

The cerebral mechanism of Tuina for treating knee osteoarthritis pain: study protocol for a randomized controlled parallel trial

Hui Xu

Shanghai University of TCM: Shanghai University of Traditional Chinese Medicine

Lianbo Xiao (✉ xiao_lianbo@163.com)

Shanghai University of Traditional Chinese Medicine Guanghua Hospital <https://orcid.org/0000-0003-4226-6002>

Chi Zhao

Shanghai University of TCM: Shanghai University of Traditional Chinese Medicine

Yuchen Xie

Henan Provincial Hospital of Traditional Chinese Medicine

Bingxin Kang

Shanghai University of TCM: Shanghai University of Traditional Chinese Medicine

Xirui Xu

Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine

A Xinyu

Shanghai University of TCM: Shanghai University of Traditional Chinese Medicine

Jun Xie

Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine

Research Article

Keywords: Tuina, Functional magnetic resonance imaging, Knee osteoarthritis, Chronic pain, Central mechanism, Study protocol

Posted Date: November 9th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-508913/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Despite the high prevalence and socioeconomic impact of knee osteoarthritis (KOA), treatments for KOA are often unsatisfactory, with wide variation in effectiveness across patients. Tuina is one treatment that is frequently prescribed for patients with KOA. However, how Tuina influences the activity of the central nervous system to alleviate KOA pain remains unclear. Our randomized controlled parallel trial was designed to address this gap through a comparative evaluation of the effect of Tuina on the resting-state functional connectivity (rsFC) of the brain in patients with KOA compared to treatment using celecoxib as the control.

Methods/design: This will be a randomized controlled parallel trial to be conducted between June 2022 and June 2024. Forty-eight participants with KOA will be enrolled and randomly allocated to one of two groups, the Tuina treatment group or the celecoxib (control) group. Participants in each of the two groups will undergo 6 weeks treatment. Resting-state functional magnetic resonance imaging (fMRI) will be performed to quantify rsFC at baseline, before treatment, and at the end of the intervention, where rsFC will be used to evaluate the effects of treatment on brain activity. The following self-reported scales will be used as clinical measures of symptomology: the Numerical Rating Scale to quantify the severity of pain, the Pain Catastrophizing Scale to quantify emotional response to pain, and the Hamilton Anxiety Scale and the Hamilton Depression Scale to quantify the cognitive response to pain. Scale scores will be obtained before and after treatment to measure clinical change. Adverse events will be documented and assessed throughout the trial.

Discussion: The results of our trial will provide evidence of the effect of Tuina treatment on the rsFC of patients with KOA and identify the possible relationship between a change in the rsFC and improvement of clinical variables, thus elucidating the central mechanism by which Tuina improves pain in KOA.

Trial registration: Registered in the Chinese Clinical Trial Registry (<http://www.chictr.org.cn/searchproj.aspx>, ChiCTR2100045990). Date of registration: 1 May 2021.

Background

Knee osteoarthritis (KOA) is a common degenerative joint disease, which is characterized by a failure of cartilage self-repair and secondary hyperosteoegeny. The main symptoms of KOA are knee joint pain and limited range of motion secondary to progressive joint deformity and instability [1–3]. KOA is reputedly the most common musculoskeletal disease of the lower limb and the main cause of pain and disability among elderly individuals, with 80% of individuals over the age of 65 years showing radiological symptoms of KOA [4]. In China, the overall prevalence rate of KOA is estimated at 15%, with the prevalence increasing to 50% among individual over the age of 60 years and 80% among those over the age of 75 years [5]. Pain is the most important and common symptom of KOA. Early KOA pain often occurs intermittently during exercise and weight bearing. However, with progression of joint degeneration,

the pain often becomes persistent, including at rest and at night. The mechanism of KOA pain is unclear, which makes its treatment challenging.

Current management for KOA includes physical activity modification and pain relief using a combination of non-pharmacological and pharmacological interventions [6, 7]. Among non-pharmacological treatment, massage has been used for the management of KOA pain. Massage is an ancient therapeutic art that is based on the application of pressure [8]. Tuina is a specific massage technique that has been a component of Traditional Chinese Medicine for over 2000 years. Tuina combines traditional Chinese Medicine practice with current evidence-based parameters of intervention, such as biomechanical function, anatomy, pathology, and physiology.

