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STUDY PROTOCOL

Efficacy of Magnetic Seizure Therapy in Patients with Schizophrenia and Combined fMRI-EEG to Explore the Regulatory Mechanisms of Brain Networks

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Background: Magnetic Seizure Therapy (MST) is an emerging psychiatric physical therapy in recent years, and the MST technique induces seizures by stimulating the local cortex. Numerous studies have shown that compared to electroconvulsive therapy (ECT), magnetic shock therapy (MST) has relatively little effect on cognitive function, and thus has certain advantages in clinical application. However, as far as magnetic shock therapy itself is concerned, there are few studies specifically focusing on its efficacy in depth, and the mechanism of MST in treating schizophrenia is still unclear.

Methods: This study centered on the key question of "the efficacy of magnetic stunning therapy for patients with schizophrenia and the combined fMRI-EEG to explore the regulatory mechanisms of brain networks". The study protocol describes our interventional clinical trial aimed at developing magnetic convulsive therapy as an effective and safe treatment for SCZ. The study population consisted of SCZ patients and healthy controls (Hc). Clinical symptoms, cognitive function, EEG and fMRI data were collected from the patient group at baseline, post-treatment and follow-up phases. We systematically assessed the clinical features and cognitive functions of the patients, combined with EEG and fMRI indexes to explore the brain network connectivity abnormalities in SCZ patients, and jointly explored the neuroimaging mechanisms in SCZ patients.

Conclusion: Positive results from this trial may have a direct and significant impact on patients with SCZ. Once the MST demonstrates significant antipsychotic efficacy with high perceived safety, it will have significant implications for clinical practice. Brain network abnormality may be one of the core pathological mechanisms of SCZ. Therefore, by combining neurophysiological imaging techniques to scientifically verify the abnormality of SCZ brain network, the elucidation of this issue can help to further reveal the pathological mechanism of SCZ and provide a scientific basis for the effective and precise treatment of the disease.

Trial Registration: ChiCTR2000038361 Registered on September 21, 2020.

Keywords: Schizophrenia, Magnetic Seizure Therapy, Electroencephalogram, Functional Magnetic Resonance Imaging

Introduction

Schizophrenia (SCZ) is a mental illness characterized by delusions, disturbed speech, hallucinations and impaired executive functioning. It affects approximately 1% of the world's population and is one of the top ten causes of disability worldwide.[1] SCZ is also widely recognized as a disorder of abnormal brain connectivity. Numerous studies have shown that people with SCZ almost always exhibit impaired structural connectivity.[2–4] There is now a growing body of research

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realizing that the symptoms of schizophrenia are not only related to brain structure, but potentially to disruption of the integrated network of brain regions. In previous imaging studies of SCZ, it has been shown that increased activation of the visual attention network (VAN) and decreased activation of the default mode network (DMN) and the cognitive appraisal network (CAN) has been observed in SCZ, especially in patients with significant delusions.[5,6] Higher-level cognitive processes, such as reasoning and executive functioning, and social cognition tend to be associated with more networks in patients with SCZ than in those in other cognitive domains.[7] A functional neuroimaging review published in 2019 found that patients with treatment-resistant schizophrenia (TRS) exhibited abnormalities in several brain networks, including the frontotemporal lobe networks, auditory networks, temporoparietal associative networks, default mode networks, subcortical networks, limbic system-corticostriatal networks, and cortico-striatal networks. These networks were generally characterized by extensive brain activation and abnormal connectivity patterns.[8]

Magnetic Seizure Therapy (MST) is an emerging psychiatric physical therapy in recent years. The MST technique utilizes transcranial magnetic stimulation to continuously stimulate the cerebral cortex with a high-frequency strong pulsed magnetic field. It induces seizures by stimulating the local cortex. Compared with electroconvulsive therapy (ECT), MST can induce electrical currents more accurately on the surface area of the cerebral cortex and selectively stimulate the localized cerebral cortex without affecting the deep brain nuclei.[9] In a small sample study that included 8 SCZ patients who underwent MST only, significant improvements in clinical symptoms and quality of life were reported without significant cognitive side effects.[10] In a randomized controlled trial of ECT for SCZ, MST was shown to have antipsychotic efficacy similar to that of short-pulse bilateral temporal lobe ECT, with fewer effects on cognitive impairment.[11] Previous studies have shown that MST has a certain modulating effect on the brain structure of SCZ patients. 2023 The Suzhou team found that PANSS scores of SCZ patients decreased significantly after MST, while immediate and delayed memory did not show any significant changes and MRI results showed that the volume of hippocampal sub-structures changed less. Therefore, this may be related to the cognitive preservation mechanism of MST.[12] However, limited research has been conducted on the mechanisms that regulate brain networks. Despite the initial recognition of the potential of MST as an alternative to ECT, there are only a limited number of studies that have specifically explored the efficacy of MST on its own. With this in mind, the aim of our study was to explore the effect of MST on SCZ improvement using sham stimulation and a healthy population as a control group. Meanwhile, the brain network is regarded as a potential biomarker for in - depth analysis.

