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Repetitive transcranial magnetic stimulation for hallucination in schizophrenia spectrum disorders

A meta-analysis

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Research Highlights

(1) Studies addressing repetitive transcranial magnetic stimulation for treatment of auditory hallucination in patients with schizophrenia spectrum disorders were included. We enrolled seven randomized controlled trial studies published after 2008 to compare repetitive transcranial magnetic stimulation on cognitive function to evaluate effectiveness and safety.
(2) Literature retrieval using PubMed, ISI, EMBASE, Medline and Cochrane Central Registration database was performed for randomized controlled trials. Previous studies only searched part of the above databases.
(3) Data analysis and quality evaluation were performed in accordance with Cochrane systematic review. Selected studies included randomized controlled trials with sham stimulation controls.

Abstract

OBJECTIVE: This study assessed the efficacy and tolerability of repetitive transcranial magnetic stimulation for treatment of auditory hallucination of patients with schizophrenia spectrum disorders.
DATA SOURCES: Online literature retrieval was conducted using PubMed, ISI Web of Science, EMBASE, Medline and Cochrane Central Register of Controlled Trials databases from January 1985 to May 2012. Key words were “transcranial magnetic stimulation”, “TMS”, “repetitive transcranial magnetic stimulation”, and “hallucination”.
STUDY SELECTION: Selected studies were randomized controlled trials assessing therapeutic efficacy of repetitive transcranial magnetic stimulation for hallucination in patients with schizophrenia spectrum disorders. Experimental intervention was low-frequency repetitive transcranial magnetic stimulation in left temporoparietal cortex for treatment of auditory hallucination in schizophrenia spectrum disorders. Control groups received sham stimulation.
MAIN OUTCOME MEASURES: The primary outcome was total scores of Auditory Hallucinations Rating Scale, Auditory Hallucination Subscale of Psychotic Symptom Rating Scale, Positive and Negative Symptom Scale-Auditory Hallucination item, and Hallucination Change Scale. Secondary outcomes included response rate, global mental state, adverse effects and cognitive function.
RESULTS: Seventeen studies addressing repetitive transcranial magnetic stimulation for treatment of schizophrenia spectrum disorders were screened, with controls receiving sham stimulation. All data were completely effective, involving 398 patients. Overall mean weighted effect size for repetitive transcranial magnetic stimulation *versus* sham stimulation was statistically significant (*MD* = –0.42, 95%*CI*: –0.64 to –0.20, *P* = 0.000 2). Patients receiving repetitive transcranial magnetic stimulation responded more frequently than sham stimulation (*OR* = 2.94, 95%*CI*: 1.39 to 6.24, *P* =

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0.005). No significant differences were found between active repetitive transcranial magnetic stimulation and sham stimulation for positive or negative symptoms. Compared with sham stimulation, active repetitive transcranial magnetic stimulation had equivocal outcome in cognitive function and commonly caused headache and facial muscle twitching.

CONCLUSION: Repetitive transcranial magnetic stimulation is a safe and effective treatment for auditory hallucination in schizophrenia spectrum disorders.

Key Words

neural regeneration; meta-analysis; transcranial magnetic stimulation; auditory hallucination; schizophrenia; schizophrenia spectrum disorders; schizophreniform disorder; temporoparietal cortex; cognitive function; positive symptom; grants-supported paper; neuroregeneration

INTRODUCTION

Schizophrenia spectrum disorders (including schizophrenia, schizoaffective disorder and schizophreniform disorder) are the most burdensome and costly illnesses worldwide[1]. According to the Global Burden of Disease Study, schizophrenia spectrum disorders cause a high degree of disability, which accounts for 1.1% of the total disability-adjusted life years and 2.8% of years living with disability. Schizophrenia spectrum disorders are listed as the eighth leading cause of disability-adjusted life years worldwide in the age group at 15–44 years. Besides the direct burden, there is considerable burden on the relatives who care for the patients[2].

For patients suffering from schizophrenia spectrum disorders, 60–80% of the cases can be accompanied by auditory hallucinations that often produce high levels of distress, functional disability and behavioral disorders[3]. Although antipsychotic medication, especially clozapine, is considered the most effective antipsychotic agent for patients with refractory hallucinations, not all patients achieve remission[4]. Furthermore, approximately 25–60% of patients with schizophrenia spectrum disorders do not sufficiently respond to antipsychotics, electroconvulsive therapy or psychotherapy[5-6]. Treatment of these patients has remained a persistent public health problem because they often have a low quality of life[7]. Thus, there is a need for other treatments to alleviate the symptoms of these disorders.