Tuina is an important part of Traditional Chinese Medicine which works along the meridians and collaterals of the whole body, correcting any displacement in body structure and guiding the individual to appropriate patterns of movement based on symptomology and functional assessment. Tuina is currently rapidly gaining popularity as an alternative and complementary medicine approach owing to its proven positive therapeutic effects.

Previous randomized controlled trials (RCT) have supported the effectiveness of Tuina for the treatment of different health conditions, such as musculoskeletal disorders [9, 10] and acute bronchitis [11]. With regard to KOA, two systematic reviews have shown a positive clinical effect of Tuina in improving outcomes for patients with KOA [12, 13]. An RCT demonstrated the safety and effectiveness of Tuina for improving knee extension muscle strength, increasing knee joint flexibility, and improving KOA-related disability [14].

Exploring the mechanism underlying the effectiveness of Tuina has been an issue of increasing research importance in the field of alternative and complementary medicine in recent years. Currently, the central effects of Tuina largely remain to be defined. Our randomized controlled parallel trial was designed to address this gap through a comparative evaluation of the effect of Tuina on the resting-state functional connectivity (rsFC) of the brain in patients with KOA compared to treatment using celecoxib as the control.

Objectives

The purpose of this trial will be to investigate the central mechanisms of Tuina, used as a pain management treatment for KOA, by evaluating the correlation between measured changes in the rsFC, before and after treatment, and improvement in clinical variables. This evaluation will be made against a control group, using celecoxib as the treatment.

Methods/design

Included will be patients with KOA who meet the definition of osteoarthritis as per the 1991 American College of Rheumatology (ACR) criteria [15]. Patients will be recruited through advertisement in the orthopaedic clinic of the Shanghai Guanghua Integrated Chinese and Western Medicine Hospital, Shanghai, China. We followed the SPIRIT 2013 Statement [16] to guide the development and reporting of our trial protocol. This study has been approved by the ethics committee of Guanghua Hospital of Integrated Traditional Chinese Medicine and Western Medicine (Ethics Approval Number: 2020-K-109) and registered in the Chinese Clinical Trial Registry. All participants will be asked to provide written informed consent and will be informed that the trial will not involve the collection of biological specimens for storage.

Eligibility criteria

The inclusion criteria for enrollment will be as follows: (1) 50–65 years of age and right-handedness; (2) KOA-associated pain for a duration ≥ 6 months; (3) no other treatment pursued in the 1-month prior; (4) a score on the knee pain Numerical Rating Scale (0–10 NRS) ≥ 3 in the 1-week prior; (5) a Kellgren-Lawrence radiographic score I or II; (6) patient agreement to not pursue other therapies during the treatment period of the RCT; and (7) provision of written informed consent.

Exclusion criteria

The exclusion criteria will be as follows: (1) skin damage around the knee joint; (2) prior history of knee surgery or severe knee joint trauma; (3) secondary KOA, as a complication of rheumatoid, gouty, or infectious arthritis, or other joint disease; (4) presence of diabetes, systemic infection, severe abnormality in liver and kidney function, and malignancy; (5) allergy to celecoxib, which will be used as the 'usual care' control; (6) pregnant or lactating women; (7) presence of a mental disorder or cognitive impairment; (8) presence of active gastrointestinal disorder, including ulcers, bleeding or recurrent ulcers, and bleeding; and (9) contraindications to magnetic resonance imaging, required for rsFC, including phobias, pacemakers, defibrillators, cardiac stents, and intrauterine devices.

Exit criteria and management

Exit criteria will be as follows: (1) requested by the participant; (2) severe postoperative complications (e.g., pulmonary embolism); and (3) intra-treatment side effects.

Sample size

The focus of neuroimaging research is on determining neural mechanisms of a therapeutic effect. As such, sample size calculation for RCTs in which neuroimaging provides the primary outcome is different from that of classical RCTs. For neuroimaging studies, 12 to 15 participants per group is generally sufficient to provide statistically significant results [17, 18]. In our trial, we will include 20 patients per group, namely the Tuina and the celecoxib control group. Considering an attrition rate of 20% and the possibility of unquantifiable rsFC due to head movement, our final sample size will be set to 24 participants per group.

