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Comparison of Taiji and aerobic exercise for functional constipation: study protocol for a randomised controlled neuroimaging trial

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ABSTRACT

Introduction Taiji has been proven to be effective for regulating both the physical and mental state compared with simple aerobic exercise. However, whether the improvement of Taiji for constipation is related to regulate imbalanced brain–gut axis and emotional disorder for functional constipation (FC) remains uncertain. The results of the study will demonstrate the differences in regulation brain–gut balance between Taiji and simply aerobic exercise for patients with FC and provide a potential therapy for clinical treatment of FC, and a new approach for the research of mind–body exercise.

Methods and analysis In this randomised controlled neuroimaging trial, 80 patients with FC will be allocated into two groups: Taiji group and aerobic exercise group. The two groups will receive 10 weeks of Taiji exercise or aerobic exercise, respectively. The stool diary, Cleveland Constipation Score and Patient Assessment of Constipation Symptom, Patient Assessment of Constipation Quality of Life Questionnaire will be used to evaluate the clinical efficacy, the Self-rating Depression Scale, Self-rating Anxiety Scale, Eysenck Personality Questionnaires and Mini-Mental State Examinations will be used to assess the mental state at the baseline, the 5-week intervention and the end of intervention. The 24-hour heart rate variability will be used for assessing the autonomic nervous function, functional MRI and positron emission tomography-CT will be performed for detecting the cerebral functional changes at the baseline and the end of the intervention. The clinical data and multimodal imaging data will be analysed, respectively. Correlation analysis will be conducted to investigate the relationship between cerebral functional changes and symptom improvement.

Ethics and dissemination The procedures have been approved by the Sichuan Regional Ethics Review Committee on Traditional Chinese Medicine (No. 2018KL-047) and conformed to the Declaration of Helsinki. Results will be disseminated through policy briefs, workshops, peer-reviewed publications and conferences.

Trial registration number Chinese Clinical Trial Registry (ChiCTR1800019781).

Strengths and limitations of this study

► The use of randomised controlled neuroimaging trial design will provide valid evidence about the effectiveness of simple aerobic exercise and Taiji (mind–body exercises) for treating functional constipation (FC).

► This study is the first to investigate the differences in regulation brain–gut balance between Taiji and simply aerobic exercise for patients with FC.

► This study can provide a potential therapy for clinical treatment of FC, and a new approach to investigate mind–body exercises from clinical symptoms, mental state and brain function.

is characterised by infrequent defecation, hard or lumpy stools, straining during defecation, the sensation of anorectal obstruction/blockage and incomplete evacuation.[1] The estimated global prevalence of FC ranges from 6% to 29.6%.[2–5] In addition to the higher prevalence, FC significantly influences the patients' quality of life (QoL) and brings remarkable healthcare costs.[6–8] Currently, pharmacotherapy for FC including cathartic is not satisfactory in improving persistent symptoms and the QoL of patients with FC. Besides, the side effects are often reported,[9] such as bloating,[10] diarrhoea[11] and nausea.[12] Therefore, it is urgent to find safe and effective treatment for FC.

As a safe intervention, exercise, is recommended to manage FC by the clinical practice guideline which was established by an expert workgroup in the Spanish Society of Digestive Diseases (Sociedad Espanola de Patologia Digestiva).[13–15] The reason is that the effectiveness and safety of exercise therapy for constipation has been recognised.[16 17] Among the exercise therapies, mind–body exercise has aroused widespread concern for its dual influence on the body and mind of the

INTRODUCTION

Functional constipation (FC), a common functional gastrointestinal disorder (FGID),

patients. For example, Taiji, a classical mind–body exercise originated from ancient China, has been shown to be effective for improving both symptoms and emotional disorder for patients with gastrointestinal dysfunction.[18 19]

However, whether the gastrointestinal adjustment of Taiji significantly differs from the simple aerobic exercise and the potential mechanism remains uncertain. In the last two decades, the important role of the brain–gut axis in the pathogenesis of FC has been confirmed by more and more evidence.[20] The dysfunction of central nervous system in processing the gastrointestinal signals has been thought to contribute to the occurrence of constipation.[21] In our previous studies, we found that, compared with healthy subjects (HS), patients with FC have shown significant changes in cerebral function by functional MRI (fMRI).