Repetitive transcranial magnetic stimulation uses a non-invasive and relatively painless tool to stimulate the human brain *in vivo* using very strong, pulsed magnetic fields[8]. It is also used to explore and elucidate neocortical functions and treat neuropsychiatric disorders[9]. It involves the generation of a magnetic field by an electromagnetic coil connected to a transcranial magnetic stimulation device. The generated magnetic field induces an electrical current in the brain. Depending on the characteristics of stimulation (*e.g.*, magnetic field intensity, timing of ongoing brain activity, pulse shape), transcranial magnetic stimulation can induce neuronal depolarization, intracortical inhibition or facilitation, or release of endogenous neurotransmitters, thus resulting in transsynaptic action[10].

Repeated stimulation of a single neuron at a low frequency produces long-lasting inhibition of cell-cell communications, termed long-term depression. Conversely, repeated high-frequency stimulation can improve cell-cell communication by long-term potentiation[11-12]. Long-term (days to weeks) effects of transcranial magnetic stimulation administration are reflected as sustained changes in neurotransmitter release, signaling pathways and gene expression[8, 13]. Various types of transcranial magnetic stimulation have been devised depending on the frequency and type of magnetic pulse delivered. The frequency of repetitive transcranial magnetic stimulation can range from ≤ 1 Hz to 20 Hz or more per second. During low-frequency repetitive transcranial

magnetic stimulation of ≤ 1 Hz, stimulation is applied for a longer duration (10–15 minutes), resulting in long-term depression of cortical neurons. High-frequency repetitive transcranial magnetic stimulation (or fast repetitive transcranial magnetic stimulation) at > 1 Hz frequency for a shorter duration manifests as neuronal long-term potentiation[11].

In recent decades, repetitive transcranial magnetic stimulation has presented an interesting and promising therapeutic strategy for various neuropsychiatric disorders[14-15], because of its ability to specifically modulate distinct brain areas. In schizophrenia patients, hyperactivity of temporoparietal cortex areas plays a role in the pathophysiology of positive symptoms such as hallucinations[16], for which low-frequency (≤ 1 Hz) repetitive transcranial magnetic stimulation of temporoparietal cortex has been used. For negative symptoms, which are associated with hypoactivity of prefrontal cortex areas, high-frequency repetitive transcranial magnetic stimulation has been studied[17].

In 1999, Hoffman *et al* [18] investigated repetitive transcranial magnetic stimulation for the treatment of auditory hallucination. They reported an improvement of hallucination in three schizophrenia patients with medication-resistant hallucinations after a total of 40 minutes of 1 Hz repetitive transcranial magnetic stimulation for 4 days. In a double-blind crossover study[19], 12 medicated patients underwent active and sham transcranial magnetic stimulation for 4 days. Eight of the patients reported a significant improvement in auditory hallucination with repetitive transcranial magnetic stimulation, and the improvement was significant after 4 days of stimulation. Since then, increasing numbers of studies on this topic have been published. Case reports have also demonstrated the efficacy of repetitive transcranial magnetic stimulation in reducing auditory hallucination[20]. In 2006, a review by Saba and colleagues[21] demonstrated that two aspects of auditory hallucination, frequency and attentional salience, could be significantly improved after active repetitive transcranial magnetic stimulation compared with sham stimulation. Growing evidence has demonstrated that low-frequency repetitive transcranial magnetic stimulation in the left temporoparietal cortex can relieve auditory hallucinations[22-23], although some studies are non-randomized controlled design[22, 24-25].

To date, four reviews have been published with a similar scope to our analysis[26-29], which all concluded that repetitive transcranial magnetic stimulation has a moderate to good effect on auditory hallucination in schizophrenia. However, many randomized controlled studies reporting negative results have been published[23, 30-31]. Unfortunately, the most recent reviews[7, 32] were narrative reviews that reported either significant improvement or failed to prove a therapeutic effect of repetitive transcranial magnetic stimulation. As current treatment strategies have not yielded substantial improvement, it is important to reevaluate the efficacy of repetitive transcranial magnetic stimulation in treatment of auditory hallucination in schizophrenia spectrum disorders.

This meta-analysis aims to provide a quantitative review of studies for the efficacy and tolerability of low-frequency repetitive transcranial magnetic stimulation in left temporoparietal cortex compared with sham stimulation treatment of auditory hallucination symptoms in patients with schizophrenia spectrum disorders. We also considered the response rate, global mental state, adverse effects and cognitive function of repetitive transcranial magnetic stimulation.

