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Functional MRI in the Effect of Transcranial Magnetic Stimulation Therapy for Patients with Schizophrenia: A Meta-analysis protocol

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Date of this study
This study has not started yet. Study selection process will be conducted in April 2020. Date of data extraction will be started on 1st April 2020 and will be intended to finish by 10th May 2020. Data analysis will be completed by 10th June 2020. The results of this study will be intended to be submitted in a peer-reviewed journal by 20th August 2020.

ABSTRACT

Introduction Schizophrenia is a psychiatric illness associated with brain function alterations and varying degree of treatment resistance, often leading to severe social malfunctioning. In recent decades, numerous studies have been investigating the therapeutic potential of transcranial magnetic stimulation (TMS) as a noninvasive therapy for schizophrenia. However, its clinical efficacy remains controversial, as a number of clinical trials indicated moderate therapeutic effect while others failed to reproduce the positive result. Moreover, the neurobiological mechanism of action remains unclear, possibly constricting the application of TMS in clinical practice. The present protocol of meta-analysis aims to investigate the TMS-related functional neuroimaging (i.e., functional magnetic resonance imaging, fMRI) features and alterations in schizophrenic subjects, and to discuss the potential of fMRI in TMS researches.

Methods and Analysis We search in the following databases: PubMed, Embase, OVID, China National Knowledge Infrastructure (CNKI) and Wanfang Data, from their respective dates of inception to May 1, 2020, with language restricted to English and Chinese. Studies focusing on the brain functional alterations in patients with schizophrenia treated by TMS will be retrieved. The study selection process will follow the Preferred Reporting Items for Meta-Analyses guideline and quality assessment will be conducted with a customized checklist. Data will be doubly extracted by two independent reviewers using a standard data extraction spreadsheet, any inconsistency between reviewers will be reconsidered and the result determined by the third reviewer. Data will be reported following PRISMA guidelines.

Ethics and Dissemination Ethical approval is not required as primary data will not be collected. This review will be published in a peer-reviewed journal.

Strengths and limitations of this study

1.This is a novel systematic review and meta-analysis focusing particularly on brain fMRI in the TMS therapy for schizophrenia.

2.This study will be informative to evaluate the clinical efficacy and shed light on the neural substrate of action.

3.The result may help to design effective TMS regimen for schizophrenia, with optimal stimulation intensity, frequency and target.

4.The limit of this study may be connected with high levels of heterogeneity between studies, which affects the external validity.

5.We use public data that will be freely available after publication.

Introduction

Known for its prominent psychotic symptoms such as hallucination and delusion, schizophrenia (SZ), with a lifetime prevalence of 0.30% to 0.66% in the general population,[1-3] is a severe psychiatric illness that tends to be chronic and recurrent, leading to varying degrees of cognitive impairment and social disability.

Considering a substantial proportion of patients are resistant to first-line antipsychotics, pharmacological interventions are sometimes insufficient in the treatment for SZ.[4] As a noninvasive neurostimulation technique, transcranial magnetic stimulation (TMS) seems to be a promising add-on therapy that regulates brain function in an effective and safe manner by activating or suppressing neural activity, even though the evidences are controversial. A number of previous studies have confirmed the role of TMS in the treatment of cognitive deficit,[5] auditory hallucinations(AH) and negative symptoms.[6] For instance, 20-Hz repetitive TMS (rTMS) over left dorsolateral prefrontal cortex (DLPFC) was considered a safe and well-tolerated treatment for negative symptoms and cognitive deficit of SZ.[7-8] However, a randomized, double-blind, sham-controlled trial suggests that therapeutic rTMS when administered to the DLPFC in SZ does not result in robust cognitive enhancing effects.[9] Data from several studies using fMRI have supported that rTMS on language-perception area can alleviate AH without any impact on functional connectivity (FC) within the language network,[10-12] while few other studies have found the FC alteration as the symptom relieved.[13-16] In an update (2014-2018) of the evidence-based guidelines on the therapeutic use of rTMS, experts reviewed its curative effect on AH and negative symptoms; unfortunately, the strong heterogeneity between studies failed to support a more extensive clinical application of such treatment.[17]