So in this study, we try to (1) evaluate the clinical efficacy of simple aerobic exercise and Taiji (mind–body exercises) for treating FC with a randomised control design to investigate the differences in influencing intestinal function between aerobic exercise and Taiji practice; (2) detect the cerebral activity changes in patients with FC elicited by simple aerobic exercise and Taiji boxing using fMRI and positron emission tomography (PET)-CT to investigate the differences in influencing brain function between aerobic exercise and Taiji practice; (3) assess the difference in influence psychological state between aerobic exercise and Taiji practice; (4) analyse the potential correlations between the clinical improvements and cerebral activity changes, so as to partly explore the impossible mechanism of Taiji regulating gastrointestinal function, and provide an approach for FC treatment.

METHODS AND ANALYSIS
Study design
The trial is designed as a randomised control trial. A total of 80 patients with FC will be randomly assigned to the Taiji group or aerobic exercise group (1:1 ratio). The study procedure is outlined in figure 1.

Sample size calculation
We will compare the reduction in the severity of FC symptoms between the two groups (measured by the complete spontaneous bowel movements (CSBMs)). The sample size was calculated by specifying an effect size based on minimal clinically important differences. In the case of symptoms of FC, we calculated an 80% power of detecting a conservative effect size of 0.7. Considering $\alpha=0.05$, $1-\beta=0.8$ and 2.0 of the SD, the study design required sample size of 68, with a drop-out rate of 15%. A total of 80 patients with FC will be finally recruited.

According to previous neuroimaging studies,[22 23] 15 subjects represent a reasonable sample size for the measurement of stable cerebral responses. In this study, 15 participants in each group will be randomly chosen to undergo both MRI and PET-CT scans.

Participants and recruitment strategy
Patients who match the inclusion criteria will be recruited. They will be informed of the possible benefits and risks of exercise in the study before recruitment. And then the participants will be required to fill out informed consent and can withdraw from the study without any conditions.

Inclusion criteria
Patients will be included if they: (1) meet the Rome IV Diagnostic Criteria for FC which was designed in 2016 (online supplementary material 1); (2) are right-hand and aged 18–35 years; (3) has less than three CSBMs per week; (4) get more than 10 scores when are evaluated by Cleveland Constipation Score (CCS) and (5) provide written informed consent.

Exclusion criteria
Patients will be excluded if they (1) are pregnant, or intend to pregnant in 3 months, or be lactating; (2) are not physically fit for exercise; (3) have a history of head trauma and loss of consciousness; (3) have diabetes or serious cardiovascular, neurological, psychiatric, renal or respiratory disease; (4) have moderate or above symptoms of depression and anxiety; (5) cannot maintain silence in a lying position for 20 min; (6) have any contraindications to fMRI scanning including the presence of metal stent, metal denture or claustrophobia; (7) have participated in other exercises that may improve constipation symptoms (including meditation and yoga) over 30 min per week in the last 3 months; (8) have taken gastrointestinal dynamic medicine, non-steroidal anti-inflammatory drugs and steroids during the last 15 days; or have taken traditional treatments (including surgery, diet modification, biofeedback or probiotics) in the previous 1 month and (9) have participated in any other clinical trials in the past 3 months.

Recruitment strategy
Participants with FC will be recruited from the First Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (TCM) and the campus of Chengdu University of TCM by advertisement from December 2018 to November 2020.

Randomisation and blinding
Using a computer-generated randomisation digital table. The randomisation will entail in two steps: (1) 80 patients will be equally allocated into the two treatment arms; (2) 15 patients will be randomly chosen from each group to receive fMRI scans and PET-CT scans. We will use opaque, sealed envelopes to conceal the sequence until interventions are assigned.