Recruitment strategies and enrollment

Participant registration will be conducted between June 2022 and June 2024. Written informed consent will be obtained from all participants and will include consent for the use their data in scientific publications. Figure 1 presents the trial flow, which includes participant recruitment, eligibility screening, randomization, intervention, and outcome assessments. Figure 2 presents an overview of the trial design, conduct, review, and analysis. A completed SPIRIT 2013 checklist (Word) is included (Additional File 1).

Randomisation and blinding

An independent research staff will generate a randomly-numbered sequence, using SPSS21.0 software (SPSS Inc., Chicago, IL, USA), for complete randomization of enrolled participants to the Tuina or celecoxib treatment groups,. The number sequence will be sealed by an independent assistant in an opaque envelope containing treatment information. Eligible and consenting patients with KOA will be randomly assigned to the Tuina group and celecoxib groups using a 1: 1 allocation ratio, with 24 patients per group.

Only the therapist in charge of treatment is authorized to open the envelope and enrol participants. All outcome assessors and data statisticians will be blinded to group allocation.

Interventions

A panel of two therapists with an academic background in Tuina and complementary therapy treatments and hospital health care professionals agreed to develop a standard protocol for the Tuina treatment. The feasibility of the protocol was tested to determine whether it was realistic and workable and to identify practical issues and any adverse effects caused by the procedures. No changes were needed and no adverse events were identified. Participants in the pilot study were not included in the actual trial.

Clinical medicine professionals who have ≥ 3 years of working experience and expertise in Tuina were recruited. Training was provided to ensure that the agreed standard procedures are followed. Clinicians will be requested to strictly adhere to the treatment protocol, following the exact steps stated in the manual of standard procedure to minimize differences in the components of treatment provided. Participants in the Tuina group will receive a 20-min massage session, three times a week (ideally every other day), for 6 consecutive weeks. Participants in the celecoxib group will be treated using celecoxib capsules, using a daily dosage of 200 mg orally, for 6 consecutive weeks.

Tuina treatment

Tuina is based on the meridian system theory, which considers that there are many fixed channels of flowing Qi energy interlaced as a network throughout the body [19]. There are mainly three kinds of Tuina techniques for the treatment of KOA: the first is soft tissue massage to stimulate acupoints in the meridian system; the second is joint mobilization; and the third is to guide patients to practice Qi Gong

energy exercises [14]. For this study we chose to stimulate acupoints in the meridian system around the knee and knee mobilization in alignment with the most common guiding ideology of Tuina to ‘emphasize both bones and tendons’ for the treatment of musculoskeletal diseases. Pressure will be applied to five acupoints which are common local points used to treat knee problems and reduce knee pain [20, 21]. Based on the World Health Organization standard acupuncture point location [22], the following acupoints were selected on the affected side: XUEHAI (SP10), LIANGQIU (ST37), YANGLINGQUAN (GB34), YINLINGQUAN (SP9) and XIYAN (EX-LE5). Knee joint mobilization will be performed by pressing on the inferior pole of patella and asking patients to slowly stand from sitting and return to sitting, with 3 repetitions completed.

Celecoxib treatment

Participants in the celecoxib group orally taken a celecoxib capsules (approval number J20140072, manufactured by Pfizer Pharmaceutical Co. Ltd.) at a daily dosage of 200 mg for 6 weeks.

MRI data acquisition

MRI will be performed at the MRI Center at Guanghua Hospital of Integrated Traditional Chinese Medicine and Western Medicine. Resting-state functional magnetic resonance imaging (fMRI) will be used to quantify rsFC at baseline, before treatment, and at the end of the 6 weeks of treatment. MRI data will be acquired using a 3.0-T magnetic resonance scanner (General Electric, Wauwatosa, WI, USA), with a 32-channel phase-array head coil, Participants will be asked to remain awake and keep motionless, with eyes closed, during the full scanning period.

Blood-oxygen-level-independent (BOLD) resting-state functional images will be acquired using the following parameters: TR = 2000 ms, TE = 30 ms, flip angle = 90°, 33 axial slices, and field of view (FOV) = 220 mm×220 mm. T1-weighted images will be collected using the following parameters: TR = 1900 ms, TE = 2.93 ms, flip angle = 9°, 160 axial slices, field of view (FOV) = 256 mm×256 mm. T2-weighted images will be collected with the following parameters: TR = 6300ms, TE = 86.0 ms, flip angle = 150°, 25 axial slices, field of view (FOV) = 240 mm×240 mm.