In recent studies of meta-analysis, researchers believed that the placebo effect, publication bias and the frequently mentioned cross-trial heterogeneity contributed to the uncertain efficacy of TMS therapy for SZ.[5 6 15 16 18] Therefore, except for simply investigating the effect of TMS by focusing on changes of symptomatic features, more researches regarding optimizing stimulation parameters, or the neurobiological factors associated with treatment response, are warranted, in order to provide experimental evidences for more stable and effective treatment strategies.

In fact, neuroimaging technique plays an important role in terms of evaluating the therapeutic efficacy of TMS and exploring its neurobiological mechanism of action. In 2012, a systematic review including 12 studies -- three of which involving fMRI -- discussed the main contributions of neuroimaging in TMS research in mainly two aspects:(1) For guiding the coil placement. (2) For understanding the functional activation and connectivity in Schizophrenia.[19] For example, according to some later studies, the stimulation targets in the treatment of AH are usually identified by fMRI scan, with a language task performed in order to activate the language-related area. [21-22] In a 2013 study, the n-back task was performed on a group of patients while they

received fMRI scan before and after the treatment, to observe their brain activation patterns.[23] Another resting-state fMRI (rs-fMRI) study showed that alterations in the functional connectivity activity of the default-mode network (DMN) may be related to hallucinations. With the ability to modulate activity of targeted cortical sites and their associated networks, rTMS should be a promising method for modulating altered connectivity associated with schizophrenia.[24] In addition, a multimodal fMRI-rTMS approach could demonstrate changes in cortical plasticity in human during executive cognition.[20]

Here, we intend to describe the protocol for a meta-analysis aims to summarize the TMS-related functional neuroimaging features in schizophrenic subjects, in order to further evaluate its clinical efficacy and explore the mechanism of action.

OBJECTIVE

This review aims to integrate and assess the features of brain function in schizophrenia before and after receiving transcranial magnetic stimulation.

METHODS

This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols 2015 statement.[25]

Patient and public involvement

This work will be based on published studies; therefore, patient or public involvement will be not required. Relevant results will be published in peer-reviewed journals.

Eligibility criteria

Study types

Case control studies, cohort studies and randomized controlled trials will be included only if the original neuroimaging data are available. Case reports, narrative or systematic reviews, meta-analyses, letters and other secondhand studies will be excluded.

Study design

Both resting-state and task neuroimaging studies concerning functional activity or connectivity that centered on the differences between SZ patients treated with TMS or sham-TMS and healthy controls will be included. Longitudinal studies focusing on the management of SZ will also be considered as long as the baseline neuroimaging data are available. Studies that (1) did not report whole brain analyses, or (2) did not report coordinates in either Montreal Neurological Institute (MNI) 47 or Talairach 48 space, or (3) merely focusing on brain structure will all be excluded.

Participants

Studies with SZ patients and parallel healthy controls (both without any known severe neurological condition or head trauma) are required. The minimum sample size will be 12 subjects per group, according to previous studies.[26-27] Race, age and medication (i.e., drug-naïve or medicated) of participants will not be restricted in this review.

Interventions
TMS or rTMS, and sham-TMS.

Outcome measures
The main outcomes of the included studies should be presence of MNI or Talairach coordinates related to brain function including whole-brain functional activity orfunctional connectivity (fMRI based on blood-oxygen-level dependent signal or cerebral blood flow).

Given the focus on neuroimaging effect of TMS treatment for SZ, the secondary result of this review will be informative for the treatment of psychotic symptoms, such as the score of Positive and Negative symptom Scale [28] or the Auditory Hallucination Rating Scale, or any other published scale (e.g., the Manchester Scale) for the assessment of overall schizophrenic symptomatology.