It is difficult to blind instructors and patients in this trial for different interventions. However, outcome assessors and statistical analysts will be blind to the procedure and result of randomisation, group allocation and intervention.
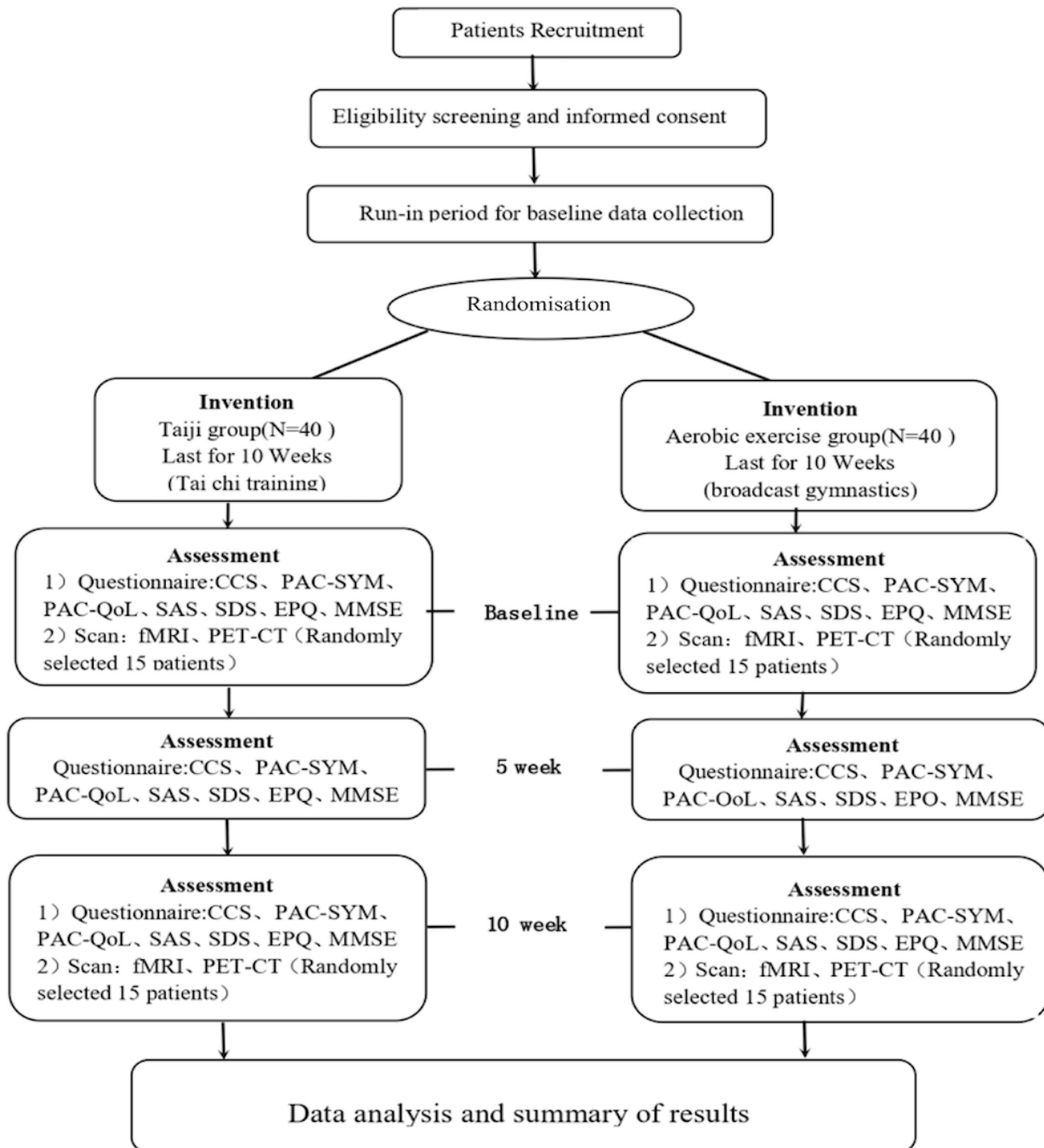
Figure 1 Flowchart of the participants (procedure) through the trial.

Patient and public involvement

During the development of the study protocol , some patients were interviewed about the acceptability of taking photo or video in the procedure, and they supported the study and expressed no concerns regarding the photo or video. The patients are asked if they would like to receive a copy of the outcomes of the study after the invention and an email address or telephone number are collected to facilitate the distribution of any relevant publications. The patients will be informed of the result of this study after the intervention. Results will be disseminated through policy briefs, workshops, peer-reviewed publications and conferences.