To ensure compliance with treatment, participants will be required to register for treatment.

Outcomes evaluations

The clinical outcomes will including pain sensation, pain emotion, and pain cognition.

All evaluations will be performed twice, at baseline and after the 6-week intervention. All evaluations will be evaluated by two licensed physicians who have received training in the use of the outcome measures selected. These are the pressure pain threshold, the Numerical Rating Scale, the Pain Catastrophizing Scale, the Hamilton Anxiety Scale score, and the Hamilton Depression Scale.

Demographic / medical variables

The following demographic and medical variables will be collected for analysis: sex, age, marital status, occupation, ethnicity, education level, blood pressure, temperature, respiration, pulse, height, weight, body mass index, the combination of disease and medication, the Kellgren-Lawrence classification, the KOA course, and history of major surgeries.

Adverse events of treatment

The safety of patients to participate will be evaluated before and after enrollment and allocation to group, and will be based on liver and renal function. The following events will be treated immediately by the researchers until resolved: syncope, ecchymosis, pain caused by massage techniques, and symptoms, such as nausea, abdominal pain, indigestion, or increased pain and swelling with the use of celecoxib. All adverse events that occur during the trial will be recorded, including the time of occurrence, symptoms of discomfort, specific signs, severity, specific treatment provided, time course of improvement, time to resolution, and date of termination of the treatment and trial.

Data management and monitoring

Clinical data will be carefully saved using printed and electronic case report forms (CRFs). To guarantee data quality, only outcome assessors will access the CRFs for data entry. CRFs will be verified for double-entry and accuracy. During the trial, the Guanghua Hospital of Integrated Traditional Chinese Medicine and Western Medicine will be responsible for making regular visits (once a week) to review the trial conduct. The ethics committee will monitor for protocol violations on a weekly basis and ensure that there are no conflict of interest with the sponsors or researchers. Only statisticians will access the final trial dataset, which will only contain coded data. The safety, progress, study integrity, and design aspects will be monitored at several meetings of the research team.

Statistical analysis

Before analysis, researchers will provide a statistical scheme to the statisticians. The scheme will include the required data and processing methods. The data will be processed and analyzed by statisticians in accordance with the agreed-upon scheme.

Behavioral data analysis

Measurement data: A Shapiro-Wilk test will first be used to verify the normality of distribution of continuous variables. For data with normal distribution, independent sample t-tests will be used to compare baseline characteristics among the two groups. For non-normally distributed data and categorical variables, a Mann-Whitney U test will be used to compare between-group differences.

Count and grade data: Count data will include the ratio of men and women (sex variable) and the knee joint constituent ratio of the affected side and will be compared between the two groups using a Fourfold Table Chi-Squared Test or row * list Fisher's exact probability Test. The body mass index (BMI) classification, Kellgren-Lawrence classification, and NRSR score are grade data, with the Mann-Whitney U

test used for between-group comparison and the Wilcoxon symbolic test for intra-group comparison. Statistical significance will be set at a p -value < 0.05 (two-sided) for all tests.

Seed-to-voxel resting state functional connectivity analyses

Seed-to-voxel functional connectivity analyses will be calculated using the MATLAB R2013b platform with the CONN v17.C software functional connectivity toolbox (<http://www.nitrc.org/projects/conn>). Pre-processing will be as follows: (1) removing data from the first 10 time points to reduce machine instability and the impact of the environment; (2) spatial calibration to estimate and correct head motion; (3) time alignment to unify collection time at all levels; (4) detection of time points with large head movements as covariates of subsequent regression models to remove their effects; (5) registration of the T1 structural image to the functional space and segmented to obtain gray matter, white matter, cerebrospinal fluid and related information matrix, and standardization of the functional image to Montreal Neurological Institute (MNI) space, according to the correlation matrix information; (6) Gaussian smoothing of the standardized functional image, using a 6 mm kernel; (7) removal of the smoothed functional image, which includes the influence of 12 head movement parameters, time point signal of large head movement, white matter, cerebrospinal fluid, and other covariables; and (8) a final filtering, using a 0.01Hz ~ 0.1Hz bandwidth.