Approach/Design

This study strictly complies with the ethical principles of the Declaration of Helsinki, ensuring that the health and rights of all subjects are the top priorities in all research activities. Before the commencement of the study, all subjects signed informed consent forms, fully understanding the purpose, methods, potential risks, and benefits of the research, and they had the right to withdraw from the study at any time. The research protocol has been reviewed and approved by the Ethics Committee of the First Hospital of Shanxi Medical University (Approval No.: KX002). During the research process, we strictly abided by the guidance and supervision of the Ethics Committee to ensure the scientific and ethical nature of the research. This trial was registered with the China Clinical Trial Registry, with the identification code ChiCTR2000038361. Sample collection was performed at the Department of Mental Health, the First Hospital of Shanxi Medical University.

Recruitment and Retention

Two groups of subjects, SCZ patients and healthy controls (Hc), were to be included in this study. The SCZ group was into MST and pseudostimulation groups. All enrolled subjects participated voluntarily and signed informed consent. The specific inclusion and exclusion criteria are shown below:

Inclusion Criteria

A. Patients with schizophrenia: 1) 18–50 years of age. 2) Right-handed. 3) Diagnosed by at least 2 attending psychiatrists according to the Structured Clinical Interview for DSM-5-Clinician Version (SCID-5-CV). 4) Positive and Negative Symptom Scale (PANSS) scores ≥ 60 at the Screening Interview and the Baseline Interview.

B. Healthy controls: 1) Age 18–50 years. 2) Right-handed. 3) Does not meet the diagnostic criteria for any mental disorder as assessed by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), Structured Clinical Interview for DSM-5-Clinician Version (SCID-5-CV). 4) There were no other neurological disorders in third-generation relatives. 5) Matched to the case group by age, sex, and years of education.

Exclusion Criteria

A. Patients with schizophrenia: 1) Have a major physical illness, unstable physical illness, or a history of craniocerebral trauma. 2) Meet DSM-5 for any of the mental disorders other than a diagnosis of schizophrenia. 3) Have alcohol or drug abuse within the three months prior to screening or drug dependence within the previous six months. 4) Patients who are allergic to anesthetic and muscle relaxant medications. 5) Previously treated with MST. 6) Have significant abnormal laboratory test results. 7) Without a guardian. 8) Pregnant or breastfeeding women, or those who plan to become pregnant. 9) Have a contraindication to magnetic resonance imaging.10) Have participated in another clinical trial within 30 days.

B. Healthy controls: 1) Exclude individuals with any history of mental illness (including but not limited to SCZ, depression, anxiety disorders, etc) or neurological diseases (such as epilepsy, cerebrovascular diseases, brain tumors, etc). 2) Exclude individuals with severe physical illnesses, such as uncontrolled hypertension, diabetes, cardiovascular diseases, hepatic and renal insufficiency, etc. 3) Exclude individuals who are taking medications that may affect the function of the central nervous system, such as antipsychotic drugs, antidepressant drugs, sedative - hypnotic drugs, central stimulants, etc. 4) Exclude individuals who show obvious cognitive impairment or mood disorders in standardized psychological tests. 5) Exclude individuals with a history of alcohol or drug abuse, as well as those with a history of head trauma that has led to loss of consciousness or left neurological sequelae.

Withdrawal Criteria

Subject or family member requests to withdraw from the study; intolerance of MST occurs during the course of the study.

Randomization and Blinding

This study used a non-randomised and single-blind design. The choice of non-randomisation was mainly based on practical considerations. The group of patients with schizophrenia is unique, with a wide range of factors such as severity of illness, previous treatment history, and individual adherence. If randomised grouping is adopted, a large number of eligible patients may be excluded in the process of screening and recruiting patients due to the need to rigorously match numerous complex factors, which in turn makes it difficult to achieve the ideal sample size and affects the reliability and generalisability of the study results. By setting rigorous inclusion and exclusion criteria, the homogeneity of enrolled patients was ensured as much as possible, and confounding factors were controlled to a certain extent.

In terms of the single-blind design, a series of measures were taken to ensure blinding. During the course of the study, participants were unaware of whether they were receiving MST treatment or sham stimulation. To achieve this, the sham-stimulation group was set up to rotate the stimulation coil 180 degrees so that the magnetic field penetrating the brain was extremely weak and considered to have no therapeutic effect. During implementation, the treatment process was explained in detail to the participants by the therapists without mentioning the grouping. For researchers who assessed patients' clinical symptoms and cognitive function, we similarly did not inform them about the grouping of participants to reduce subjective bias in the assessment process. This blinded design can effectively reduce the expectation effect of participants and evaluators due to the knowledge of the grouping, so that the results of the study can more realistically reflect the therapeutic effect of MST.

Informed Consent

Informed consent for this trial describes in detail the electrophysiology, image acquisition, and any risks associated with the study. In addition, a verbal explanation suitable for individual understanding is provided, including a brief overview of the MST procedure. Written documentation of informed consent is provided for this additional.

