

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Figures

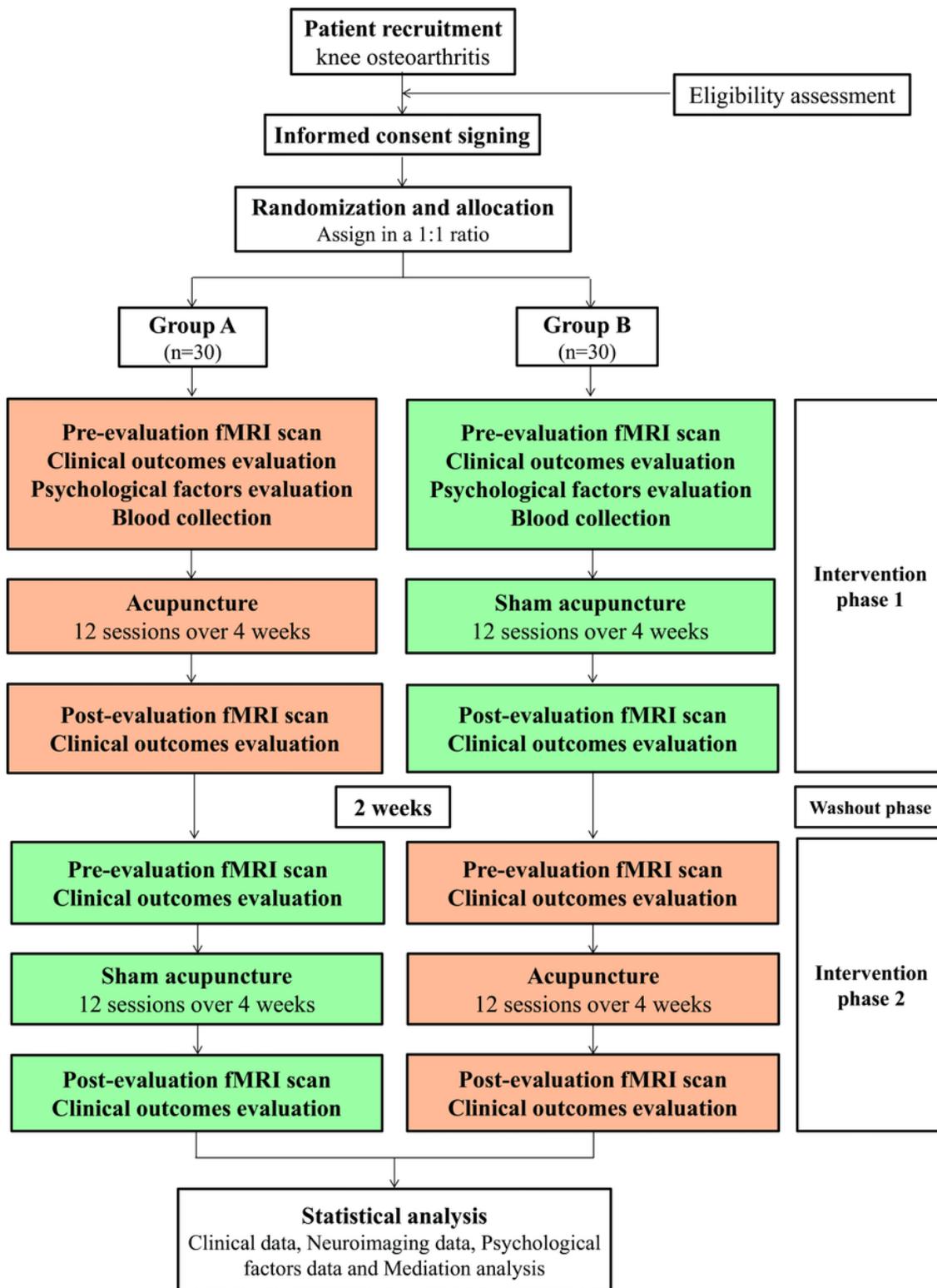


Figure 1

Study flow diagram.