Seed-based functional connectivity analysis

Given that the thalamus and periaqueductal gray (PAG) play important roles in the ascending and descending pain pathways respectively, they will be defined as a priori regions of interest (ROIs), using Automated Anatomical Labeling (AAL), for the functional connectivity analyses of resting-state fMRI data. A threshold of voxel-wise $p < 0.005$, uncorrected, and cluster-level $p < 0.05$ false discovery rate (FDR), corrected at cluster, will be applied in the data analysis.

Discussion

Our proposed resting-state fMRI trial will be the first to evaluate the central mechanisms of Tuina treatment for KOA. Our rsFC analysis will enhance our understanding of the mechanisms underlying the pain relief effect of Tuina in patients with KOA.

Pain is the most important and common symptom of KOA. Early KOA pain often occurs intermittently during exercise and weight bearing; however, with knee joint disease progression, the pain often becomes persistent, at rest and at night. KOA pain can lead to joint dysfunction, reduce patients' physical fitness and ability to cope with activities of daily life, as well as cause anxiety and depression [6, 23, 24]. With aging of the general population, the prevalence of KOA is gradually increasing, which will cause a significant economic and social burden. Modern medicine is still unclear regarding the mechanism of KOA pain. Previous studies have proposed that peripheral factors, such as articular cartilage destruction and synovial inflammation, may play a key role. However, many studies have found that the severity of radiographic KOA and of the inflammatory response of the synovial membrane does not positively correlated with the pain of KOA [25–27]. Therefore, peripheral mechanism cannot fully explain the pain of

KOA. At the same time, patients with KOA have increased pain sensitivity in non-affected areas. Researchers speculate that an "abnormal central processing" of long-term pain afferent signals may, thus, be a key factor in KOA pain [28, 29].

Tuina can safely and effectively relieve the pain, stiffness, movement limitation, and other clinical symptoms of discomfort associated with KOA[30]. Tuina was included as a component of physiotherapy intervention for KOA in the 2018 Expert Consensus on Step Treatment of Knee Osteoarthritis statement in China [31]. With the recent advances in MRI technology, resting-state fMRI can now play an important role in exploring the central mechanism of Tuina. As a non-invasive, in vivo, technique, resting-state fMRI provides a high spatial resolution technique to objectively and reliably quantify the central effect of Tuina which can be correlated to clinical measures to understand the mechanisms by which Tuina relieves pain in KOA.

In summary, this resting-state fMRI trial is designed to investigate the central mechanism of Tuina in the treatment of KOA-associated pain, against treatment using celecoxib as the control. We expect that our findings can provide a neuroimaging-based reference for the clinical application of Tuina.

Study limitations

Patients cannot be blinded to the treatment received. However, group allocation will be concealed from the researchers, therapists, and outcome assessors.

Trial status

- Protocol version number: V6.0: 20 November 2020
- Date of recruitment: 1 June 2022
- Date of recruitment completed: 1 June 2024

Abbreviations

AAL: Automated Anatomical Labeling; CRFs: case report forms; BMI: body mass index; FDR: false discovery rate; fMRI: functional magnetic resonance imaging ; KOA: knee osteoarthritis; MNI: Montreal Neurological Institute; PAG: periaqueductal gray; ROIs: regions of interest; rsFC: resting-state functional connectivity; TKA: total knee arthroplasty.

Declarations

1. Ethics approval and consent to participate

This trial adheres to the principles of the Helsinki Declaration (2013) and was approved by the ethics committee of the participating hospital (Ethics approval numbers: 2020-K-109). All the participants will provide written informed consent before the trial.

2. Consent for publication

Consent for publication will be obtained from participants.

3. Availability of data and materials

The datasets and the informed consent form can be obtained from the corresponding authors upon reasonable request.

4. Competing interests

There are no conflict of interests to declare.

5. Funding

This trial will be supported by the Shanghai Municipal Key Clinical Specialty Construction Project (No.shslczdzk04801) and the Changning District Science and Technology Committee Project (No.CNKW2020Y23). The funding organization had no role in the design of the trial nor in its conduct, including data collection, management, analysis, and interpretation; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

6. Authors' contributions

LBX will be the trial sponsor. HX and CZ will be responsible for designing and supervising the trial. HX and CZ drafted and revised the protocol manuscript, with equal contribution. YCX designed the statistical analysis scheme. BXK was responsible for clinical trial registration and ethics approval. XYA and XRX will be the principal evaluators. JX will be responsible for data collection. All the named authors meet the authorship guidelines of Trials. All authors have agreed to publication of the protocol.