Organization of the Study

According to the SCZ intervention, patients were categorized into MST and sham stimulation groups. The patients in the MST group should have completed 8–12 treatments after enrollment. Patients were assessed for clinical symptoms, cognitive function, EEG and MRI data acquisition at baseline and at the end of 4 and 8 weeks of acute treatment, and were followed up to the end of 12 weeks.

Treatment

The MST treatment was performed by a physician with the title of attending physician or above in the Department of Mental Health of the First Hospital of Shanxi Medical University. MST Group: The treatment was performed with the MST device (Mag Super Super Magnetic Stimulator, Wuhan Iridium New Technology Co., Ltd.) manufactured by Wuhan Iridium, with the maximum frequency of 100 hz and the maximum stimulation time of 10s. The MST was accompanied by the MST round coil, which was located in the middle of the frontal parietal area. The stimulation position was the middle part of the frontoparietal area, so that the stimulation point was close to the bilateral motor cortex, which was easier to induce convulsions without affecting the rest of the brain areas. During the treatment, positive pressure oxygen was administered artificially, and the oxygen saturation was kept above 95%. After the patients signed informed consent, we made preoperative preparations, communicated with the patients, relaxed, and eliminated the patients' nervousness; the patients were lying on their backs, the venous access was opened, the cardiac monitoring was connected, the local skin was cleaned, and the oxygen was continuously administered by the masks; we chose the "MST mode"-setting the parameter "Frequency 100 hz, intensity 80–100%, time parameter is adjusted according to the patient's age and other characteristics (stimulation time 6–10s)"; 2–4 minutes before the treatment, according to the patient's ECG data, intravenously inject 0.5–1.0mg of atropine; use of anesthesia drugs: intravenously inject propofol (1–2mg/kg) Give succinylcholine (0.5–0.6mg/kg) until the patient's consciousness disappears and the transient reflex disappears, put in the mouth protector, with earplugs, and connect the electroencephalography equipment, the injection can be seen in the patient's eyes and face, mouth and whole body muscle twitching and muscle relaxation, and the spontaneous respiration stops in about 1 minute, then it is the best time to stimulate; get the consent of the anesthesiologist and the operation nurse and then press the therapeutic button; after the seizure stops, continue to assist ventilation After the seizure stops, continue assisted ventilation until the patient resumes spontaneous respiration; observe the patient for at least 30 minutes to prevent falls and return to the ward after the signs are stable.

Pseudostimulation group: In the control group, the design of the intervention in the sham stimulation group was highly consistent with that of the MST group, Prior to treatment, uniform pre-treatment preparations were performed for all devices. In the anesthesia drug injection session, the sham group received the same drug injection arrangement as the MST group. The sham group was identical to the MST group in terms of drug type, dose, injection apparatus, injection site, and injection technique. The sham stimulation group was designed to simulate the MST procedure. The simulated treatment device produces an electromagnetic sound similar to that of the MST treatment, and the coils are rotated 180 degrees so that the magnetic field penetrating the brain is very weak and does not actually produce a magnetic field that would effectively stimulate the brain (Figure 1).

The HC group did not receive MST and sham stimulation in this study.

Clinical Assessment Tools

Scale assessments and cognitive assessments were completed by consistently trained psychiatric professionals. 1. Clinical symptom assessment tool: a detailed history was taken along with age of onset, duration, and treatment history. The Positive and Negative Symptom Scale (PANSS) was used to assess the presence or absence of positive, negative, and general pathologic symptoms and the severity of each symptom. The Clinical General Impression (CGI) was used to assess the overall functioning, the Side Effects Scale (UKU) was used to assess the side effects, and the Personal and Social Functioning Scale (PSP) at was used to assess the social functioning of the patients. 2. Cognitive functioning assessment tools: The MATRICS Consensus Cognitive Battery (MCCB) was used to assess cognitive functioning. The MATRICS test consists of 9 items: The Connectivity Test (TMT); Brief Cognitive Assessment of Schizophrenia: Symbol