Report characteristics
Peer-reviewed original studies in English or Chinese will be included. Conference proceedings and unpublished theses will be excluded. Publication time will be restricted to prior to May 1, 2020 (the anticipated completion date of this review).

Searching strategy
The following sources will be searched: PubMed, OVID, Embase, CNKI and Wanfang Data, using Medical Subject Headings terms. The searching strategies of PubMed (English) and CNKI (Chinese) are displayed in Table 1 and will replicated for the other electronic databases.

Table1. Searching strategy

PubMed searching strategy	CNKI searching strategy
#1 Schizophrenia (MeSH Terms)	#1 精神分裂症（主题词）
#2 Schizophrenia (All Fields)	#2 经颅磁刺激（主题词）
#3 Schizophren* (All Fields)	#3 重复经颅磁刺激（主题词）
#4 1 OR #2 OR #3	#4 #2 OR #3
#5 Transcranial Magnetic Stimulation (MeSH Terms)	#5 神经影像学
#6 TMS (All Fields)	#6 磁共振成像（主题词）
#7 #5 OR #6	#7 功能磁共振成像（主题词）
#8 Functional Neuroimaging (MeSH Terms)	#8 fMRI（主题词）
#9 Functional Neuroimaging (All Fields)	#9 #5 OR #6 OR #7 OR #8

#10 Functional Magnetic resonance* (MeSH Terms) #11 fMRI (All Fields) #12 8 OR #9 OR #10 OR #11 #13 Final search terms: #4 AND #7 AND #12	#10 Final search terms: #1 AND #4 AND #9

Selection process

EndNote X7 software (Thomson Reuters, New York, NY, US) will be used to manage literatures. After removing duplicates, studies identified by the literature search will be removed independently by SZ and YF, based on title and abstract. Then, they will assess the rest of the literature by screening full text for the final inclusion for this review. Any disagreement between the two reviewers will be reconsidered by a third reviewer, BZ. Reasons for study exclusion will be reported.

Data collection

The two independent reviewers (SZ and YF) will doubly extract data using a standard data extraction spreadsheet in Excel. Again, any inconsistency between reviewers will be reconsidered and the result determined by the third reviewer (BZ). The following information will be retrieved and extracted from each record. Publication information: title, first author, publishing time, unit, country or region and funding support. Details of methodology: participants, sample size, diagnostic criteria, demographic characteristics (including age, gender, etc.), imaging modalities, scanner resolution, data analysis strategies, clinical assessment and clinical variables (e.g., illness duration and severity, etc.).

Results: the significantly altered cerebral regions (described by MNI/Talairach coordinate, cluster size and statistical threshold); the value of clinical characteristics; and the correlations between imaging data and clinical data.

Any missing information or questions about the above data will be settled by contacting the authors. If no clarification is provided after 4 weeks, the study will be included in the final analysis with the missing information marked.

QUALITY ASSESSMENT

There is no standard checklist for assessing the quality of individual functional neuroimaging studies. We will adopt a checklist published in the previous meta-analysis. [29-30] The checklist is shown in Table 2.

Two independent authors (SZ and YF) will assess the characteristics of the sample size, methods of randomization and blinding, the completeness of outcome data, selective reporting and other bias, using the Cochrane Collaboration's tool. The assessment will be done at study level. If disputes arose, resolution was made by discussion, after working with a third reviewers (BZ).