7. Acknowledgements

Not applicable.

8. Authors' information

1Department of Orthopaedics, Shanghai University of Traditional Chinese Medicine Guanghai Hospital, Shanghai 200050, China

2 Shanghai Guanghai Integrated Chinese and Western Medicine Hospital, Shanghai 200000, China

3School of Acupuncture and Tuina, Henan University of Traditional Chinese Medicine, Zhengzhou 450003, China

4Henan Provincial Hospital of Traditional Chinese Medicine, Zhengzhou 450003, China

References

1. Andriacchi TP, Koo S, Scanlan SF. Gait mechanics influence healthy cartilage morphology and osteoarthritis of the knee. *J Bone Joint Surg Am*, 2009;91(Suppl 1):95–101 Available from: <http://med.wanfangdata.com.cn/>.
2. Dimitroulas T, Duarte RV, Behura A, et al. Neuropathic pain in osteoarthritis: A review of pathophysiological mechanisms and implications for treatment. *Seminars in Arthritis & Rheumatism*, 2014;44(2):145–154 Available from: <https://www.sciencedirect.com/science/article/abs/pii/S004901721400105X>.
3. Kumar D, Swanik C, Reisman DS, et al. Individuals with medial knee osteoarthritis show neuromuscular adaptation when perturbed during walking despite functional and structural impairments. *Journal of Applied Physiology*, 2014;116(1):13–23 Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3921367/>.
4. Ye J, Cai S, Zhong W, et al. Effects of tai chi for patients with knee osteoarthritis: a systematic review. *Journal of physical therapy science*, 2014;26(7):1133-7 Available from: <https://pubmed.ncbi.nlm.nih.gov/25140112/>.
5. Liao Defa. Current status of epidemiological investigation of osteoarthritis in China. *Minimally Invasive Medicine*. 2017;12(04):521 – 24 Available from: <http://www.cnki.com.cn/article/cjfdtotal-wcyx201704022.htm>.
6. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis cartilage*. 2014;22(3):363–88.
7. Bruyère O, Cooper C, Pelletier JP, et al. An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Seminars in Arthritis & Rheumatism*, 2014;44(3):253–263 Available from: <https://www.sciencedirect.com/science/article/pii/S0049017214001085>.
8. G C Goats. Massage—the scientific basis of an ancient art: Part 1. The techniques. *British Journal of Sports Medicine*. 1994;28(3):149–152 Available from: <https://pubmed.ncbi.nlm.nih.gov/8000809/>.
9. Qiling Y, Tuanmao G, Liang L, et al. Traditional Chinese Medicine for Neck Pain and Low Back Pain: A Systematic Review and Meta-Analysis. *Plos One*, 2015;10(2):e0117146 Available from: <https://pubmed.ncbi.nlm.nih.gov/25710765/>.
10. Plastaras CT, Schran S, Kim N, et al. Complementary and Alternative Treatment for Neck Pain: Chiropractic, Acupuncture, TENS, Massage, Yoga, Tai Chi, and Feldenkrais. *Physical Medicine & Rehabilitation Clinics of North America*, 2011;22(3):521–537 Available from: <https://www.sciencedirect.com/science/article/abs/pii/S1047965111000283>.