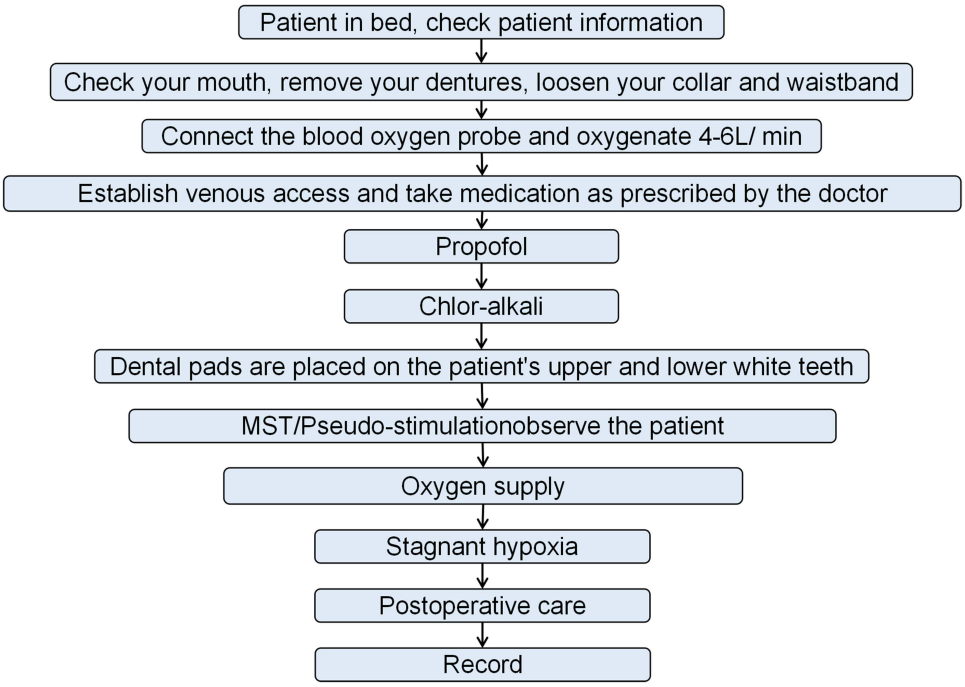

Figure 1 Treatment flow chart.

Coding (BACS-SC); Hopkins Word Learning Test (HVLT-R); Wechsler Memory Scale - Third Edition (WMS-III): Spatial Breadth; Neuropsychological Assessment Battery (NAB): Mazes; Visual Learning Assessment - Brief Visual Memory Test (BVMT-R); Category Fluency Test (CF): Animal Naming (Fluency); Measures of Emotional Intelligence: Emotional Management (MSCEIT); Continuous Operations Test - Identical Pairs (CTP-IP).

Resting-State EEG, MRI Data Acquisition

Resting-State EEG Acquisition

This experiment was conducted in a soundproof, airtight, temperature-controlled EEG acquisition room. Subjects sat comfortably and relaxed in the soundproofed, airtight, temperature-controlled EEG acquisition room, and the acquisition was performed with eyes open and closed for 5 minutes each. Resting EEG was recorded by a 64-channel/electrode system using a Neuroscan acquisition system (Compumedics, Abbotsford, VIC, Australia). The 64-Ag/AgCL electrode caps were based on the International 10–20 system. Reference electrodes were placed on the binaural mastoids (M1, M2) and the parietal lobe was placed squarely on the ground electrode (GND). The resistance of the reference electrode to the scalp lead was 5 kq. The sampling rate (A/D) was 1000 hz, the low-pass filtering frequency was 0.05 hz, and the high-pass filtering frequency was 70 hz. Reference M1 and M2 electrodes were collected for offline processing. Prior to the experiment, subjects were asked to wash and blow-dry their hair and rub their nipples and foreheads with alcohol to reduce skin resistance. The forehead was rubbed with alcohol to reduce skin resistance.

Resting-State MRI Acquisition

Subjects were required to be quiet, eyes closed, breathing steadily, with the body in a relatively comfortable position, without any movement of the limbs and without any thinking activities. Brain MRI was performed using a Magnetom Skyra 3.0T MRI scanning instrument manufactured by Siemens AG, Germany-Erlangen, applying a standard head coil for radiofrequency emission and reception of MRI signals.

Scanning Sequence

(1) Resting-state fMRI: echo planar imaging (EPI) sequence, 220 scans in axial position, 47 layers, layer thickness=3mm, layer spacing=0mm, TR=2620ms, TE=30ms, acquisition matrix=64×64, FOV=192×192mm2, FA=90°. (2) Conventional

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T2-weighted image: axial scan, 21 layers, layer thickness=5mm, layer spacing=0mm, TR=9000ms, TE=85ms, acquisition matrix=64×64, FOV=230×230mm2, FA=90°, used to exclude the presence of intracranial organic lesions. (3) Whole brain 3D high-resolution T1-weighted image: T1-weighted 3D magnetized intensity preparatory gradient echo sequence (T1WI 3D MP-RAGE sequence), sagittal scanning, 192 layers, layer thickness=1mm, layer spacing=0mm, TR=1900ms, TE=3.97ms, acquisition matrix=64×64, FOV=192×192mm2, FA=85°, used to exclude the presence of intracranial organic lesions. 192mm2, FA=8° (Figure 2).

Results

The aim of this experiment was to test the efficacy of MST in terms of improving symptoms of schizophrenia and to explore the neuroimaging mechanisms of MST in the treatment of SCZ through a combined fMRI - EEG study. Therefore, we propose the following hypothesized results:

(1) MST is effective in improving the symptoms of schizophrenia with minimal effects on cognition.

(2) MST produces therapeutic effects on SCZ by modulating brain networks.