DATA AND METHODS

Literature retrieval

A literature search in PubMed, ISI Web of Science, EMBASE, Medline and Cochrane Central Register of Controlled Trials databases from 1985 to May 2012 was performed by conducting a cross-reference search of eligible articles to identify additional studies not found in the electronic search. The search terms used (language not specified) were “transcranial magnetic stimulation” OR “repetitive transcranial magnetic stimulation” AND “hallucination” AND “schizophrenia” OR “schizoaffective disorder” OR “schizophreniform disorder” OR “psychiatric disorder”. Some journals were manually retrieved and all references were checked.

Inclusion and exclusion criteria

Inclusion criteria

(1) All relevant randomized controlled trials were included. (2) Participants aged 16 years or older, of both sexes and with a primary diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or schizotypal disorders according to any of the standard criteria: Diagnostic and Statistical Manual of Mental Disorders 3rd and 4th Edition, or the International Statistical Classification of Diseases and Related Health Problems, 10th revision, were included. (3) The experimental intervention was low-frequency repetitive transcranial magnetic stimulation in the left temporoparietal cortex used for the treatment of auditory hallucination in schizophrenia spectrum disorders. No restrictions on frequency,

intensity, number of trains per session, duration of each session and duration of treatment were applied. (4) Comparator intervention was defined as a sham stimulation, which was administered at the same location, intensity, and frequency with a placebo coil being indistinguishable to the active coil. (5) The hallucination severity was assessed by the Auditory Hallucination Rating Scale[33], Hallucinations Subscale of Psychotic Symptom Rating Scale[34], Positive and Negative Syndrome Scale-Auditory Hallucination Item[35], and Hallucination Change Scale[33]. Positive and Negative Symptom Scale-Positive Symptom Subscale or Scale for the Assessment of Positive Symptoms were applied if the above scales were not available. If multiple measures were used, Auditory Hallucination Rating Scale was the first choice for data extraction. We accepted any definition of score criterion from the authors. (6) Medication therapy in all participants was continued as required during the trial but commencing new medication or increases in antipsychotic medication were not allowed during the trial or 4 weeks prior to study entry.

Exclusion criteria

(1) Repeated published literature. (2) Overviews, letters, reviews, editorials and other non-original research. (3) Studies without a sham group. (4) Studies without intact data or those that did not provide data in an adequate form to permit calculation of effect sizes (means and standard deviations or *F* or *t* values). (5) Active repetitive transcranial magnetic stimulation located in right or bilateral temporoparietal cortex. (6) Animal studies.

Quality evaluation and data extraction

Two independent reviewers extracted data and assessed the quality of methodological reporting of selected studies using data extraction forms. Criteria for quality assessment were based on recommendations from the Cochrane Handbook for Systematic Reviews of Intervention[36]. Where a study involved more than two treatment arms, if relevant, we presented the additional treatment arms in comparisons. For crossover studies, only data from the first crossover sequence were used. Where disputes arose, we acquired the full report for more detailed scrutiny. The two reviewers inspected these articles independently to assess their relevance to this review. Again, where disagreement occurred we attempted to resolve this through discussion.

Main outcome measurements

The primary outcome in this systematic review was measured by hallucination scales, including the Auditory Hallucination Rating Scale, Hallucinations Subscale of Psychotic Symptom Rating Scale, Positive and Negative Syndrome Scale-Auditory Hallucination Item, and Hallucination Change Scale. If a hallucination scale was not provided, we looked for the Positive and Negative Syndrome Scale-Positive Symptom Subscale, and Scale for the Assessment of Positive Symptoms[37]. If no scale or none of the cut-offs specified above was provided, we accepted any definition of outcome from the authors. The secondary outcomes included the effective response rate, global mental state, adverse effects and cognitive function.

Statistical analysis

A random effect model was used in this meta-analysis. Individual effect sizes (Cohen *d*) of each study were calculated with reported significance values using an effect size program developed using Review Manager 5.1 software (http://ims.cochrane.org/revman/download; Cochrane Collaboration). For binary outcomes, the relative risks were calculated using a Mantel-Haenszel fixed-effect model and 95% confidence intervals (*CI*) were calculated. When data on different scales rating the same effect were available, the data were summarized, and a standardized mean difference was calculated. Heterogeneity refers to variability among studies in a systematic review, which may be caused by clinical and methodological diversity. Significant heterogeneity limits a reliable interpretation of the results. Heterogeneity was assessed using chi-square and I^2 tests ($I^2 \geq 50\%$ was initially identified of heterogeneity). Potential publication bias was described using a funnel plot. Significance was set at $P < 0.05$.

RESULTS

Data retrieval

One hundred and ninety-three studies were initially identified through the electronic search, cross-reference search and manual search. After reading their titles and abstracts, 38 studies were considered potentially relevant for further inspection. Of these, two studies were excluded because they were duplicate publications; six studies were not randomized; four studies did not use sham stimulation as a comparator; seven studies either failed to measure the hallucination symptoms or had not extracted useful data, and two studies were letters to the journal. Thus, we included data from 17 randomized controlled trials[19, 23, 31, 38-51] comparing repetitive transcranial magnetic stimulation with sham stimulation in our meta-analysis (Figure 1).