Table2.Quality assessment of individual studies

Category 1: Sample characteristics (10)

1. Patients were evaluated with specific standardized diagnostic criteria (1)
2. Important demographic data (age and gender) were reported with mean (or median) and standard deviations (or range) (2)
3. Healthy comparison subjects were evaluated to exclude psychiatric and medical illnesses and demographic data was reported (1)
4. Important clinical variables (e.g., positive and negative symptom, medication status, and illness duration and severity) were reported with mean (or median) and standard deviations (or range) (4)
5. Sample size per group > 10 (2)
Category 2: Methodology and reporting (10)
6. Whole brain analysis was automated with no a-priori regional selection (3)
7. Magnet strength at least 1.5T (1)
8. At least 5 minutes of resting state acquisition (1)
9. Whole brain coverage of resting scans (1)
10. The acquisition and preprocessing techniques were clearly described so that they could be reproduced (1)
11. Coordinates reported in a standard space (1)
12. Significant results are reported after correction for multiple testing using a standard statistical procedure (Alpha Sim, FDR, FWE or permutation-based methods) (1)
13. Conclusions were consistent with the results obtained and the limitations were discussed (1)

DATA SYNTHESIS

The collected data will be put together in a table. The total and average sample size, age range of subjects and mean duration of patients will be calculated, while schizophrenia-related measurement and other significant clinical scales will also be summarized. We will perform a qualitative analysis to summarize the functional brain alterations in SZ patients between pre- and post-TMS treatment. Also, we will integrate these studies according to task or testing design. If feasible, we will launch a quantitatively meta-analysis to synthesize the differences in brain functional change using an Activation Likelihood Estimation (ALE) meta-analysis. We will use GingerALE Version 3.0.2 (http://www.brainmap.org/) to perform this analysis. If necessary, subgroup analysis will be performed by divided according to frequency or intensity of TMS and kind of schizophrenia (i.e., first-episode or chronic)

REGISTRATION INFORMATION

Our protocol is being assessed by PROSPERO.

AUTHOR CONTRIBUTIONS

BZ and LC was responsible for this study. All authors conceived and designed the study. BZ, SZ and YH participated in drafting the protocol and preparing the manuscript. All authors read and approved the final manuscript.

FUNDING

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COMPETING INTERESTS

None declared.

PATIENT CONSENT FOR PUBLICATION

Not required.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

DATA AVAILABILITY STATEMENT

Not required.

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Abstract

Introduction: Schizophrenia is a psychiatric illness associated with brain function alterations and varying degree of treatment resistance, often leading to severe social malfunctioning. In recent decades, numerous studies have been investigating the therapeutic potential of transcranial magnetic stimulation (TMS) as a noninvasive therapy for schizophrenia. However, its clinical efficacy remains controversial, as a number of clinical trials indicated moderate therapeutic effect while others failed to reproduce the positive result. Moreover, the neurobiological mechanism of action remains unclear, possibly constricting the application of TMS in clinical practice. The present protocol of meta-analysis aims to investigate the TMS-related functional neuroimaging (i.e., functional magnetic resonance imaging, fMRI) features and alterations in schizophrenic subjects, and to discuss the potential of fMRI in TMS researches.

Methods and analysis: The study selection process will follow the Preferred Reporting Items for Meta-Analyses guideline and quality assessment will be conducted with a customized checklist. We plan to search in the following databases: PubMed, Embase, OVID, China National Knowledge Infrastructure (CNKI) and Wanfang Data, from their respective dates of inception to May 1, 2020, with language restricted to English and Chinese. Studies focusing on the brain functional alterations in patients with schizophrenia treated by TMS will be retrieved.

Ethics and dissemination: This work does not require ethics approval as it will be based on published studies. This systematic review will be publicly disseminated in peer-reviewed journals.

Strengths and limitations of this study

1. This is a novel meta-analysis focusing particularly on brain fMRI in the TMS therapy for schizophrenia.
2. This study will provide informative evaluation of the clinical efficacy of rTMS and shed light on its neural substrate of action.
3. The present protocol mainly focuses on the brain functional changes and the general symptomatic improvement induced by TMS, therefore fails to discuss the effect of different stimulation parameters.
4. The limit of this study is connected with the cross-study heterogeneity that affects the external validity.
5. We use public data that will be freely available after publication.

Introduction

Known for its prominent psychotic symptoms such as hallucination and delusion, schizophrenia (SZ), with a lifetime prevalence of 0.30% to 0.66% in the general population,[1-3] is a severe psychiatric illness that tends to be chronic and recurrent, leading to varying degrees of cognitive impairment and social disability.