Statistical Methods

To achieve the main objectives of this study, the following between - group comparison strategies were constructed:

Baseline Comparison

At the initial baseline stage of the study, a comprehensive comparison was made between the SCZ patient group and the HC group in terms of multiple indicators such as brain network connectivity, clinical symptoms, and cognitive function. The data were statistically analyzed using the SPSS 23.0 software package. Continuous variables were expressed as mean±standard deviation (when the data were normally distributed) or median and interquartile range (when the data were not normally distributed). If the data showed a normal distribution, t - tests were used to compare the differences in the means of the two groups in specific frequency bands of the resting - state EEG power spectrum; if the data did not meet the conditions for normal distribution, non - parametric tests were used to analyze the differences between the two groups. These baseline differences provided key reference points for subsequent assessment of the efficacy of MST.

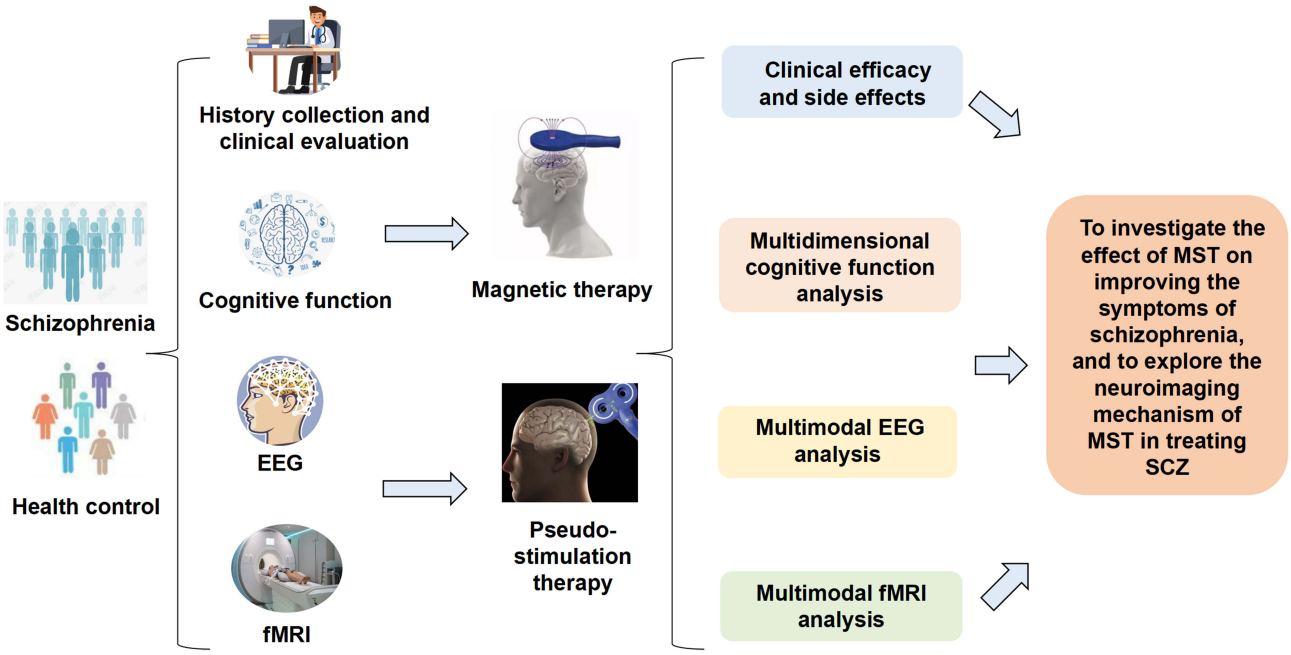

Figure 2 Diagram of the research model.

Within - Patient - Group Comparison Before and After Treatment

The SCZ patients were randomly divided into the MST group and the sham - stimulation group. During the treatment, data on clinical symptoms, cognitive function, EEG, and fMRI were collected from both groups at baseline, 4 weeks after treatment (at the end of the treatment course), 8 - week follow - up, and 12 - week follow - up. The changes in various indicators before and after treatment in the MST group were compared to determine the effects of MST treatment on the brain network connections and clinical symptoms of SCZ patients. At the same time, the changes in the indicators before and after treatment in the sham - stimulation group were compared to exclude the interference of factors such as time and natural recovery. Repeated - measures analysis of variance (ANOVA) was used to analyze the main effects of time factors (different time points) on dependent variables (such as clinical symptom scores, EEG - and fMRI - related indicators, etc), as well as the interaction effects between time and treatment modality (MST treatment or sham stimulation). According to the data distribution, methods such as Pearson correlation, Spearman correlation, and regression analysis were used to analyze the correlations between indicators at each level and demographic, clinical, cognitive, brain network connection, and other indicators, reflecting the phenotypic characteristics of each group of study subjects at different levels.