Baseline analysis and quality estimation

Among 17 studies[19, 23, 31, 38-51], a total of 398 patients

matching both inclusion and exclusion criteria were selected. Table 1 summarizes the disease characteristics from each study. The majority of patients were aged 18–65 years. The duration of treatment was various, ranging from 4 to 28 days, with an intensity of 80% to 115% of the motor threshold. Follow-up duration was no longer than 3 months. All studies used the Auditory Hallucination Rating Scale, Positive and Negative Syndrome Scale-Auditory Hallucination Item, Hallucinations Subscale of Psychotic Symptom Rating Scale, or Hallucination Change Scale as a primary outcome. According to the Cochrane Quality Evaluation Standards for Randomized Controlled Trials, the baseline of the 17 selected studies was similar. However, only five studies[19, 31, 40, 42, 49] were not introduced in detail in random allocation methods. The quality of articles were all grade B[36].

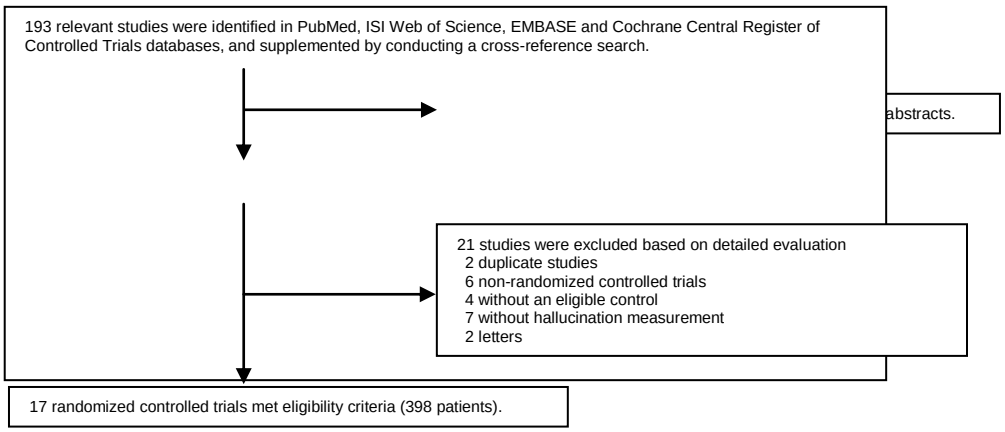

Figure 1 Flowchart of literature retrieval and screening.

Table 1 Characteristics of randomized controlled trials included in the meta-analysis

Author	Study design	Sample size (*n*)	Treatment settings	Hallucination scale	Psychotic symptom scale	Follow-up phase
Blumberge *et al*, 2012[31]	Parallel	34	115% MT, 20 min, 5 sessions per week for 4 weeks	AHRS	PANSS, RBANS, PSYRATS, HCS	1 month
Brunelin *et al*, 2012[38]	Parallel	30	2 mA, 20 min, twice a day for 5 days	AHRS	PANSS	3 months
Brunelin *et al*, 2006[39]	Parallel	24	90% MT, 5 sessions per week for 2 weeks	AHRS	SAPS, memory tasks	–
de jesus *et al*, 2011[40]	Parallel	17	90% MT, 8–20 min, 5 sessions per week for 4 weeks	AHRS	BPRS, CGI	1 month
Fitzgerald *et al*, 2005 [41]	Parallel	33	90% MT, 15 min, 5 sessions per week for 2 weeks	PSYRATS-AH	HCS, PANSS	–
Hoffman *et al*, 2000[19]	Crossover	12	80% MT, 4–16 min, 4 sessions	HCS	PANSS	–
Hoffman *et al*, 2005[42]	Parallel	50	90% MT, 8–16 min, 9 sessions	HCS	AHRS, CGI, PANSS	–
Jandl *et al*, 2006[43]	Crossover	16	100% MT, 15 min, 5 sessions per week for 1 week	PSYRATS-AH	SAPS, SANS	4 weeks
Lee *et al*, 2005[44]	Parallel	27	90% MT, 20 min, per day for 10 days	AHRS	PANSS, CGI	–
Martinot *et al*, 2010[45]	Parallel	28	100% MT, 5 sessions per week for 2 weeks	SAPS	–	–
McIntosh *et al*, 2004[46]	Crossover	16	80% MT, 4–16 min, 4 sessions	PANSS-AH	VAS, AVLT	–
Poulet *et al*, 2005[47]	Crossover	10	90% MT, 2 × 17 min for 5 days	AHRS	PANSS, SAPS	3 months
Rosa *et al*, 2007[48]	Parallel	11	90% MT, 16 min, 5 sessions per week for 2 weeks	AHRS	VAS, PANSS, CGI	4 weeks
Rosenberg *et al*, 2012[49]	Parallel	10	110% MT, 10 min, 10 sessions	AHRS	SAPS, SANS, CGI, QLESQ	–
Saba *et al*, 2006[50]	Crossover	16	80% MT, 5 sessions per week for 2 weeks	PANSS-AH	CGI	–
Slotema *et al*, 2011[23]	Parallel	40	90% MT, 20 min, 5 sessions per week for 3 weeks	AHRS	PANSS, PSYRATS	3 months
Vercammen *et al*, 2009[51]	Parallel	24	90% MT, 20 min, twice daily for 6 days	AHRS	PANSS	1 week

