Effects of repetitive transcranial magnetic stimulation on fear of cancer recurrence and its underlying neuromechanism

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ABSTRACT

Introduction: Many breast cancer patients suffer from fear of cancer recurrence (FCR). However, effective physical intervention for FCR has been scarce. Previous studies have confirmed that repetitive transcranial magnetic stimulation (rTMS) can help improve patients' anxiety, depression, fear, and stress level. Therefore, this study aims to assess the efficacy of rTMS in the treatment of FCR in breast cancer patients and explore its underlying neural mechanism.

Methods and analysis: and analysis: Fifty breast cancer patients with high FCR (FCR total score >27), and fifty age- and gender-matched patients with low FCR (FCR total score <7) will be recruited to participate in this study. Patients in the high FCR group will be randomly assigned to receive 4-week low-frequency rTMS targeting the right dorsolateral prefrontal cortex (rDLPFC) + treatment as usual (TAU) (n = 25), or to receive sham stimulation + TAU (n = 25). Patients in the low FCR group will only receive TAU. All participants will take a baseline fMRI scan to examine the local activities and interactions of brain activity between the prefrontal cortex (DLPFC), amygdala and hippocampus. Fear of Cancer Recurrence Questionnaire (FCRQ7), Patient Health Questionnaire (PHQ9), Generalize Anxiety Disorder (GAD7), Numeric Rating Scale (NRS), and Insomnia Severity Index (ISI7) will be used to measure an individual's FCR, depression, anxiety, pain, and insomnia symptoms at week 0 (baseline), week 4 (the end of intervention), week 5 (1 week post-treatment), week 8 (1 month post-treatment), and week 16 (3 months post-treatment). Participants in the high FCR group will receive a post-treatment fMRI scan within 24 h after intervention to explore the neural mechanisms of rTMS treatment. The primary outcome of the study, whether the rTMS intervention is sufficient in relieving FCR in breast cancer patients, is measured by FCRQ7. Additionally, task activation, local activity and functional connectivity of the DLPFC, amygdala and hippocampus will be compared, between high and low FCR group, and before and after treatment.

Discussion: Studies have shown that low-frequency rTMS can be used to treat patient's FCR. However, there is a lack of relevant evidence to support the efficacy of rTMS on FCR in cancer patients, and the neural mechanisms underlying the effects of rTMS on FCR need to be further investigated.

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Abbreviations

rTMS	Repetitive Transcranial Magnetic Stimulation
FCR	Fear of Cancer Recurrence
RCT	Randomized Controlled Trial
DLPFC	Dorsolateral Prefrontal Cortex
TAU	Treatment as Usual
PTSD	Post-Traumatic Stress Disorder
FCRQ7	ear of Cancer Recurrence Questionnaire (7-item)
GAD7	Generalize Anxiety Disorder (7-item)
PHQ9	Patient Health Questionnaire (9-item)
NRS	Numeric Rating Scale
ISI7	Insomnia Severity Index (7-item)
SD	Standard Deviations
ITT	Intention to Treat
GLMM	Generalized Linear Mixed Model
REML:	Restricted Maximum Likelihood

1. Background

Breast cancer is the most common cancer in women [1]. Due to early diagnosis and effective treatments, life expectancy of breast cancer survivors is often extended [1]. Between 2011 and 2020, the mortality rate of breast cancer has decreased by an average of 1.3 % per year, with the five-year survival rate reaching 90.6 % [2]. At the same time, women with breast cancer suffer from a variety of psychological distresses, among which the fear of cancer recurrence (FCR) is one of the most common problems. FCR is defined as "*Fear, worry or concern relating to the possibility that cancer will come back or progress*" [3]. Studies have reported that up to 70 % of the breast cancer patients experience FCR [4, 5]. FCR could be a chronic factor that seriously compromises breast cancer patients' quality of life. It has been proved that breast cancer patients with high FCR were more likely to report repetitive body checking, over-screening and overtreatment, nonsensically and irrationally [6].