Between - Patient - Group Comparison Before and After Treatment

The SCZ patients were randomly divided into the MST group and the sham - stimulation group. During the treatment process, data on clinical symptoms, cognitive function, EEG, and fMRI of the patients were collected at baseline, the end of 4 - week treatment, and the end of 8 - week treatment. By using independent - samples t - tests or non - parametric tests to compare the changes in these indicators before and after treatment between the MST group and the sham - stimulation group, the differences in the efficacy of MST compared to sham stimulation in improving schizophrenia symptoms, cognitive function, and regulating the brain network could be directly evaluated.

Comparison Between the Patient Group and the HC Group After Treatment

At the end of the treatment, the patients in the MST group and the sham - stimulation group were compared with the HC group again. Observe whether the brain network connections and clinical indicators of SCZ patients after treatment are closer to those of the HC group. Here, if the data are normally distributed, independent - samples t - tests can be used to compare the differences between the two groups; if the data are not normally distributed, non - parametric tests are used. If the differences between certain brain network connectivity indicators in the MST group and the HC group are reduced compared to the pre - treatment level and the clinical symptoms are significantly improved, it further supports the regulatory effect of MST on the brain network of SCZ patients and the therapeutic effect of MST.

Sample Size

At present, domestic and international research on MST for schizophrenia is still in the preliminary stage, and the reported clinical case studies are small samples, taking α=0.05 (taking bilateral), 1-β=0.9, and according to the schizophrenia MST group and the pseudostimulation group in the ratio of 1:1, the sample size of 48 cases in each group was calculated by using the PASS software. And considering a 10% dropout rate, 52 schizophrenia patients were finally included in each group, and a total of 104 schizophrenia patients were included in the 2 groups. The cross-sectional study also matched 104 healthy controls.

Quality Control

EEG Data Analysis

Preprocessing: the data were preprocessed using EEGLAB. Before processing, the EEG data were examined to remove some trials with obvious artifacts and interpolate the bad electrodes. The data of all subjects were band-pass filtered in the range of 0.1 ~ 70 hz with a sampling rate of 1000 hz. The data recorded by EEG were segmented every 2 s, and then the artifacts such as detector glasses, myoelectrics, cephalic side, and defective electrodes were rejected by using independent component analysis (ICA). Finally, trials with voltage amplitudes exceeding 100 μV were removed from artifacts by polarization and re-referenced.

Data analysis: (1) Source localization analysis: Using the FieldTrip toolbox to calculate the inverse solution based on the potential signals recorded from the head table using the minimum number of exemplars (MNE), the location, direction, and intensity information of the estimated source of neural activity in the brain was back-projected. (2) Power Spectrum Analysis: Using Fast Fourier Transform, the original time-domain EEG signals (time on the horizontal axis, voltage values on the vertical axis) are converted to the frequency domain (frequency on the horizontal axis, power on the vertical axis; each frequency point represents a power value), and the intensity of the activity at each frequency point can be calculated, which in turn yields the intensity of each frequency band. (3) Connectivity analysis: Coherence, phase synchronization and other indicators are used to analyze the information communication between the subject's channels and channels, taking into account the interconnection between electrodes and electrodes (brain area and brain area).

MRI Data Analysis

Based on the MATLAB2013b (MathWorks, Sherborn, MA) platform, voxel-based morphometry (VBM) software VBM8 (http://dbm.neuro.unijena.de/vbm8/), statistical parameter mapping (Statistical Parameter Mapping (SPM) software SPM12 (http://www.fil.ion.ucl.uk/spm/), REST software (RESTing-state fMRI data analysis toolkit, http://resting- fmri.sourceforge.net), and DPARSF software (http://rfmri.org/DPARSF) were used for the routine preprocessing of resting-state fMRI image data, such as time-layer correction, head-motion correction, spatial normalization, smoothing, and de-embedding of linear trends, as well as the calculation of basic metrics; and Freesurfer image analysis software package (version 5.0.1) was used for the analysis of the resting-state fMRI image data.

Validity and Safety Evaluation

PANSS and CGI were used to evaluate symptomatic changes, UKU to evaluate side effects, PSP to evaluate social function, and MATRICS to evaluate cognitive function. According to the outcome of treatment, patients can be categorized as: A. Significantly effective (≥50% reduction in the corresponding disease scale and PANSS, most of the overall severity of the disease has been reduced, and the clinical judgment is that the disease has been significantly relieved, and most of the social functions have been restored); B. Partially effective (corresponding to the disease scale and PANSS reduction rate <50% and ≥30%, clinical judgment of partial remission of the disease, the overall severity of the disease has not been alleviated, social function partially recovered; C. Ineffective (corresponding to the disease scale and the PANSS reduction rate <30%, clinical observation of the disease has not been alleviated, the overall severity of the disease has not been alleviated, social function did not recover). At the same time, the awake time, orientation recovery time and the occurrence of adverse events were recorded, and the patients were equipped with corresponding emergency measures (Figure 3).