MT: Motor threshold; AHRS: Auditory Hallucination Rating Scale; PANSS: Positive and Negative Syndrome Scale; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; PSYRATS: Psychotic Symptom Rating Scale; HCS: Hallucination Change Scale; SAPS: Scale for the Assessment of Positive Symptoms; BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression; SANS: Scale for the Assessment of Negative Symptoms; VAS: visual analogue scale; AVLT: auditory verbal learning test; QLESQ: Quality of Life Enjoyment and Satisfaction Questionnaire; –: no data; min: minutes.

Meta-analysis results

Auditory hallucination symptom scores following repetitive transcranial magnetic stimulation

The effect of repetitive transcranial magnetic stimulation on severity of auditory hallucination symptoms was analyzed using the Auditory Hallucination Rating Scale, Positive and Negative Syndrome Scale-Auditory Hallucination Item, Hallucinations Subscale of Psychotic Symptom Rating Scale, Hallucination Change Scale or Scale for the Assessment of Positive Symptoms. Results favored the repetitive transcranial magnetic stimulation group compared with the sham stimulation group (17 randomized controlled trials, *n* = 398, *MD* = –0.42, 95%*CI*: –0.64 to –0.20, *P* = 0.000 2; Figure 2).

Response rate of patients following repetitive transcranial magnetic stimulation

In six trials[31, 41-43, 45, 51], response to treatment was defined as the number of participants with at least 30% reduction of hallucination scale scores from baseline or definition of outcome from the authors. Patients treated with repetitive transcranial magnetic stimulation responded significantly more frequently than those receiving sham stimulation (six randomized controlled trials, *n* = 181, odds ratio (*OR*) = 2.94, 95%*CI*: 1.39–6.24, *P* = 0.005; Figure 3).

Change in mental state after repetitive transcranial magnetic stimulation

The effect of repetitive transcranial magnetic stimulation on positive symptoms was also analyzed, using the Positive and Negative Syndrome Scale-Positive Symptom Subscale or Scale for the Assessment of Positive Symptoms. There was no significant difference between repetitive transcranial magnetic stimulation and sham stimulation[23, 31, 38-39, 45, 46, 48-50] (nine randomized controlled trials, *n* = 210, *MD* = –0.39, 95%*CI*: –0.44 to 0.10, *P* = 0.23). No significant differences were observed in scores using Positive and Negative Syndrome Scale-Negative Symptom Subscale[38, 46, 48, 50] (four randomized controlled trials, *n* = 73, *MD* = 2.59, 95%*CI*: –3.16 to 8.35, *P* = 0.38), although the data were heterogeneous (I^2 = 66%). In addition, Positive and Negative Syndrome Scale-General Psychopathology Subscale scores were equivocal and without statistical significance[31, 39, 46, 48, 50] (five randomized controlled trials, *n* = 77, *MD* = –2.02, 95%*CI*: –6.47 to 2.44, *P* = 0.38).

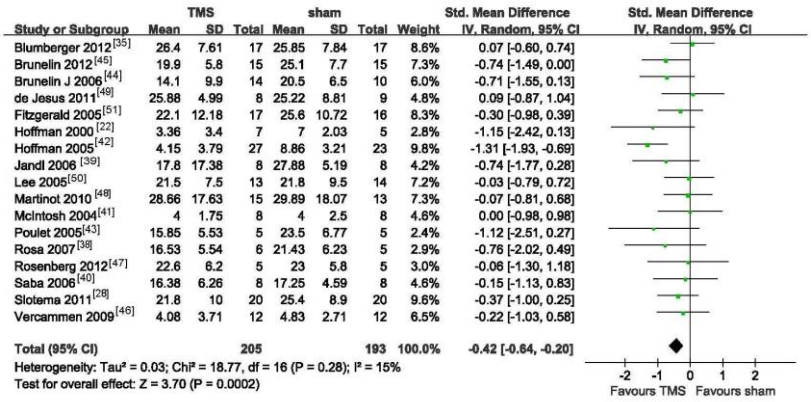

Figure 2 Forest plot of comparison of auditory hallucination scales in active repetitive transcranial magnetic stimulation *versus* sham stimulation.