Anxiety and depression are also commonly reported psychological problems in breast cancer patients. The prevalence of anxiety and depression in breast cancer patients was reported to be at 41.9 % and 32.2 % respectively [1,7]. Luo et al., has reported that depression and anxiety symptoms were positively associated with high FCR in cancer patients [8], and a long-term research lasting 2 years confirmed that elevated anxiety and depression at baseline can help predict higher FCR [9]. Brent et al. found that cancer patients with more emotional distress were at a greater risk for Emergency Department visits and hospitalizations, experienced longer hospital stays, and accrued higher healthcare costs [10]. Treatment for psychological distresses has included drug therapy, physiotherapy and psychotherapy. Increasing number of studies have shown that non-drug intervention could help lessen psychological distress and promote quality of life of patients with cancer. For example, cancer pain could be alleviated through exercise, music, and meditation [11–13]. However, these interventions require long training and consistent adherence to the intervention, demanding considerable energy and time from the patients [11–13].

Repetitive transcranial magnetic stimulation (rTMS) is a safe, effective, noninvasive, and nonconvulsive neuromodulation therapy. rTMS can modulate the physiological dynamics across brain regions and networks, and has the potential to therapeutically modulate aberrant circuit properties across neuropsychiatric conditions with maladaptive circuit dynamics [14]. In 2018, Sriram et al., conducted transcranial microcurrent stimulation therapy for patients with advanced cancer and found that patient's anxiety, depression and insomnia symptoms were significantly improved after 4 weeks of intervention [15]. Similar studies were conducted by Tang et al., which showed that patients with advanced non-small cell lung cancer treated with rTMS had better pain relief, as well as better emotional state and quality of life [16]. rTMS has been considered as an effective treatment option for patients with anxiety and depression. However, there are limited studies that have evaluated the efficacy of rTMS for other neuropsychiatric disorders such as FCR among cancer patients.

Relevant reviews suggest that when low-frequency (frequency ≤1 Hz) rTMS is applied to the right dorsolateral prefrontal cortex (rDLPFC), patients' anxiety and depressive symptoms improved; and the longer the course of the treatment, the better the effect [17,18]. A randomized controlled trial (RCT) study evaluating the efficacy of rTMS (rDLPFC, 1 Hz, 110RMT, 1800 pulses) in the treatment of panic disorder combined with depression found that patient's symptoms improved after the 4-week treatment. During the subsequent 6 months of follow-up, patients showed continuous improvement in both panic disorder and depression [19]. Additionally, rTMS can increase the release of neurotransmitters such as 5-HT and brain-derived neurotrophic factor, and subsequently regulate the whole brain activity [17,18].

The prefrontal cortex (PFC) is one of the most important brain regions in which emotional function is regulated [20]. The medial prefrontal cortex (mPFC) exerts inhibitory "top–down" control over amygdala activity, limiting its output and thus preventing inappropriate emotional expression [21]. If the prefrontal cortex fails to inhibit over-activation of the amygdala during fear stimulation, individuals are more likely to report high levels of fear [22]. Additionally, the hippocampus is the neural basis for encoding and consolidating fear memories, and studies in mice have shown that the development of fear memories is significantly associated with increased connections between the hippocampus and the amygdala. Therefore, weakening the connections between the hippocampus and the amygdala might help reduce fear memories [23].

In recent years, the interaction of the prefrontal cortex, amygdala, hippocampus and other brain regions has attracted increasing attention [21,23,24]. Future intervention targeting an individual's PFC, amygdala and hippocampus might be helpful in disrupting fear-memory reconsolidation and might help prevent the return of fear.

1.1. Research objectives

This study aims to 1) examine the efficacy of the 4-week low-frequency rTMS on FCR in breast cancer patients, and 2) explore the underlying neural mechanisms as well as examine the interactions of the prefrontal cortex (DLPFC), amygdala and hippocampus of FCR patients by fMRI scans between the high and low FCR group, and before and after the rTMS intervention. The primary hypothesis for the trial is: low-frequency rTMS treatment can alleviate FCR in breast cancer patients.

2. Methods

2.1. Participants

Fifty breast cancer patients with high FCR, and fifty age- and gender-

matched breast cancer patients with low FCR (100 in total) will be recruited at Guangdong Provincial People's Hospital. To be included, participants must fulfil the following inclusion criteria: a) Adult; b) Breast cancer patients undergoing treatment for the first time; c) Able to understand and sign informed consent; and d) Being able to comply with the intervention. The exclusion criteria for this study are as follows: a) Minors; b) Having a diagnosis for a significant untreated mental or medical illness (e.g., consciousness disturbances, mania, acute phase of schizophrenia, major depressive disorder, etc.); c) Patients with recurrent cancer; and d) Hospice patients.