Since a substantial proportion of patients are resistant to first-line antipsychotics, pharmacological interventions are sometimes insufficient in the treatment for SZ.[4] As a noninvasive neurostimulation technique, transcranial magnetic stimulation (TMS) seems to be a promising add-on therapy that regulates brain function by activating or suppressing neural activity in an effective and safe manner, even though the evidences are controversial. A number of previous studies have explored the role of TMS in the treatment of cognitive deficit,[5] auditory hallucinations(AH) and negative symptoms.[6] For instance, 20-Hz repetitive TMS (rTMS) over left dorsolateral prefrontal cortex (DLPFC) was considered a safe and well-tolerated treatment for negative symptoms and cognitive deficit of SZ.[7-8] However, a randomized, double-blind and sham-controlled trial suggested that therapeutic rTMS administered to the DLPFC in SZ did not result in evident cognitive enhancing effects.[9] Data from several studies using fMRI have supported that rTMS on language-perception area can alleviate AH without any impact on functional connectivity (FC) within the language network,[10-12] while few other studies have found the FC alteration as the symptom relieved.[13-16] In an update (2014-2018) of the evidence-based guidelines on the therapeutic use of rTMS, experts reviewed its curative effect on AH and negative symptoms; unfortunately, the strong heterogeneity between studies failed to support an extensive clinical application of such treatment.[17]

In recent studies of meta-analysis, researchers believe that the placebo effect, publication bias and the frequently mentioned cross-trial heterogeneity contributed to the uncertain efficacy of TMS therapy for SZ.[5 6 15 16 18] Therefore, in addition to focusing solely on the change of symptomatic features, further explorations on optimization of stimulation parameters, as well as the neurobiological factors associated with treatment response, are of clinical necessity, so as to provide experiment basis for reliable and effective treatment strategies.

In fact, neuroimaging technique plays an important role in evaluating the therapeutic efficacy of TMS and exploring its neurobiological mechanism of action. A systematic review including twelve studies -- three of which involving fMRI -- discussed the major contributions of neuroimaging to TMS research in mainly two aspects: (1) For guiding the coil placement, and (2) for understanding the functional activation and connectivity in schizophrenia.[19] For example, according to some later studies, the treatment targets for AH are mostly identified by performing a language task during fMRI. [20-21] In a 2012 study, the n-back task was performed twice on a group of patients during the pre- and post-treatment fMRI scan, in order to investigate

treatment-related brain activation.[22] Another brain connectivity and AH review indicated that functional connectivity alterations of the default-mode network (DMN) may be related to hallucinations, and therefore rTMS – with its neuromodulatory effects on targeted cortical sites and their associated networks -- is a promising treatment option for symptoms associated with altered connectivity in schizophrenia.[23] In addition, a multimodal fMRI-rTMS study demonstrated changes in cortical plasticity in human during executive cognition.[24]

Despite the extensive fMRI research, we mentioned earlier, considerable variability of results exists between these studies, and as far as we are aware of, there has been no meta-analysis to date on studies investigating brain functional alteration induced by therapeutic TMS for schizophrenia. Here we intend to describe the protocol for a meta-analysis aiming to summarize the TMS-related functional neuroimaging features in schizophrenic subjects, and consequently, to evaluate its clinical efficacy and explore the neural mechanism of action.

OBJECTIVE

This meta-analysis aims to integrate and assess the features of brain function in schizophrenia after receiving transcranial magnetic stimulation.

Methods

This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols 2015 statement.[25]

Eligibility criteria

Study types

Cohort studies and randomized controlled trials will be included only if the neuroimaging results are available. Case control studies, case reports, narrative or systematic reviews, meta-analyses, letters and other second-hand studies will be excluded.