CI: Confidence interval; TMS: transcranial magnetic stimulation; Std: standard; SD: standard deviation.

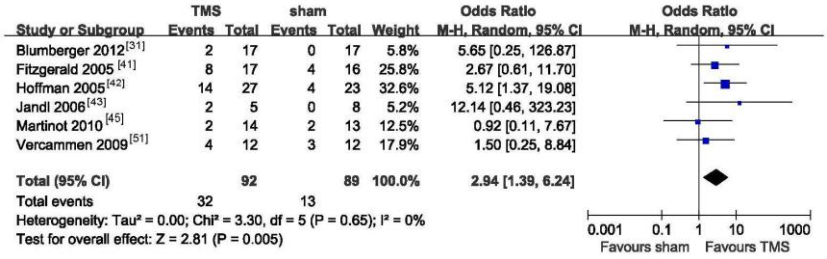

Figure 3 Forest plot of comparison of response rate in active repetitive transcranial magnetic stimulation *versus* sham stimulation.

CI: Confidence interval; TMS: transcranial magnetic stimulation.

Change in cognitive function after repetitive transcranial magnetic stimulation

One study[42] (*n* = 47) reported data on a series of cognitive function tests after repetitive transcranial magnetic stimulation and sham stimulation. Outcomes were equivocal and without statistical significance (*MD* = –2.02, 95%*CI*: –6.47 to 2.44, *P* = 0.39). Another study[46] (*n* = 16) addressing the auditory verbal learning test showed no significant differences between two stimulation groups (*MD* = 2.6, 95%*CI*: –6.89 to 12.09, *P* = 0.59). In addition, a small trial[31] regarding the Repeatable Battery for the Assessment of Neuropsychological Status did not show any significant differences between groups (*n* = 30, *MD* = 3.13, 95%*CI*: –5.20 to 11.46, *P* = 0.46). Compared with the sham stimulation group, repetitive transcranial magnetic stimulation had an equivocal outcome in memory tasks evaluated by Source Monitoring Performance Assessments[39] (*n* = 24, *MD* = 0.00, 95%*CI*: –1.50 to 1.50, *P* = 1.00).

Adverse effects after repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation commonly caused headaches[19, 23, 40, 44, 47-48, 51] (seven randomized controlled trials, *n* = 147, *OR* = 3.72, 95%*CI*: 1.32–10.46, *P* = 0.01), facial muscle twitching[23, 51] (two randomized controlled trials, *n* = 64, *OR* = 15.5, 95%*CI*: 2.60–92.72, *P* = 0.003). No significant differences were observed for dizziness and tremor[23, 44] (two randomized controlled trials, *n* = 69, *OR* = 1.07, 95%*CI*: 0.15–7.91, *P* = 0.95), scalp discomfort[23] (one randomized controlled trial, *n* = 42, *OR* = 3.14, 95%*CI*: 0.12–81.35, *P* = 0.49), or nausea[23] (one randomized controlled trial, *n* = 42, *OR* = 2.86, 95%*CI*: 0.11–74.31, *P* = 0.53) between repetitive transcranial magnetic stimulation and sham stimulation.

Publication bias

The funnel plot implied publication bias. Figure 4 is a funnel plot of 17 studies that addressed auditory hallucination scale scores following repetitive transcranial magnetic stimulation or sham stimulation, without significant bias.

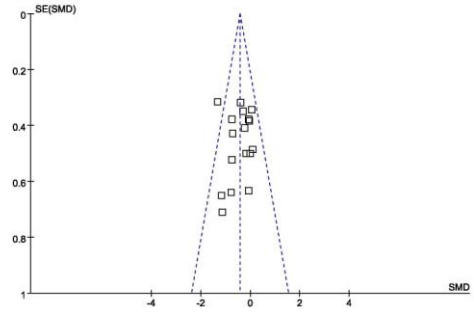

Figure 4 Funnel plot of auditory hallucination scale scores in active repetitive transcranial magnetic stimulation *versus* sham stimulation.

SMD: Standardized mean difference.

DISCUSSION

This meta-analysis involved 17 randomized controlled studies (including 398 patients) and provided support for the efficacy and tolerability of repetitive transcranial magnetic stimulation treatment in the reduction of severity of auditory hallucinations in patients with schizophrenia spectrum disorders.