11. Feng H, Rong J, Pei K, et al. A systematic review protocol of Tuina for children with acute bronchitis: A protocol for systematic review. *Medicine*, 2020;99(4):e18899 Available from: <https://www.researchgate.net/directory/publications>.
12. Field T. Knee osteoarthritis pain in the elderly can be reduced by massage therapy, yoga and tai chi: A review. *Complement Ther Clin Pract*, 2016;22:87–92 Available from: <https://www.sciencedirect.com/science/article/abs/pii/S1744388116300019>.
13. Lee NW, Kim GH, Heo I, et al. Chuna (or Tuina) Manual Therapy for Musculoskeletal Disorders: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Evid Based Complement Alternat Med*, 2017;8218139 Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5758860/>.
14. Qingguang Z, Jianhua L, Min F, et al. Effect of Chinese massage (Tui Na) on isokinetic muscle strength in patients with knee osteoarthritis. *Journal of Traditional Chinese Medicine*, 2016;36(3):314–320 Available from: <https://d.wanfangdata.com.cn/periodical/zyzz-e201603007>.
15. Altman RD. Classification of disease: Osteoarthritis. *Seminars in Arthritis & Rheumatism*, 1991;20(6):40 – 7 Available from: <https://www.sciencedirect.com/science/article/abs/pii/004901729190026V>.
16. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of internal medicine*, 2013;158(3):200–207 Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5114122/>.
17. Desmond JE, Glover GH. Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses. *Journal of Neuroscience Methods*, 2002;118(2):115–128 Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0165027002001218>.
18. Hayasaka S, Peiffer AM, Hugenschmidt CE, et al. Power and sample size calculation for neuroimaging studies by non-central random field theory. *NeuroImage*, 2007;37(3):721–730 Available from: <https://www.sciencedirect.com/science/article/abs/pii/S1053811907005204>.
19. Qingguang Z, Min F, Li G, et al. Gait analysis of patients with knee osteoarthritis before and after Chinese massage treatment. *Journal of Traditional Chinese Medicine*, 2015;35(4):411–416 Available from: <https://www.sciencedirect.com/science/article/pii/S0254627215301175>.
20. YAN JT. *Chinese Massage (Tui Na)*. Beijing: China Press of Traditional Chinese Medicine; 2008. p. 177.
21. Xuezhong W, Yuelong C, Xiang W, et al. A systematic review of manual treatment of knee osteoarthritis. *Chinese Journal of Orthopaedics and Traumatology*, 2011(2): 3–5 Available from: <http://www.cnki.com.cn/Article/CJFDTotat-ZGZG201102001.htm>.
22. OFFICE W R. *WHO standard acupuncture point locations in the western pacific region*. Geneva: WHO Publications; 2008. pp. 63–119.
23. Roos EM, Arden NK. Strategies for the prevention of knee osteoarthritis. *Nature Reviews Rheumatology*, 2016 Available from: <https://www.nature.com/articles/nrrheum.2015.135>.

24. Axford J, Heron C, Ross F, et al. Management of knee osteoarthritis in primary care: pain and depression are the major obstacles. *Journal of Psychosomatic Research*, 2008;64(5):461–467 Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0022399907004527>.
25. Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. *Journal of Rheumatology*, 2000;27(6):1513–1517 Available from: http://med.wanfangdata.com.cn/Paper/Detail/PeriodicalPaper_PM10852280.
26. Felson DT. The sources of pain in knee osteoarthritis. *Current Opinion in Rheumatology*, 2005;17(5):624 Available from: http://med.wanfangdata.com.cn/Paper/Detail/PeriodicalPaper_PM16093843.
27. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature. *Bmc Musculoskeletal Disorders*, 2008;9(1):116–116 Available from: <https://link.springer.com/article/10.1186/1471-2474-9-116>.
28. Arendt-Nielsen L, Graven-Nielsen T. Central sensitization in fibromyalgia and other musculoskeletal disorders. *Current Pain & Headache Reports*, 2003;7(5):355 – 61 Available from: http://med.wanfangdata.com.cn/Paper/Detail/PeriodicalPaper_PM12946288.
29. Arendt-Nielsen L, Nie H, Laursen MB, et al. Sensitization in patients with painful knee osteoarthritis. *Pain*, 2010;149(3):573–581 Available from: http://med.wanfangdata.com.cn/Paper/Detail/PeriodicalPaper_PM20418016.
30. Qinguang X, Bei C, Yueyi W. The Effectiveness of Manual Therapy for Relieving Pain, Stiffness, and Dysfunction in Knee Osteoarthritis: A Systematic Review and Meta-Analysis. *Pain Physician*. 2017;20(4):229–43.
31. Bo W, Nansheng Y. Expert consensus on step treatment of knee osteoarthritis (2018 edition). *Chinese Journal of Joint Surgery (Electronic Edition)*, 2019;13(01):124–130 Available from: <http://www.cqvip.com/QK/88767X/201901/90727174504849574849485052.html>.