Study design

Both resting-state and task neuroimaging studies investigating functional activity or connectivity in SZ patients treated with active or sham TMS will be included. Longitudinal studies focusing on the management of SZ will also be considered, but only if the baseline neuroimaging data are available. Studies that (1) did not report whole-brain analyses, or (2) did not report coordinates in either Montreal Neurological Institute (MNI) or Talairach space, or (3) solely focusing on brain structure, will all be excluded.

Participants

Studies with SZ subjects with or without a healthy control group (all without any known severe neurological condition or head trauma) are required. The minimum sample size will be 12 subjects per group, according to previous studies.[26-27] Race, age and medication (i.e., drug-naïve or medicated) will not be restricted.

Interventions

Active TMS or rTMS, and sham-TMS.

Outcome measures

Since we focus on therapeutic TMS-induced neuroimaging alteration in SZ, the main outcomes of the included studies are brain regions that indicate significant functional changes, including whole-brain functional activity or functional connectivity, and should be presented in MNI or Talairach coordinates.

The secondary result will be psychotic symptom improvement indexed by the score of Positive and Negative symptom Scale (PANSS)[28], the Auditory Hallucination Rating Scale, or any other clinical assessment scales (e.g., the Manchester Scale) reported in the included studies.

Report characteristics

Only published and peer-reviewed original studies in English or Chinese will be included. The date of publication should be prior to May 1, 2020, the anticipated completion date of this review.

Searching strategy

The following sources will be searched: PubMed, OVID, Embase, CNKI and Wanfang Data, using Medical Subject Headings terms. The searching strategies of PubMed (English) and CNKI (Chinese) are presented in Table 1 and will be applied to the other databases.

Table 1. Searching strategy

PubMed searching strategy	CNKI searching strategy
#1 Schizophrenia (MeSH Terms)	#1 精神分裂症（主题词）
#2 Schizophrenia (All Fields)	#2 经颅磁刺激（主题词）
#3 Schizophren* (All Fields)	#3 重复经颅磁刺激（主题词）
#4 #1 OR #2 OR #3	#4 #2 OR #3
#5 Transcranial Magnetic Stimulation (MeSH Terms)	#5 神经影像学
#6 TMS (All Fields)	#6 磁共振成像（主题词）
#7 #5 OR #6	#7 功能磁共振成像（主题词）
#8 Functional Neuroimaging (MeSH Terms)	#8 fMRI（主题词）
#9 Functional Neuroimaging (All Fields)	#9 #5 OR #6 OR #7 OR #8
#10 Functional Magnetic resonance* (MeSH Terms)	#10 Final search terms: #1 AND #4 AND #9
#11 fMRI (All Fields)	
#12 #8 OR #9 OR #10 OR #11	
#13 Final search terms: #4 AND #7 AND #12	

Selection process

EndNote X7 software (Thomson Reuters, New York, NY, US) will be used to manage

literatures. After removing duplicates, studies identified by the literature search will be removed independently by SZ and YF, based on title and abstract. Then, the rest of the literature will be assessed by full-text screening for the final inclusion for this review. Any disagreement between the two reviewers will be reconsidered by a third reviewer, BZ. Reasons for study exclusion will be reported.

Data collection

The two independent reviewers (SZ and YF) will doubly extract data using a standard data extraction spreadsheet in Excel. Again, any inconsistency between reviewers will be reconsidered and the result determined by the third reviewer (BZ). The following items will be extracted from each record. (1) Publication information: title, first author, publishing time, unit, country or region, and funding support. (2) Details of methodology: participants, sample size, diagnostic criteria, demographic characteristics (including age, gender, etc.), imaging modalities, scanner resolution, data analysis strategies, clinical assessments, and clinical variables (e.g., illness duration and severity, etc.). (3) Results: the significantly altered cerebral regions (defined by MNI/Talairach coordinates, cluster size and statistical threshold); the results of clinical assessments, and the correlations between imaging data and clinical data.

Any missing information or questions about the above data will be settled by contacting the authors. If no clarification is provided within 4 weeks, the study will be included in the final analysis with its missing information reported.