2.2. Research design

Fifty breast cancer patients with high FCR (FCR total score >7), and fifty age-and gender-matched patients with low FCR (FCR total score <7) will be recruited to participate in the study. Patients in the high FCR group will be randomly assigned to receive 4-week low-frequency rTMS + TAU (n = 25), or to receive sham stimulation + TAU (n = 25). Patients in the low FCR group will only receive TAU.

A written informed consent will be completed before participation in the study. All participants will be first asked to complete a personal information sheet. Fear of Cancer Recurrence Questionnaire (FCRQ7), Patient Health Questionnaire (PHQ9), Generalize Anxiety Disorder (GAD7), Numeric Rating Scale (NRS), and Insomnia Severity Index (ISI7) will be used to measure individual's FCR, depression, anxiety, pain, and insomnia symptoms from week 0 (baseline), week 4 (the end of intervention), week 5 (1 week post-treatment), week 8 (1 month post-treatment), and week 16 (3 months post-treatment).

At baseline, all participants will have a fMRI scan to examine the local activities and interactions between the prefrontal cortex, amygdala and hippocampus. Subsequently, Participants in the high FCR group will receive a post-treatment fMRI scan within 24 h after intervention to examine the underlying neural mechanism of rTMS. The research design is summarized in Fig. 1 for reference.

2.3. Randomization

Participants with high FCR fulfilling the study criteria will be randomly allocated to rTMS + TAU group or sham + TAU group using simple randomization (computer-generated random numbers) [25]. The allocation ratio of this study will be 1:1 [26]. To reduce the risk of selection bias, allocation concealment will be implemented [26]. The randomization sequence will be kept by a third person who will not be involved in any other parts of this study. After a participant is formally enrolled and the baseline data collection is completed, the research assistants will contact the third person for the allocation. No allocation sequence will be revealed before a participant is ready for randomization [26].

2.4. Blinding

The study will be a single-blind label trial in which participants will know nothing about the assignment, however, it will be impossible for the intervention facilitator to be blinded. Data analysts will know nothing about group assignments and research assistants.

2.5. Assessment points

Assessments will be conducted at week 0 (baseline), week 4 (the end of intervention), week 5 (1 week post-treatment), week 8 (1 month post-treatment), and week 16 (3 months post-treatment).

2.6. Planned intervention

After baseline assessment, participants with high FCR will be randomly assigned to receive 4-week rTMS treatment + TAU, or sham stimulation +

TAU. For patients in the rTMS group, we will first determine the intensity of the rTMS protocol by assessing the individual resting motor threshold (RMT). After determination of each individual's RMT, we will apply a single train of low-frequency rTMS over the DLPFC at 1 Hz for a total duration of 30 min (100 % RMT, 2000 pulses). For patients in the sham group, we will apply rTMS over the DLPFS in sham modality.

2.7. Assessment of safety

Studies have reported that the most common adverse effects of rTMS are scalp pain during stimulation and transient headache after stimulation, with the incidence of 35%–40 % and 25%–30 %, respectively [27]. These symptoms are gradually alleviated during treatment and are usually effective to over-the-counter analgesics [27]. In the current study, participant's anxiety, depression, FCR, insomnia, and pain symptoms will be continuously monitored by subjective measurements during treatment and at follow-ups. Any participant who reports worse symptoms after the completion of the intervention will be introduced to receive standard medication and/or psychological treatment.

2.8. Data collection

The research coordinator will obtain consent from all the eligible patients, and collect the baseline data which will include the socio-demographic and clinical characteristics such as gender, age, weight, height, religion, marital status, employment status, education level, financial condition, treatment(s), time since diagnosis, physical comorbidities, etc. Fear of Cancer Recurrence Questionnaire (FCRQ7), Generalize Anxiety Disorder (GAD7), Patient Health Questionnaire (PHQ9), Numeric Rating Scale (NRS), and Insomnia Severity Index (ISI7) will be used to measure individual's FCR, anxiety, depression, pain, and insomnia symptoms. Assessments will be conducted at week 0 (baseline), week 4 (the end of intervention), week 5 (1 week post-treatment), week 8 (1 month post-treatment), and week 16 (3 months post-treatment).