Discussion

Positive symptoms of SCZ, such as delusions and hallucinations, are associated with false salient attributions. In contrast, negative symptoms, such as apathy and poor socialization, may be associated with dysfunction of brain networks. Dysregulation of cognitive control systems is thought to be a driver of cognitive and clinical impairment in SCZ. Current studies on neuroimaging have identified functional abnormalities in multiple brain regions in SCZ that are not limited to a single brain region, but are more often caused by abnormal functional connectivity and communication between brain regions.[13] The Default Mode Network (DMN) is a network of brain regions that are active when the brain is at rest, covering areas such as the medial prefrontal cortex, posterior cingulate cortex, and angular gyrus. Under normal conditions, the DMN is involved in cognitive functions such as self-reflection, introspection and memory extraction. However, in patients with SCZ, the DMN function is abnormal. With the help of rs-fMRI, the DMN was found to be hyperactive and hyperconnected at rest, which may cause the patients to overfocus on their own internal experiences and thoughts, leading to positive symptoms such as delusions.[14] The study also showed that the strength of functional connectivity between key brain regions in the DMN, such as the medial prefrontal cortex, posterior cingulate cortex, and precuneus, was significantly weaker in SCZ patients than in healthy individuals. This can lead to impaired information transfer and errors in the brain's processing and integration of information, triggering positive symptoms such as hallucinations, where the patient may hear or see things that are not there, which may be related to the DMN's inability

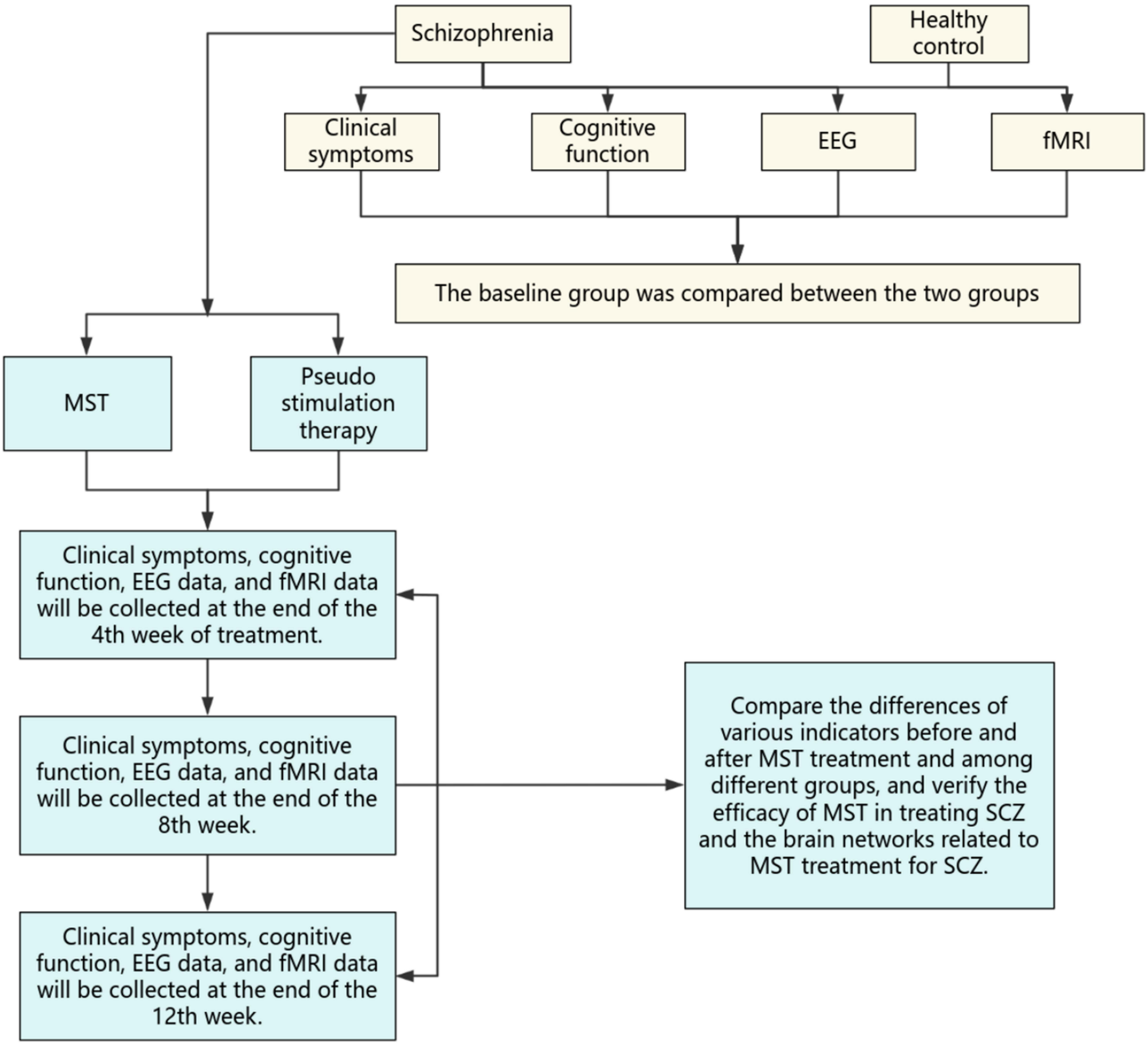

Figure 3 Flow chart of population-level research.