Intervention

Taiji group

Because none of the participants in Taiji group had practiced Taiji, they will undergo a 5-day training session with 24-style Yang's Taiji (online supplementary material 2), and be required to master the movement essentials of Taiji before the formal trial.

The formal Taiji practice will be performed four times a week (Monday, Tuesday, Thursday and Friday) and last for 10 weeks. Each practice session takes 60 min and includes 10- min warm-ups, 40 min Taiji practice and 10 min relaxation.

Time point	Baseline Day-14—Day0	Middle of intervention Day35（5 weeks）	After intervention Day90（10 weeks）
Eligibility screen	√		
Informed consent	√		
Medical history collecting			
Demographics	√		
Diagnosis	√		
Past medical history	√		
Exercise interventions		√	√
Clinical assessments			
BMI	√		√
HRV	√		√
patients reported outcomes the exercise self-rating scale	√	√	√
CCS	√	√	√
PAC-QOL	√	√	√
PAC-SYM	√	√	√
Stool Diary	√	√	√
SDS,SAS	√	√	√
EPQ	√	√	√
SF-36	√	√	√
MMSE	√	√	√
Image data outcomes			
fMRI	√		√
PET-CT	√		√
Safety observation			
Blood Routine Test	√		√
Urine Routine Test	√		√
Stool Routine Test	√		√
Adverse Events			√

Figure 2 Time schedule of enrollment, interventions and assessments: at the baseline, the median of intervention (5-week exercise) and the end of intervention (10-week exercise), the stool diary, Cleveland Constipation Score (CCS) and Patient Assessment of Constipation Symptom (PAC-SYM) will be used to evaluate the clinical efficacy of different interventions; the Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QoL) will be used to assess the health-related QoL; the Self-rating Depression Scale (SDS), Self-rating Anxiety Scale (SAS), Eysenck Personality Questionnaires (EPQ) and Mini-Mental State Examinations (MMSE) will be used to consider the effect of psychological factors on the patients symptoms. All participants will be assessed the 24 hours heart rate variability (HRV) to evaluate the autonomic nervous function at the baseline and the end of the10-week intervention. Functional MRI scans and positron emission tomography-CT scans will be performed to detect the cerebral functional changes in 15 patients in each group both at the baseline and at the end of the intervention.

The 24-style Yang's Taiji will be trained by two professional Taiji instructors with over 10 years of training experience. To ensure correct posture and speed of movement, all sessions will be monitored by regular reviews of video recordings and feedback sessions to ensure correct instructions.

Aerobic exercise group

In the aerobic exercise group, patients will undergo the broadcast gymnastics (online supplementary material 3) for 10 weeks. As same as Taiji group, they will undergo a 5-day training session with broadcast gymnastics, and be required to master the movement essentials of broadcast gymnastics before the formal trial.

The formal broadcast gymnastics practice will be performed four times a week (Monday, Tuesday, Thursday and Friday) and last for 10 weeks. Each practice session takes 60 min, including breathing, warm-ups, stretching movement training and relaxation.

To ensure correct posture and speed of movement, the broadcast gymnastics will be trained by two professional instructors, and all sessions will be monitored by regular reviews of video recordings and feedback sessions.

Concomitant medications

If the constipation symptom of participants gets worse and interfere with daily life, or less than two bowel movements per week, the investigators will administer the Glycerine Enemas as a necessary concomitant medication. And the concomitant medications will be detailed and recorded in case report forms.

MEASUREMENTS

The measurements will be drawn from independent assessors who have been trained prior to the study. All outcomes will be recorded regardless of whether the participants complete the research programme. The schedule of the study, including enrollment, interventions, assessments and visits for participants, is shown in figure 2.

General information collection

General information includes the demographic data and vital sign. The demographic data include age, gender, level of education, nationality and BMI. The vital sign includes body temperature, heart rate, respiratory rate and blood pressure. Among them, the heart rate of each patient will be immediately recorded after every training.