Our experimental findings have both clinical significance and fundamental implications. In clinical practice, low-frequency repetitive transcranial magnetic stimulation could be a promising and effective treatment for auditory hallucination in schizophrenia spectrum disorders. The largest study to date by Hoffman *et al* [42] (*n* = 50) demonstrated that hallucination frequency was significantly decreased during repetitive transcranial magnetic stimulation compared with sham stimulation, and that frequency was a moderator of repetitive transcranial magnetic stimulation effects. It is necessary to compare the effect size of repetitive transcranial magnetic stimulation treatment and antipsychotic medication for the treatment of auditory hallucination. Unfortunately, meta-analysis of the efficacy of medication treatments in schizophrenia spectrum disorders has not been reported for hallucination symptoms. Chakos *et al* [52] demonstrated that clozapine *versus* typical antipsychotics in treatment-resistant schizophrenia patients yielded a mean effect size of 0.48 (range 0.14–0.81), which is similar to the effect size in our analysis. This provides evidence that low-frequency repetitive transcranial magnetic stimulation might have equivalent efficacy to antipsychotics. Nonetheless, large clinical trials are warranted to establish further the clinical significance of this novel treatment.

The improvement effects of repetitive transcranial magnetic stimulation in left temporoparietal cortex on hallucination symptoms may suggest mechanisms related to the pathophysiology of auditory hallucinations. Reduced cortical excitability in speech perception areas might relieve hallucinations, which suggests that abnormal activation of language perception areas may be the origin of auditory hallucinations. As receptive language areas seem to be critically involved in auditory hallucinations, this is consistent with models suggesting dysfunc-

tion of speech perception or auditory imagery may be involved[29, 53]. With regards to the neurochemical basis of repetitive transcranial magnetic stimulation effects on hallucinations, it is important to use neuroimaging methods, such as functional magnetic resonance imaging, positron emission tomography and single-photon emission computed tomography, to evaluate this putative mechanism.

The overall treatment effect size of 0.43 in this study was medium and was lower than previous data obtained by Aleman and colleagues[29] (*MD* = 0.76), Tranulis *et al* [26] (*MD* = 0.51) and Freitas and colleagues[28] (*MD* = 1.04). However, it did approach the medium range according to the criterion of Cohen[54].

There may be several reasons for these results. First, this meta-analysis narrowed down our inclusion criteria to randomized controlled trial design, low-frequency repetitive transcranial magnetic stimulation, location in left temporoparietal cortex and sham stimulation as a control group. Previous studies reported a large-size effect of 0.76 to 1.04 for repetitive transcranial magnetic stimulation in patients with auditory hallucination, which involved either open studies or non-randomized controlled trials with positive results. Open studies or non-randomized controlled trials should not be included in meta-analysis, which should only evaluate the efficacy of repetitive transcranial magnetic stimulation treatment, and therefore these discrepancies between studies may be due to increased numbers of positive results. However, other stimulating locations may also show equal or superior efficacy[44]. The localizing technique can be improved by using stereotaxic neuronavigational tools and functional neuroimaging[55-56]. Evidence[57] that priming repetitive transcranial magnetic stimulation at 6 Hz could enhance the depression of motor cortex excitability by 1 Hz treatment suggests that 5–6 Hz or higher frequency transcranial magnetic stimulation priming will also have an enhancing effect on auditory hallucination symptoms. Therefore, the effect size would be mutative when high-frequency repetitive transcranial magnetic stimulation or location in the right or bilateral temporoparietal cortex was excluded from the present study.

Second, the published bias should be taken into account. When a new treatment is being introduced, the initial reports tend to feature small sample sizes and positive findings. As studies with larger sample sizes are conducted in the later phase, negative findings tend to be published. Thus, the effect size trends show a decrease. Unlike previous meta-analyses, our study included several recent large-size studies with negative results[23, 31]. As a result, the effect value in this study was lower than for previous reviews. Nevertheless, our study was considered an objective description of the efficacy of low-frequency repetitive transcranial magnetic stimulation in left temporoparietal cortex for treatment of auditory hallucination in patients with schizophrenia spectrum disorders. We also assessed the impact of repetitive transcranial magnetic stimulation on other schizophrenia symptoms. The current meta-analysis demonstrated that low-frequency repetitive transcranial magnetic stimulation in the left temporoparietal cortex did not appear to be an optimal protocol for the treatment of positive or negative symptoms. Systemic reviews by Aleman[29] and Freitas[28] and their colleagues demonstrated that repetitive transcranial magnetic stimulation had no significant effect on a composite index of general psychotic symptoms.