to properly inhibit extraneous sensory inputs or incorrectly integrate them. The negative symptoms of SCZ are often thought to be related to prefrontal cortex dysfunction.[15] Using a task measuring target neglect combined with fMRI, one study found that patients with SCZ who had significant negative symptoms had lower activation in the left prefrontal cortex, right dorsolateral prefrontal cortex, bilateral anterior insula, and bilateral subparietal lobule compared with healthy controls, and that patients with significant negative symptoms had reduced activation in the left prefrontal cortex, left dorsolateral prefrontal cortex, and left subparietal lobule compared with patients without negative symptoms, suggesting that left prefrontal cortex, left dorsolateral prefrontal cortex, and left subparietal lobule activation is reduced in patients with significant negative symptoms. This suggests that reduced activation in regions such as the left prefrontal cortex may be a factor related to brain function in SCZ negative symptoms.[16] In healthy individuals, functional connectivity of the frontoparietal control network (FPCN) predicts memory inhibition, and abnormalities in this functional connectivity in patients with SCZ may lead to decreased memory inhibition, which in turn affects cognitive function.[17] Taken together, abnormal functional connectivity of specific brain networks plays a key role in both positive

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and negative symptoms of SCZ. In-depth study of these functional connectivity mechanisms is expected to provide new ideas and methods for the diagnosis and treatment of SCZ.

Antipsychotics, as the first-line regimen for the treatment of SCZ, have been effective in controlling positive symptoms, but the adverse effects of traditional medications as well as the problem of treatment resistance in some patients have limited their application. In contrast, transcranial magnetic stimulation (TMS), especially repetitive transcranial magnetic stimulation (rTMS), has been shown to be effective in improving negative symptoms and cognitive functioning in patients with SCZ, but the efficacy of the treatment is relatively mild. For patients with severe symptoms, rTMS is often difficult to achieve the desired therapeutic effect.[18] ECT, as an effective option for medication-resistant patients, may lead to cognitive decline, especially in the early stages of treatment, although it can significantly reduce the total PANSS score and the scores of various subscales.[19,20] More and more studies have confirmed tha- t the clinical application of MST is very promising. Some studies have found that MST and MECT have comparable efficacy in the treatment of SCZ and MDD, respectively, and have less impact on cognition.[21,22] In addition, MST also plays an important role in the treatment of bipolar disorder, and can significantly improve the suicidal ideation of patients, which is of great significance in reducing the risk of suicide and improving the quality of life of patients with bipolar disorder.[23] MST is a promising alternative treatment option for patients who are not responding well to medication or who have a high need for cognitive protection.[11] However, more protocols are currently being studied in comparison with MECT, the number of trials of the benefits of MST is limited, and the underlying mechanisms of MST are unclear. Previous studies have found that changes in brain networks, such as a significant increase in theta connectivity in frontal and parieto-occipital channels, can be observed after MST relieves symptoms in depressed patients.[24] And increased functional connectivity between the submandibular anterior cingulate cortex (sgACC) and parietal cortex after MST treatment. Decreased functional connectivity between the right anterior hippocampus and prefrontal cortex was associated with less clinical and cognitive improvement.[25] Although the study targeted patients with major depressive disorder, the regulation mechanism of brain functional networks may have some similarities in patients with schizophrenia. Therefore, in the actual treatment, the specific pattern of abnormal brain network of patients can be clarified through neuroimaging technology, and if the brain network of a patient is found to be changed, the MST stimulation parameters can be adjusted to change the stimulation intensity, stimulation frequency or stimulation site, so as to accurately improve the abnormal brain network connection and alleviate the symptoms. For patients with low overall brain network function, brain network-related indicators can be used as biomarkers for treatment effect prediction and prognosis assessment. Pre-treatment acquisition of patients' brain network data by neuroimaging technology to predict their therapeutic response to MST.

In summary, if MST can effectively alleviate the psychotic symptoms of SCZ while having a smaller impact on cognition, more patients may agree to try this treatment. Based on the combined multimodal EEG-fMRI technique to explore whether there are abnormal brain network loops in SCZ patients, and whether MST treatment affects SCZ patients by targeting the modulation of the loops, it will provide an important basis for the effective treatment of SCZ and the precision treatment.

Experimental State

The study was registered on September 21, 2020 (ChiCTR2000038361), recruited on December 31, 2020, and enrollment is expected to be completed by December 2024.

Protocols.io: https://www.chictr.org.cn/showproj.html?proj=61456.

Data Sharing Statement

The final dataset generated from the current protocol will be available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Ethical approval was obtained from the Ethics Committee of the First Hospital of Shanxi Medical University. All participants provided written consent to participate in the trial using the Study Consent Document, and participants were provided with a complete consent form detailing the study intervention, study procedures, and risks.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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