Exercise evaluation

After each training, the exercise self-rating scale from the American College of Sports Medicine will be filled by all participants to evaluate exercise intensity scoring and grading that can control the levels of exercise both objectively and subjectively to obtain the exercise requirement.

Symptoms measurement

The following scales will be used to evaluate the constipation symptoms of patients at the baseline, the median of intervention (5-week exercise) and the end of intervention (10-weeks' exercise).

The stool diary

It consists of seven sections: (1) weekly CSBMs; (2) the Bristol Stool Form Scale[24] containing seven types of stool evacuation; (3) straining; (4) defecating time; (5) incomplete feeling; (6) unsuccessful defecation frequency in 24 hours and (7) anus fall bilge feeling.

Cleveland Constipation Score

CCS is a designated scale to evaluate patients' gastrointestinal or anorectal symptoms. CCS[25] will be formulated by

the American Gastroenterology Society, including eight aspects of the constipation symptoms. The higher score obtained by the participants indicating the more serious the degree of constipation.

Patient Assessment of Constipation Symptoms

Patient Assessment of Constipation Symptom (PAC-SYM) is also to evaluate patients with gastrointestinal symptoms. PAC-SYM consists of 12 items of faecal traits, rectal symptoms and abdominal symptoms. Each item is scored from 0 to 4, a higher score indicating more severe symptoms.

Measurements for the quality of life

The following two questionnaires will be used to evaluate the QoL of patients at the baseline, the median of intervention (5-week exercise) and the end of intervention (10-week exercise).

Patient Assessment of Constipation Quality of Life Questionnaire

Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QoL)[26] is an internal consistency reliability scale consisting of 28 items namely, body discomfort, psychological discomfort, worries and concerns, and satisfaction. It used to assess the quality of life of patients with FC.

Psychological state assessment

Considering the effect of psychological factors on the patients with symptoms, the Self-rating Depression Scale (SDS),[27] the Self-rating Anxiety Scale (SAS),[28] the Eysenck Personality Questionnaires (EPQ)[29] and the Mini-Mental State Examinations (MMSE)[30] will be performed on all the patients at the baseline, the median of intervention (5-week exercise) and the end of intervention (10-week exercise).

Evaluation of autonomic nervous function

Because the autonomic nervous plays an important role in regulating intestinal function,[31 32] this study selected the heart rate variability (HRV) to evaluate the autonomic nervous function. HRV is a sensitive, quantitative and intuitive indicator for non-invasive assessment of autonomic nervous activity.[33] All participants will be assessed during the 24-hour HRV at the baseline and the end of the 10-week intervention. At least 12 hours prior in the examination period, medication (including FC medications), tobacco, alcohol, caffeine, tea or other stimulating beverages will be forbidden. Data collection will begin at 17:00 and conclude at 17:00 the next day. During the 24-hour period, participants will be allowed sufficient sleep and will avoid strenuous exercise and emotional fluctuations. The device (CT-086S, BENE WARE, CHINA) will capture the R–R intervals through the attachment of electrodes to the chest.

Neuroimaging scans

A total of 15 participants in each group will receive both MRI scans and PET-CT scans at the baseline and the end of the intervention.

MRI scan

The tridimensional structural image scanning parameters will be as follows: repetition time/echo time=1900 ms/2.26 ms; slice thickness=1 mm; slice number=30; matrix size=128×128 and the field of view=256×256 mm. The Blood Oxygenation Level-Dependent fMRI (BOLD-fMRI) scanning parameters will be as follows: repetition time/echo time=2000 ms/30 ms; flip angle=90°; slice number=30; matrix size=128×128; field of view=240 × 240 mm, slice thickness=5 mm; total volume=240. Diffusion Tensor Imaging (DTI) data will be acquired using a single-shot spin-echo echo planar image sequence with the following parameters: field of view=240×240 mm; repetition time/echo time=6800 ms/93 ms; matrix size=128 × 128; slice thickness=3 mm with no gap. Two diffusion-weighted sequences will be acquired using gradient values $b=1000 \ s/mm^2$ and $b=0$, with the diffusion-sensitising gradients applied in 30 non-collinear directions.

ositron emission tomography-CT scan

The PET-CT images will be initially acquired using the following parameters: 130 KV; 100 mAs; matrix size=256×256; magnification=2×; slice thickness=5 mm; slice interval=2.5 mm; pitch=9.2 mm. PET will then be performed using the following parameters: bed=1, model=3D, scanning time=8 min and total counts=$3×10^9$. Following data acquisition, images will be reconstructed using ordered-subset expectation maximisation with four iterations and eight subsets.