Figures

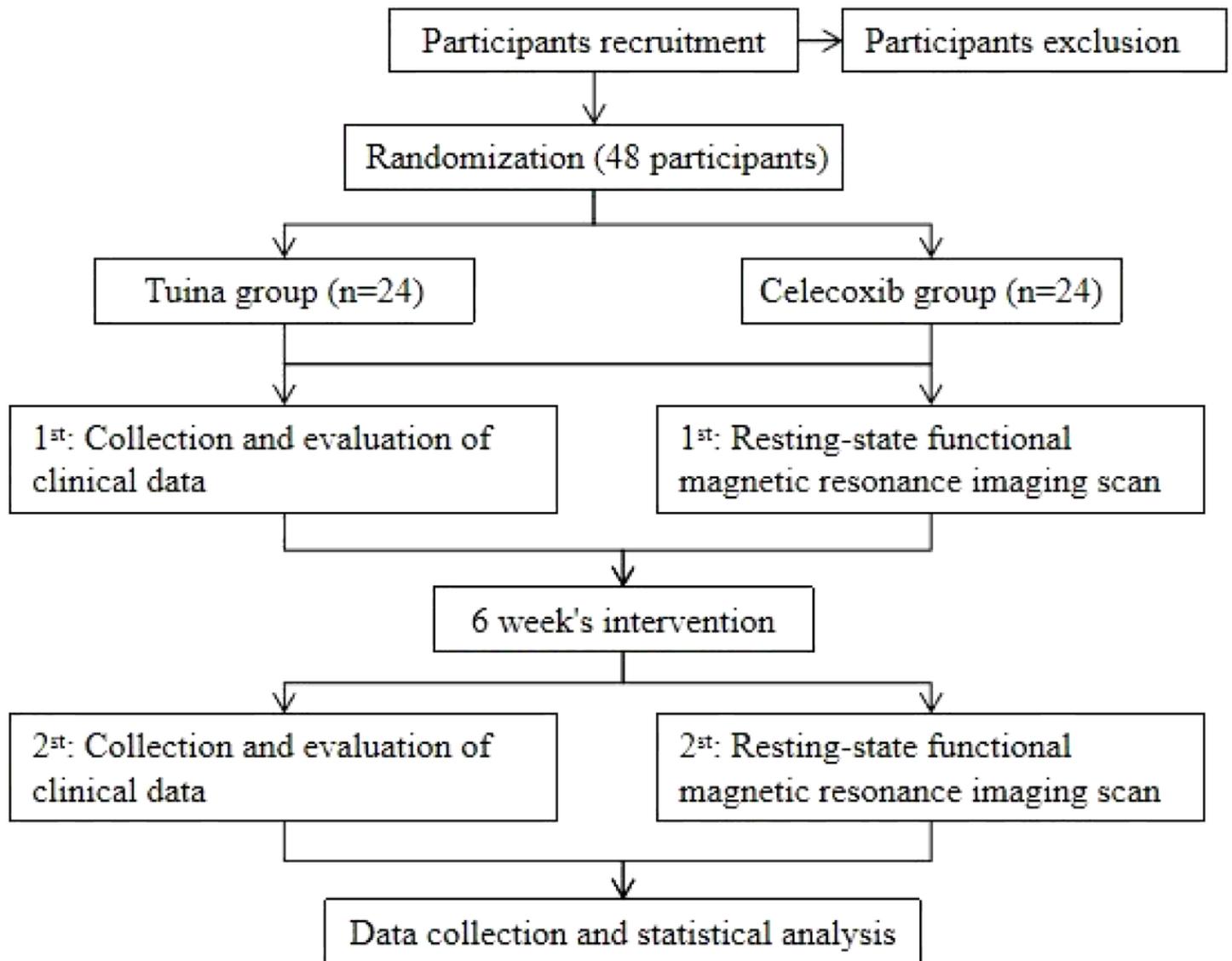


Figure 1

Flowchart of the trial.

TIMEPOINT	Study Period			
	Enrollment	Allocation	Baseline (0-week)	Intervention phase (6-week)
Eligibility Screen	×			
Demographic information informed	×			
Medical information	×			
Allocation		×		
Consent			×	
Resting-state fMRI scan			×	×
Numerical Rating Scale			×	×
Pain Catastrophizing Scale			×	×
Hamilton Anxiety Scale score			×	×
Hamilton Depression Scale			×	×
Adverse events of EA				×

Figure 2

The schedule of enrollment of participants into the trial, interventions, and assessments. fMRI, functional magnetic resonance imaging.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SPIRITChecklistforrandomisedstudies.doc](#)