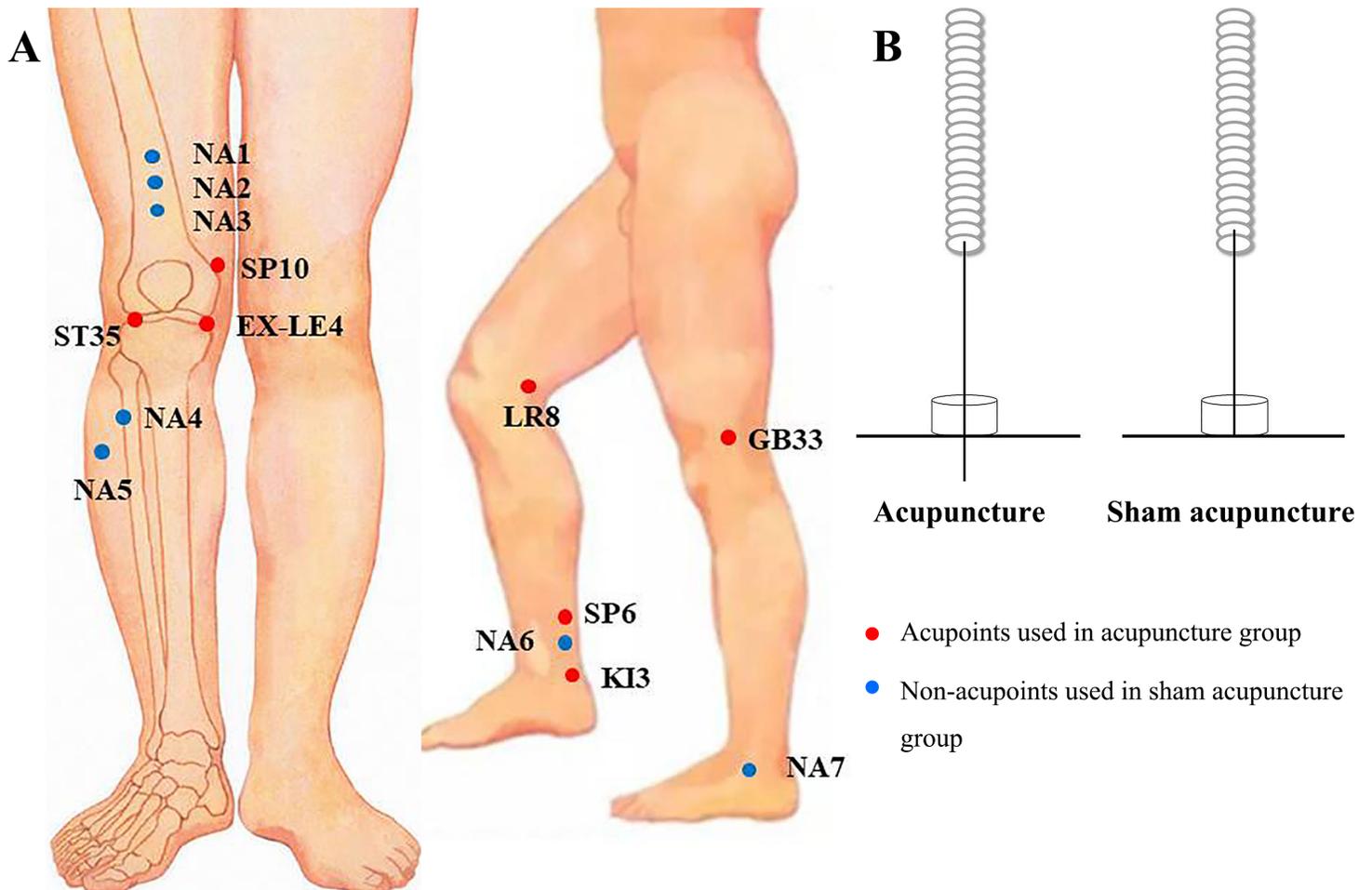


Figure 2

The picture of acupuncture and sham acupuncture. (A) Location of acupoints and non-acupoints. Red circles: Acupoints used in acupuncture group. Blue circles: Non-acupoints used in sham acupuncture group. (B) The diagrammatize of acupuncture and sham acupuncture. Abbreviation: ST35 Dubi, EX-LE4 Neixiyan, LR8 Ququan, GB33 Xiyangguan, SP10 Xuehai, SP6 Sanyinjiao, KI3 Taixi. NA, Non-Acupoint.