Safety assessments

Participants will be monitored during the study intervention for the occurrence of adverse events. Adverse events associated with this study will occur during the exercise period or during neuroimaging data scanning. All adverse events will be detailed and recorded on an adverse event case report form during the study intervention. All events will be evaluated for their relevance to the intervention and severity, according to the gastroenterology clinician.

Statistical analysis
Clinical data analysis

Clinical data will be analysed by an independent statistician blinded to the test settings using SPSS V.20.0 statistical software. Data analysis will be based on the intention-to-treat (ITT) and per protocol (PP) principles. The results of ITT and PP analysis will be compared for consistency. A p value <0.05 will be considered statistically significant. Participants who fail to complete the study will be treated as having no change from baseline at all times. All data will be presented as the mean±SD. Categorical variables will be described with percentages (%). Clinical data among the two groups will be compared using a two-sample t-test (Taiji group vs aerobic exercise group), and comparisons between baseline and the end of treatment in each group will be performed using a paired sample t-test. Clinical data on the skewed distribution will be compared

using a non-parametric test. Categorical variables will be compared using a χ^2 test or Fisher's exact test.

Neuroimaging data analysis

For fMRI scans, all preprocessing steps will be performed using DPARSF software (http://rfmri.org/DPARSF) based on MATLAB. The main analytical methods for the cerebral responses of the different interventions will contain regional homogeneity, an amplitude of low-frequency fluctuation (ALFF) and functional connectivity. Following data preprocessing, data analysis will consist of two stages: (1) whole-brain performance analysis through ALFF and (2) functional connectivity through seed correlation analysis. In this study, the cerebral responses to Taiji in FC mainly refer to a change in the ALFFs and functional connectivity before and after treatment. A threshold of voxel-wise uncorrected p<0.005 and p<0.05 familywise error correction at the cluster level will be applied to all analyses.

SPM12 software (http://www.fil.ion.ucl.ac.uk/spm) will be used to process and analyse the PET-CT data with MATLAB 2015b. Regional brain radioactivity will be measured to assess regional cerebral glucose metabolism which directly reflects the cerebral activity.

Correlation analysis will be measured using the Pearson correlation coefficient using clinical and fMRI imaging data.

DISCUSSION

This study is the first to investigate the differences in regulation brain–gut balance between Taiji and simply aerobic exercise for patients with FC. It provides a potential therapy for clinical treatment of FC, and a new approach to investigate mind–body exercises from clinical symptoms, mental state and brain function.

The multidimensional evaluation of Taiji for treating FC

Taiji is a widely spread mind–body exercise. It has been thought of as 'moving meditation' by the National Institute of Health for its significant physical and psychological benefit. For example, it has found that comparing to aerobic exercise, Taiji as a mind–body exercise could result in similar improvement in symptoms of fibromyalgia, but greater improvement in several secondary outcomes (such as global assessment of patients with fibromyalgia; anxiety and self-efficacy and coping strategies).[34] However, there is no direct evidence to prove the therapeutic benefit of Taiji to FC. When we want to objectively evaluate the Taiji's effect on FC, we must take into account its influence on physical aspects (constipation symptoms and QoL) and psychological aspect (emotional disorder).

Furthermore, FC is a typical psychosomatic disease, the gastrointestinal factors and psychological factors play important role in the onset of this disorders, and the interaction of gastrointestinal factors and psychological factor makes FC recurrent and persistent. It is reported

that patients with FC often have depression and anxiety, and the emotion can reverse to aggravate the symptoms of constipation.[13] Moreover, more and more studies had proven that cerebral structural and functional abnormalities participated in the pathogenesis of FGIDs including FC. Comparing to HS, patients with FC have shown altered activities in emotional process modulation (dorsal anterior cingulate cortex, anterior insula, orbitofrontal cortex and hippocampus), somatic and sensory processing, and motor control (supplementary motor area and precentral gyrus).[35] Therefore, the improvements of symptoms, QoL, emotional disorder and the changes of brain function must be considered when evaluating the therapeutic effect of FC.