Quality assessment

So far, there has been no standard checklist for quality assessment of individual functional neuroimaging studies. We will adopt a checklist (see Table 2) published in a previous meta-analysis. [29-30]

Two independent reviewers (SZ and YF) will examine for any potential study bias, such as the characteristics of the sample, the methods of randomization and blinding, the completeness of outcome data, et al., using the Cochrane Collaboration's tool. The assessment will be done at study level. Inconsistencies between SZ and YF will be settled by discussions with the third reviewer (BZ).

Table 2. Quality assessment of individual studies

Category 1: Sample characteristics (10)
1. Patients were evaluated with specific standardized diagnostic criteria (1)
2. Important demographic data (age and gender) were reported with mean (or median) and standard deviations (or range) (2)
3. Healthy control subjects were evaluated to exclude psychiatric and medical illnesses and demographic data was reported (1)
4. Important clinical variables (e.g., positive and negative symptom, medication status, and illness duration and severity) were reported with mean (or median) and standard deviations (or range) (4)
5. Sample size per group > 10 (2)
Category 2: Methodology and reporting (10)

6. Whole brain analysis was automated with no a-priori regional selection (3)
7. Magnet strength at least 1.5T (1)
8. At least 5 minutes of resting state acquisition (1)
9. Whole brain coverage of resting scans (1)
10. The acquisition and preprocessing techniques were clearly described so that they could be reproduced (1)
11. Coordinates reported in a standard space (1)
12. Significant results are reported after correction for multiple testing using a standard statistical procedure (AlphaSim, FDR, FWE or permutation-based methods) (1)
13. Conclusions were consistent with the results obtained and the limitations were discussed (1)

Data synthesis

All collected data will be put together in a table, including the total and average sample size, age range of subjects, mean duration of illnesses, as well as the clinical assessment results. We will perform a qualitative analysis to examine whether the different functional patterns exist in SZ after the TMS treatment compared with the baseline. Also, we will summarize these results by task-based or resting-state fMRI.

Data analysis

First, the coordinates in MNI and Talairach space extracted from the included studies will be converted to one another for the convenience of our analysis. An activation likelihood estimation (ALE) meta-analysis will then be performed to integrate consistent brain regions with significant functional alteration reported in different studies, using GingerALE Version 3.0.2 (http://www.brainmap.org/). In the ALE algorithm, the peak coordinates extracted from studies represent their own clusters and were registered as centers in the 3D Gaussian probability distribution. The sizes of these clusters were estimated with experimental design of each study, including sample sizes, between-subject variations, normalizing methods, et al. Finally, an ALE map was calculated by merging all modeled activation (MA) maps obtained through voxel-wise aggregation of all clusters reported in each experiment. This ALE map was then compared against a randomly permuted null-distribution to test for statistical significance.

To assess the stability of the outcomes, the Leave-one-out Jackknife sensitivity analysis will be performed using GingerALE. Specifically, this is a procedure that iteratively recalculate the effect size by excluding a different study from the sample at a time and then repeating the analyses. If necessary, subgroup analysis will be performed based on different stimulation parameters of TMS (frequency, intensity, et al.) and courses of the disease (i.e., first-episode or chronic schizophrenia).

REGISTRATION INFORMATION

PROSPERO registration number is CRD42020166288.

PATIENT AND PUBLIC INVOLVEMENT

This work will be based on published studies; therefore, patient or public involvement will not be required. Relevant results will be published in peer-reviewed journals.

AUTHOR CONTRIBUTIONS

BZ was responsible for this study. SZ, YH and BZ conceived and designed the study. BZ, SZ, YF and LC participated in drafting the protocol and preparing the manuscript. SZ, YH, YF, LC and BZ read and approved the final manuscript.

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COMPETING INTERESTS

None declared.

PATIENT CONSENT FOR PUBLICATION

Not required.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

DATA AVAILABILITY STATEMENT

Not required.

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