All participants will be contacted by the same research staff throughout the study period. Participants will be invited to scan the QR code through WeChat app to complete the assessment. If the research staff fails to receive a response from a patient after three attempts, the patient will then be marked as 'loss of follow-up'.

2.8.1. fMRI data collection

2.8.1.1. Stimulation materials. We will first select 30 FCR-relevant pictures (e.g., picture of cancer center, ward, cancer-related drugs, radiotherapy and chemotherapy equipment etc.) as stimuli. All pictures will be rated by four independent raters, and the pictures with consistent categories will be selected. Ten independent raters will then classify these pictures according to emotional categories and intensities, and 24 FCR-relevant pictures will then be finally selected. Meanwhile, 24 neutral pictures (e.g., a hat) will be selected from International Affective Picture System (IAPS). Notably, the size and brightness of all pictures will be adjusted as the same.

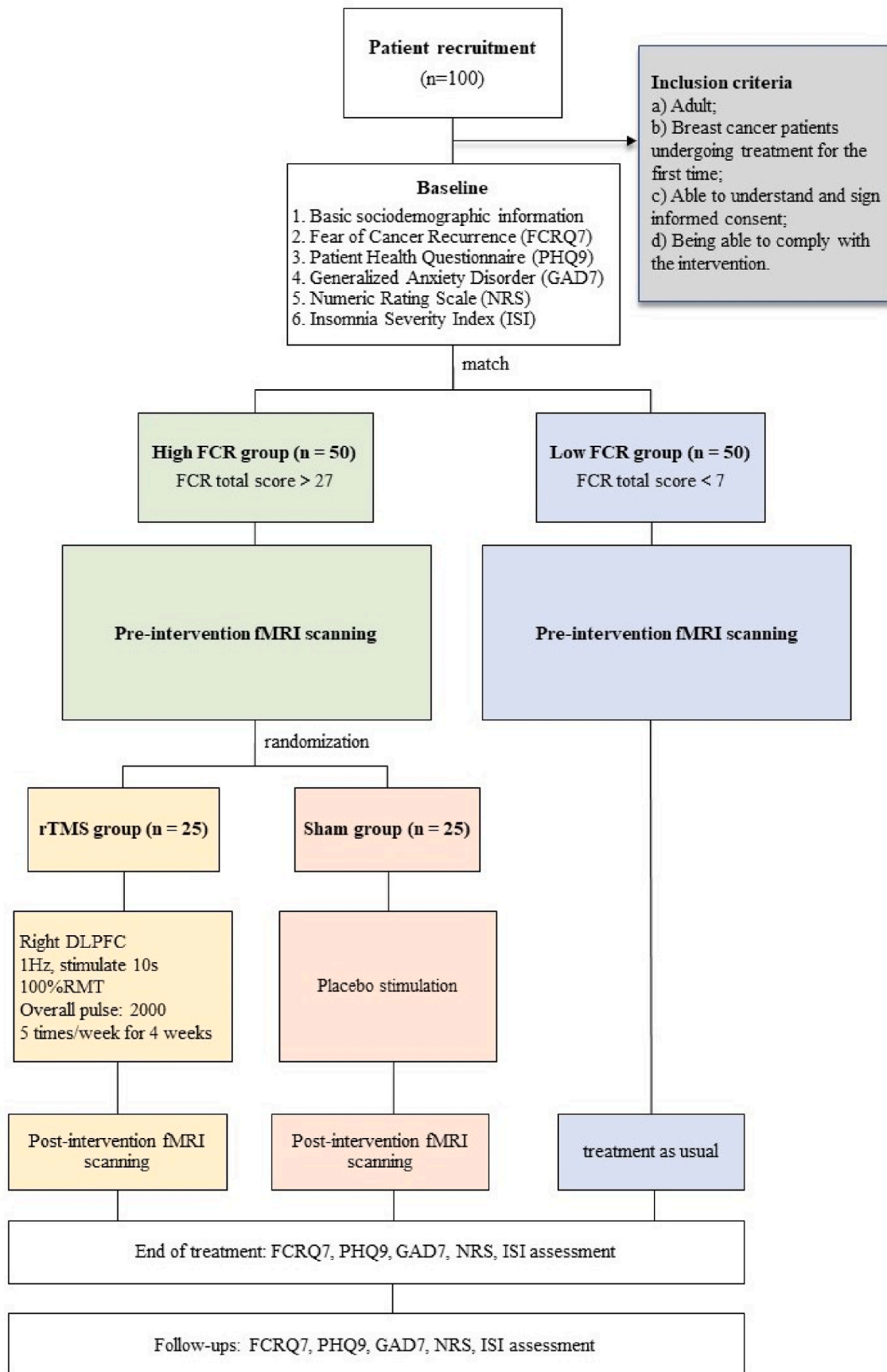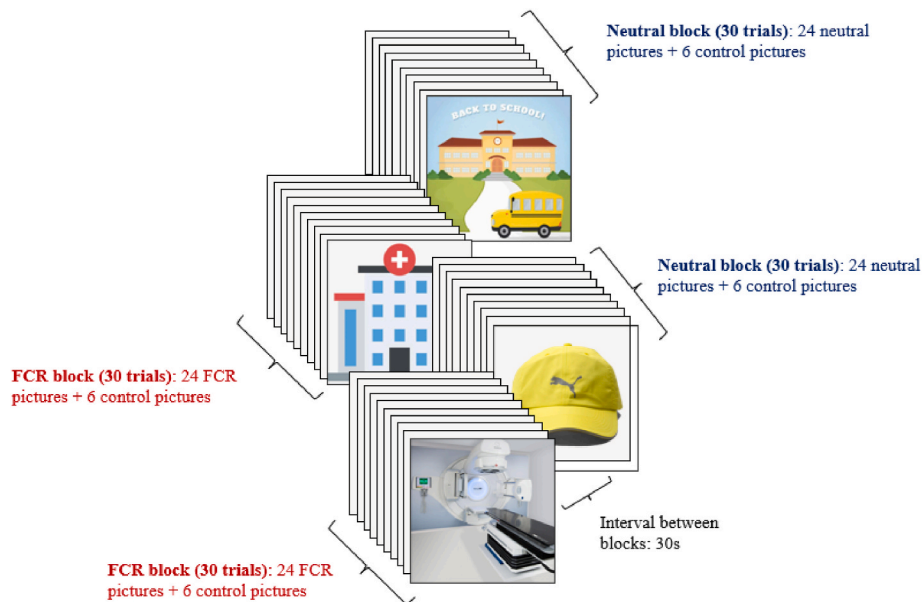24 FCR-relevant picture   24 neutral picture   6 control picture