Therefore, the assessment of Taiji for treating FC should be a multidimensional evaluation. In this study, we try to evaluate the therapeutic effect of Taiji forms the following five aspects. First, the stool diary, CCS and PAC-SYM will be used to assess the clinical symptoms. The stool diary is the self-rating recording for the clinical symptoms changes, especially the CSBM includes the patient's perception of satisfactory evacuation. For evaluating patients with gastrointestinal or anorectal symptoms, the CCS (a self-rating scale) and the PAC-SYM (an other-rating scale) will be used simultaneously. Second, the PAC-QoL is the constipation-specific questionnaire and will be used to more completely evaluate the improvements of QoL. Thirdly, SDS, SAS, EPQ and MMSE will be performed to assess the emotional and cognitive state of patients with FC. The former two are self-rating scales, and the latter two are other rating scales. Fourthly, HRV is used to evaluate the autonomic nervous function. Finally, the most commonly used neuroimaging techniques, MRI scans and PET-CT scans, will be performed to investigating the cerebral activity changes elicited by Taiji and acerbic exercise. The collaborative application of fMRI and PET-CT can define functional images with high resolution and provide biological information on molecular metabolism with high sensitivity to keep high data reproducibility.[36] Taken together, the multidimensional evaluation system is more in line with the therapeutic characteristics of Taiji and the pathogenic features of FC and will help to assess the effect of Taiji for FC more comprehensively.

The quality control criteria

To improve the reliability and reproducibility of the results, stricter quality control criteria will be designed and performed in this study.

For the participation enrollment, the strict Inclusion and Exclusion Criteria is established to improve the homogeneity of the baseline values. We will only include the participants who are naive to Taiji and have not taken other exercise that may improve constipation symptoms (including meditation and yoga).

For the Taiji and aerobic exercises, we have established the standard training procedures for Taiji and aerobic-exercises practice including the movements essential, training time and frequency. To ensure the

standardisation of movements, the training of Taiji and aerobic-exercises will be completed by two trained coaches who have performed these exercises for over 10 years. In subsequent training sessions, researchers will video-record each session and the coaches will randomly check the standardisation of the movements.

For the multimode neuroimaging scans, we have established a realistic standard operating procedure for multimode neuroimaging scans including the imaging data acquisition and fusion. To consider the dynamic variability of brain function, the acquisition of imaging data will be held with the same scanner and operator in the morning of the same day. Moreover, participants will be asked to maintain their regular lifestyle and avoid overexertion, staying up late and ingesting alcohol, tobacco, tea and coffee, in order to keep the stability of physiological and psychological status. Before the scan, each participant's emotional state will be assessed by the emotional state assessment scale. The temperature of scanning room will be kept at 18–22°C, with humidity more than 60% and noise less than 150 dB; to ensure reliability of multimodal imaging data analysis, the BOLD-MRI and PET-CT data will be collected separately and be interpreted in the same template space to cross-verify the results.

For the measurement, first the researchers, exercise instructors and outcome assessors are separated in the study process. Second, the physical and mental status of participants will be evaluated by the same clinical physician and psychological experts, respectively. Thirdly the blind method will be used for data statistics and analysis to avoid the measurement bias. The whole study design will be concealed to the outcome assessors.

In conclusion, Taiji has been shown to be effective for improving both symptoms and emotional disorder for patients with gastrointestinal dysfunction. This trial is the first randomised controlled neuroimaging trial to investigate the differences in influencing intestinal function between simple aerobic exercise and Taiji practice. The results will demonstrate the differences in regulation brain–gut balance between Taiji and simply aerobic exercise for patients with FC and provide a potential therapy for clinical treatment of FC, and a new approach for the research of mind–body exercise.

Trial status

This trial is currently in the stage of recruiting patients. The first patient was included on 1 December 2018. To date, 23 patients have been included.

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