| STUDY PERIOD | | | | | | | | | | | | |
|------------------------------|-----------|------------|----------------------|-------|-------|-------|---------|-------|----------------------|-------|-------|--------|
| | Enrolment | Allocation | Post-allocation | | | | | | | | | |
| | | | Intervention phase 1 | | | | washout | | Intervention phase 2 | | | |
| Time point (week) | Week-1 | Week0 | Week1 | Week2 | Week3 | Week4 | Week5 | Week6 | Week7 | Week8 | Week9 | Week10 |
| Enrolment | | | | | | | | | | | | |
| Eligibility screen | × | | | | | | | | | | | |
| Informed consent | × | | | | | | | | | | | |
| Randomisation | | × | | | | | | | | | | |
| Interventions | | | | | | | | | | | | |
| Group A | | | ◆————◆ | | | | / \ | | ◆-----◆ | | | |
| Group B | | | ◆-----◆ | | | | / \ | | ◆————◆ | | | |
| Assessments | | | | | | | | | | | | |
| Clinical outcomes | | | | | | | | | | | | |
| NRS | | × | | | | × | | × | | | | × |
| WOMAC | | × | | | | × | | × | | | | × |
| SF-MPQ | | × | | | | × | | × | | | | × |
| Rescue medicine | | | × | × | × | × | | | × | × | × | × |
| Adverse events | | | × | × | × | × | | | × | × | × | × |
| Blinding assessment | | | | | | × | | | | | | × |
| Psychological factors | | | | | | | | | | | | |
| BFP | | × | | | | | | | | | | |
| MAAS | | × | | | | | | | | | | |
| TMMS | | × | | | | | | | | | | |
| SETS | | × | | | | | | | | | | |
| fMRI | | × | | | | × | | × | | | | × |
| Blood tests | | × | | | | | | × | | | | |

Figure 3

Schedule of intervention and assessments. NRS, Numerical Rating Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; SF-MPQ, short form McGill pain questionnaire; BFP, Big Five Personality; MAAS, Mindful Attention Awareness Scale; TMMS, Trait Meta-Mood Scale; SETS, Stanford Expectations of Treatment Scale; fMRI, functional magnetic resonance imaging.

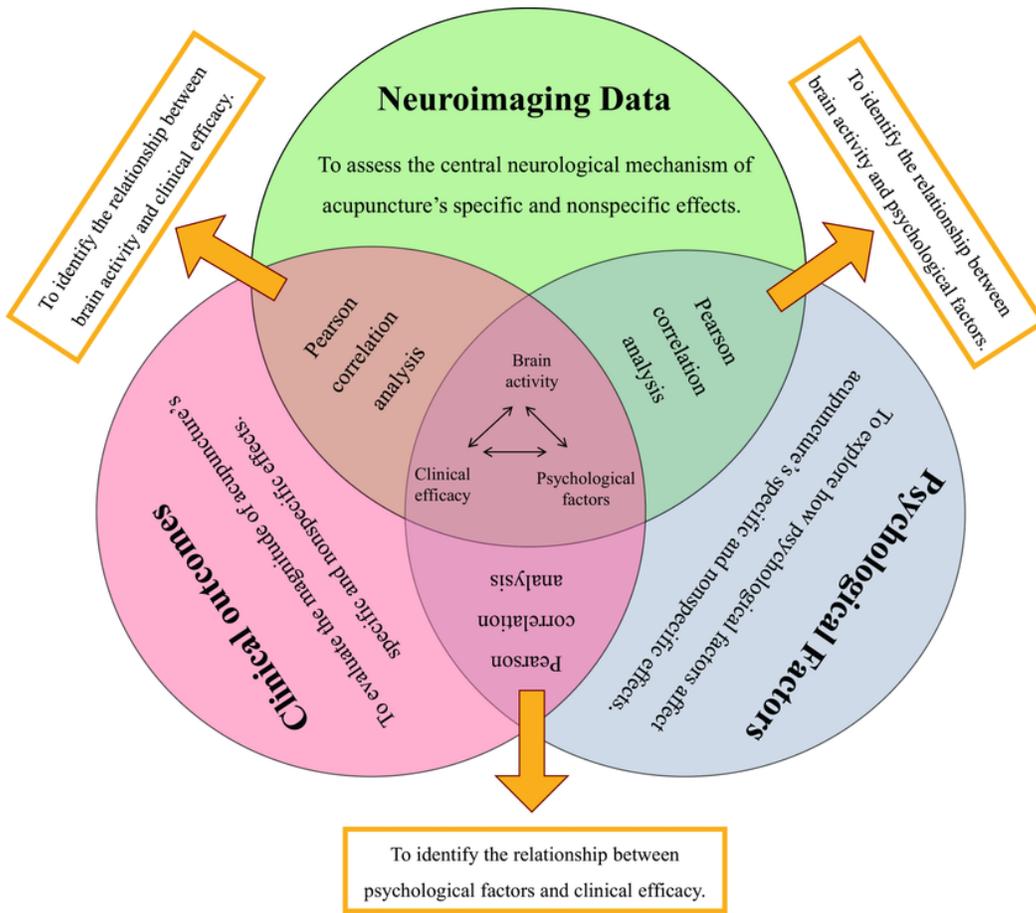


Figure 4

Statistical analysis flow.

Supplementary Files

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- [SPIRITChecklist.doc](#)