Fig. 1. Study design.

2.8.1.2. fMRI task. The fMRI task will be presented using block design. A total of 4 blocks (2 FCR and 2 neutral blocks) will be presented (each block owning 30 trials). FCR block and neutral block will be presented alternately, with an interval of 30s between blocks. In each FCR block, 24 trials will present with FCR-relevant pictures, and 6 trials will present with control pictures which will display a random digital number (i.e., number 1, 2, or 3). Similarly, in each neutral block, 24 neutral pictures will be displayed, and control pictures will be presented in 6 trials.

When FCR-relevant or neutral pictures are displayed on the screen (4 s), subjects will be simply asked to maintain attention on these pictures and not response to anything [28]. However, when control picture (the random digital number) is displayed, the participant will be asked to press the corresponding keycard (2 s). The inter-trial interval will be jittered between 5 ± 1 s. During the inter-trial interval (ITI), participants will view a white fixation cross on a black background. If a subject's accuracy response rate of the control trials is lower than 80 %, her data will be removed in the subsequent analysis.

summed up. The score above 27 indicates that the patient has significant fear, which requires certain psychological intervention and treatment. The internal consistency of the Chinese version of the scale has reached 0.87 [30].

3.3. Patient Health Questionnaire (PHQ9)

The PHQ9 strictly conforms to the 9 symptomatic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), with each item scoring 0–3 points and the total value range 0–27 points [31]. PHQ9 can be used for both screening and evaluating the severity of depression. The results of PHQ9 are graded as follows: 0–4: no depression; 5–9: mild depression; 10–14: moderate depression; 15–19: moderate to severe depression; and 20–27: severe depression [32].