Our results are in agreement with previously reported meta-analytic findings showing no significant improvement of psychiatric symptoms. However, results of general psychopathology studies demonstrate that repetitive transcranial magnetic stimulation applied to the left temporoparietal cortex of patients with schizophrenia spectrum disorders has therapeutic effects on auditory hallucinations, which do not overlap with the effects of positive or negative symptoms.

In our selected studies, cognitive function assessments were conducted before and after treatment. All studies demonstrated no significant difference in cognitive function after repetitive transcranial magnetic stimulation treatment between groups. Thus, although the putative beneficial effect of repetitive transcranial magnetic stimulation on cognition remains unclear, it is at least apparent that no adverse effects on cognitive function were observed.

Repetitive transcranial magnetic stimulation might have mild side effects in the treatment of auditory hallucination. Only headache and facial muscle twitching were statistically significant after repetitive transcranial magnetic stimulation compared with sham stimulation. Dizziness, tremor, scalp discomfort and nausea complaints associated with repetitive transcranial magnetic stimulation were no more frequent than that of the sham stimulation group. No major complications (such as convulsions) occurred during treatment and the follow-up period. This suggested that repetitive transcranial magnetic stimulation treatment was safe and well tolerated with very few adverse effects. This lack of adverse events has also been verified by other studies[58-59].

It is worth noting that only eight of 17 studies included in this meta-analysis conducted a follow-up study, and four provided follow-up data. The follow-up duration was variously between 1 week and 3 months. Poulet *et al* [47] demonstrated 50% of patients were still responders when they were followed up to 3 months. Rosa *et al* [48] observed that some auditory hallucination features were still significantly improved at the 6-week follow-up. Two non-randomized controlled trials[60-61] also found a delayed effect of repetitive transcranial magnetic stimulation on the reduction of auditory hallucination. However, recent large-scale studies[23, 32] failed to verify the efficacy of repetitive transcranial magnetic stimulation on auditory hallucination either during the treatment period or in follow-up. Therefore, further research on the duration of repetitive transcranial magnetic stimulation on auditory hallucination is needed to examine the practical significance of this treatment.

Some limitations of our quantitative review should be noted. First, studies included in this review differed in several methodological aspects, such as stimulation frequency, stimulation intensity, number of trains per session, duration of each session and duration of treatment. Relevant findings showed that 10 sessions of treatment could trigger a significant improvement regardless of the region being stimulated[62]. However, the majority of studies included in this analysis were defined in 4–10 sessions. We suggest that further studies are required to determine an optimal repetitive transcranial magnetic stimulation protocol. Another methodological defect is measurement of the treatment effect. Different auditory hallucination scales were used in this meta-analysis. Although all auditory hallucination scales have proven good for psychometric reliability and validity, the rating scales may differ in the amount of information obtained for auditory hallucination syndrome. Auditory Hallucination Rating Scale and Auditory Hallucination Subscale of Psychotic Symptom Rating Scale provide more detailed assessments of the dimensions of hallucinations than Positive and Negative Symptom Scale-Auditory Hallucination item and Hallucination Change Scale. In addition, the Hallucination Change Scale seems more sensitive to changes of repetitive transcranial magnetic stimulation effects on auditory hallucination than the other scales. Second, effect sizes in the majority of studies were measured immediately after the cessation of repetitive transcranial magnetic stimulation and were absent in the follow-up data. Thus, we could not obtain sufficient data regarding the sustained effectiveness of repetitive transcranial magnetic stimulation for the treatment of auditory hallucination. Future studies should assess auditory hallucination symptoms with longer follow-up periods to assess the long-term treatment effectiveness of repetitive transcranial magnetic stimulation. Third, a significant limitation of this meta-analysis was the small number of studies included and the total number of subjects. Larger randomized controlled trials are required to assess the clinical efficacy of this treatment and to systematically vary the repetitive transcranial magnetic stimulation parameters.

In conclusion, the results of this meta-analysis provide evidence for the efficacy and tolerability of repetitive transcranial magnetic stimulation as a treatment for auditory hallucinations in patients with schizophrenia spectrum disorders. This treatment has the advantage of causing no cognitive impairment and no serious effect events, although the effect size was medium and reduced compared with previous studies. Randomized clinical trials with larger samples are needed to determine the most effective combination of repetitive transcranial magnetic stimulation parameters. In addition, it is important to further optimize the repetitive transcranial magnetic stimulation protocol by optimizing the stimulation frequency, stimulation intensity, number of trains per session, duration of each session, duration of treatment and follow-up period. Finally, studies should preferably use the same hallucination scale to assess symptoms, for which the Auditory Hallucination Rating Scale would be a suitable candidate.

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