3.4. Generalized anxiety disorder (GAD7)

Similar to PHQ9, GAD7 is also a self-rating anxiety scale recommended by DSM-5 for screening and assessing the severity of anxiety in patients [33]. The total score is categorized as follows: 0–4: no gener-

alized anxiety; 5–9: mild generalized anxiety; 10–14: moderate generalized anxiety; and 15–21: severe generalized anxiety [34].

3. Assessment tools

3.1. MRI scanning parameters

MRI scanning will be performed on a 3.0 T scanner (MR Philips, Ingenia CX). fMRI parameters: repetition time (TR) = 800 ms, echo time = 30 ms, slice thickness/gap = 2.4/2.4 mm, in-plane resolution = 220 × 220, field of view (FOV) = 100 × 100 mm, flip angle (FA) = 52°; parameters for 3D-T1-weighted structural imaging were: slices = 192, repetition time = 8 ms, echo time = 3 ms, slice thickness/gap = 1/1 mm, in-plane resolution = 256 × 256, field of view = 100 × 100 mm, flip angle = 8°.

3.2. Fear of Cancer Recurrence Questionnaire (FCRQ7)

This scale has been applied to large-scale FCR studies many times [29]. There are 7 items scored on 5 levels, the total score of each item is

3.5. Numeric rating scale (NRS)

Participant's somatic pain level will be assessed using the "0–10" numeric rating scale (NRS) (i.e., how would you rate your pain at its worst over the past 3 days?) [35], in which 0 means 'no pain' and 10 means 'the worst pain'. Participants will be asked to select a number between 0 and 10, to indicate their current pain level. A total score of 4 or more indicates that the patient is currently suffering from pain [35].

3.6. Insomnia severity index (ISI)

The change in insomnia symptoms will be measured by the insomnia severity index (ISI) [36,37], which assesses the severity, nature, and impact of insomnia. The ISI is a 7-item self-report measure, ranging from 0 (no problem) to 4 (very severe problem). The resulting sum score of the ISI ranges from 0 to 28. Higher scores indicate more severe insomnia symptoms [36,37].

4. Statistical analysis

4.1. fMRI data analysis

4.1.1. Data processing

As we have mentioned above, if the accuracy rate of a subject in control trials is lower than 80 %, the subject will be removed from the subsequent fMRI data analysis. All the fMRI data processing will be performed using DPABI (https://rfmri.org/dpabi) and SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/).

The task fMRI data will be preprocessed as follows: 1) removing the first 3 vol; 2) slice timing; 3) realigned all volumes using all Friston-24 parameters; the subjects with headmotion higher than 3 mm translation or 3 rotations will be excluded. Normalizing to the MNI space using "New segment + DARTEL"; 4) co-registration to the T1 image; 5) normalizing to the MNI space; 5) smoothing using a Gaussian kernel with full width at half-maximum (FHWM) equals to 6 mm. Activation map of both the FCR condition and natural condition will be generated in the native space. The peak activation ROI will be defined as a sphere with 6 mm radius centered at activation peak point. Then, functional connectivity of the activation region of interest (ROI) will be conducted to estimate the connectivity patterns based on dynamic causal modeling (DCM).

The previous 6 preprocessing steps will be conducted as task fMRI except that resting state fMRI will be removed 10 volumes. After that, the fMRI images will be filtered with 0.01–0.1 Hz. The amplitude of low frequency fluctuation (ALFF)/Percent amplitude fluctuation (PerAF) and regional homogeneity (ReHo) will be used to estimate brain local activities. Moreover, the ROI-wise functional connectivity will be calculated to estimate the interactions among DLPFC, amygdala (AMYG) and hippocampus (HIP). Specifically, for the AMYG and HIP, the peak activation areas of these two brain regions will be binarized, and their overlaps with their corresponding templates (Brainnetome Atlas, http://atlas.brainnetome.org/) will be defined as AMYG and HIP region of interests (ROI). The overlap of the activation areas and previously reported left DLPFC will be selected as the left DLPFC, the right DLPFC will be defined as the overlap of the activation areas and the mirror of the left DLPFC [38,39].

For fMRI metrics, two-way ANOVA will be conducted to estimate the group effects (real/sham), the intervention effects (pre-treatment/post-treatment) and their interaction effects on local activity (ReHo/PerAF/ALFF), ROIs-wise FCs and effective connectivity. Moreover, based on the significant group or intervention effects, ROIs were generated for the correlation analysis between fMRI and clinical scores using multilinear regression analysis.

4.1.2. Quantitative data analysis

Descriptive analyses will be conducted to obtain frequencies, means, and standard deviations (SD) (where appropriate). Intention to treat (ITT) will be used for the main efficacy analysis [40]. Independent *t*-test and non-parametrical analyses, where appropriate, will be applied to compare the differences between the two groups. Repeated measurement analysis will be used to compare the changes in symptoms (e.g., FCR total Score) following treatment and at follow-ups. Additionally, the effects of baseline categorical variables on the changes of FCR total scores (dependent variable) will be examined via generalized linear mixed model (GLMM) by restricted maximum likelihood (REML), with the fixed effects of time, age, marital status, education, baseline depression, anxiety and pain, and random effects of subjects [41]. The post hoc comparisons of estimated marginal means of FCRs over time will be estimated with Bonferroni method [26]. A two-side P value $<$ 0.05 will be considered statistically significant. All the statistical analyses will be conducted with SAS software, version 9.4 (SAS Institute Inc., Cary. NC).

5. Ethics and dissemination

An informed consent form will be signed by all participants. Participants will be assured that their participation is completely voluntary, and that their information will be kept confidential. Only the research team will have access to the final data set and make the final decision to terminate the trial if necessary.

6. Patient and public involvement

Patients or the public will not be involved in the design, conduct, reporting and/or dissemination of our research.

7. Discussion

FCR is one of the most prevalent concerns cancer patients report. It can be a concern for cancer patients immediately after diagnosis or treatment; and has been shown to be stable for years for many patients [6,42]. FCR can lead to various negative consequences, such as increased psychological disturbances, poor treatment adherence, amplification of physical symptoms, and increased functional impairment [43]. A previous study showed that low-frequency rTMS could be used in humans to prevent the expression and return of fear, and rTMS treatment could be slightly more effective than psychotherapy and pharmacotherapy in patients with treatment-resistant depression [27]. A randomized controlled study also confirmed that rTMS can help improve patients' anxiety, and insomnia symptoms [44]. In addition, several studies have demonstrated that structural and functional abnormalities of the prefrontal cortex, amygdala and hippocampus play an important role in fear development and reprocessing [21,23,24]. The neuromechanism underlying the effects of rTMS on FCR warrants further investigation.

8. Limitation

Several limitations of this study should be acknowledged. First, the relatively small number of participants included may undermine the universality and representativeness of the results, thereby limiting the applicability of the conclusions. Second, the focus on breast cancer patients alone leads to potential selection bias, which may prevent the results from accurately reflecting the situation of patients with other types of cancer. In addition, as this study will be a single-blind label trial, it is impossible to blind the intervention facilitator. Finally, only self-report measurements will be used in this study. Further studies using objective measurements, such as actigraphy and polysomnography to assess sleep quality would be beneficial.

Ethical approval

This study was performed in accordance with the Helsinki standard and the study's protocol was approved by Guangdong Provincial People's Hospital Research Ethics Committee (ref No: KY-N-2022-136-01).

Consent for publication

Not applicable.

Availability of data and materials

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Strengths and limitations

- Participants in experiment group will be randomly allocated using computer-generated random numbers.
- An independent researcher will implement randomization and treatment allocation through an automated online system.
- Data analysts will be blinded to group allocation and to the research assistants.

CRediT authorship contribution statement

Wenjing Xu: Writing – original draft. **Na Zhao:** Writing – original draft. **Wengao Li:** Investigation, Formal analysis, Data curation. **Lirong Qiu:** Investigation, Formal analysis, Data curation. **Xian Luo:** Investigation, Formal analysis, Data curation. **Yuanyuan Lin:** Investigation, Formal analysis, Data curation. **Wenjing Wang:** Investigation, Formal analysis, Data curation. **Samradhvi Garg:** Writing – review & editing. **Hengwen Sun:** Writing – review & editing. **Yuan Yang:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no competing interests.

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