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Repetitive transcranial magnetic stimulation for treating the symptoms of schizophrenia: A PRISMA compliant meta-analysis

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HIGHLIGHTS

- A meta-analysis with comprehensive methodology on the effects of rTMS on auditory hallucinations and negative symptoms in schizophrenia.
- 1 Hz rTMS may reduce auditory hallucinations in schizophrenia.
- 10 Hz rTMS did not show significant effect on negative symptoms in schizophrenia.

ABSTRACT

Objective: To explore the efficacies of 1-Hz (low frequency) and 10-Hz (high frequency) repetitive transcranial magnetic stimulation (rTMS) in treating auditory hallucinations and negative symptoms of schizophrenia, respectively.
Methods: Electronic databases were searched to identify relevant literature. Standard mean difference (SMD) and 95% confidence interval (CI) values were used to evaluate the effects of rTMS. The stability and sensitivity of the results, the source of heterogeneity, and the recommended grade of the evidence were also analyzed.
Results: Thirteen studies of 1-Hz rTMS were included. The auditory hallucinations improved more in the rTMS group than in the sham group (SMD = −0.29, 95%CI = −0.57 to −0.01). However, this result was not stable after sensitivity analysis, and publication bias had a substantial impact on the results. Meta-analysis performed for seven studies of 10-Hz rTMS found that improvement of negative symptoms did not differ significantly between the real rTMS and sham groups. Finally, the grade of evidence for this meta-analysis was found to be low.
Conclusion: Although there may appear to be a therapeutic effect for 1-Hz rTMS on auditory hallucinations of schizophrenia, this needs to be confirmed by large-scale randomized controlled trials before this finding can be recommended in clinical practice.
Significance: 1-Hz rTMS might have an effect on auditory hallucinations of schizophrenia.

1. Introduction

Schizophrenia is a debilitating psychiatric disorder that affects 1% of the population. This disease has a considerable impact not only on the health and well-being of affected patients but also on those in their surrounding environment. The costs of schizophrenia management are high for both individuals and society as a whole (Millier et al., 2014; Zhao et al., 2013). The core symptoms of schizophrenia can be divided into negative and positive symptoms. Auditory hallucinations are the most common positive symptoms, and negative symptoms are defined as an absence of normal emotions and behaviors, such as cognitive deficits, apathy, anhedonia, depressive mood and affective flattening (Boutros et al., 2014).

Repetitive transcranial magnetic stimulation (rTMS) is a neurophysiological technique that can potentially influence brain

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function. It is noninvasive, safe, and well-tolerated, and thus is becoming increasingly important in the treatment of psychiatric disorders (Wolwer et al., 2014). Different stimulation patterns of rTMS can produce different effects, with high-frequency stimulation (>1 Hz) increasing the cerebral cortex excitability and low-frequency (≤1 Hz) stimulation having the opposite effect (Dougall et al., 2015).

Prefrontal dysfunction—particularly of the dorsolateral prefrontal cortex (DLPFC)—is involved in the pathophysiology of negative symptoms, as well as in the cognitive disorganization associated with schizophrenia (Rabany et al., 2014). While, the occurrence of auditory hallucinations in schizophrenia may be associated with hyperactivity of the temporal-lobe cortex (Northoff and Qin, 2011). There has been increasing interest in using high-frequency rTMS to increase the activation of the left prefrontal cortex to treat the negative symptoms of schizophrenia (Cordes et al., 2010; Guse et al., 2013; Prikryl et al., 2013; Quan et al., 2015; Wobrock et al., 2015; Wolwer et al., 2014; Zheng et al., 2012). In addition, low-frequency stimulation of left temporoparietal sites is also common, and is comparatively effective against auditory hallucinations (Lai et al., 2010; Slotema et al., 2011, 2014; Yue et al., 2013).

Randomized sham-controlled trials of rTMS have not produced consistent results for various reasons, including variations in the assessment tool used, baseline psychopathology, duration of illness, rTMS frequency, motor threshold (MT), stimulus location, total stimulation, and stimulus duration. Some meta-analyses have analyzed the effects of rTMS on the symptoms of schizophrenia (Hovington et al., 2013; Shi et al., 2014; Slotema et al., 2012), but they did not solve the problem of heterogeneity, evaluate the influence of publication bias, analyze the stability of the results, or yield the level of evidence recommendations.

In this study we reevaluated the effects of 1-Hz rTMS (a low frequency that is widely used in clinical applications) targeting the left temporoparietal cortex and of 10-Hz rTMS (a high frequency that is widely used in clinical applications) targeting the left DLPFC on auditory hallucinations and the negative symptoms of schizophrenia, respectively. We also performed meta-regression to investigate the heterogeneity and conducted a sensitivity analysis to evaluate the stability of the results. The recommended grade of the evidence was also analyzed.

2. Methods

2.1. Study selection

The PubMed, EMBASE, and Cochrane Library databases were searched up to August 31, 2015 to identify studies that have examined the effects of rTMS on the symptoms of schizophrenia. The following phrase was used in the searches: [“schizophrenia” (Mesh) OR “schizophrenia”] AND [“transcranial magnetic stimulation” (Mesh) OR “transcranial magnetic stimulation” OR “rTMS”]. The language was restricted to English or Chinese, and the species was restricted to humans. References in identified articles were also reviewed, and the authors were contacted when the reported data were incomplete.

2.2. Eligibility criteria

The following inclusion criteria were used to select articles for inclusion in the present meta-analysis:

1. Used a randomized sham-controlled design.
2. For studies of low-frequency rTMS, the frequency was 1 Hz and the location was restricted to the left temporoparietal cortex. For studies of high-frequency rTMS, the frequency was 10 Hz and the location was restricted to the left DLPFC.
3. For low-frequency rTMS, the summed score of the Auditory Hallucination Rating Scale (AHRS) was used as an outcome measure; if the summed score could not be obtained, the “frequency” item of the AHRS or a visual analog scale such as the Hallucination Change Scale was used as a second or third choice, respectively. If these were not used as the outcome, the fourth choice was the scores for positive items of the Positive And Negative Syndrome Scale (PANSS). For high-frequency rTMS, the scores for negative items of the PANSS were used as an outcome measure, otherwise, the scale for the Assessment of Negative Symptoms was used as the second choice.
4. Availability of changes in data relative to baseline or the data after treatment.
5. At least five sessions of rTMS treatment.
6. The therapeutic drug dose did not change during 4 weeks before rTMS treatment and throughout the course of treatment.
7. When duplicate data published, we selected the study with the largest sample.
8. The published type was full article.

2.3. Data extraction

The following information was extracted from all qualified studies by two of the present authors independently (He and Lu): publication year, country in which the trial conducted, study design, sample size, frequency and location of treatment, number of treatment sessions, total stimulation, type of coil, percentage of the individual MT, and outcome measure. Baseline data and posttreatment outcome data were also obtained for use in the meta-analysis.

2.4. Quality assessment

The methodological quality of the included studies was assessed using the Cochrane Collaboration’s tool for assessing the risk of bias. The tool contains seven aspects: (1) randomization method, (2) concealment of allocation, (3) blinding of outcome assessors, (4) blinding of study personnel and participants, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other sources of bias. Each bias item is categorized into one of three values: low, unclear, and high. Studies with three or more “high” values were classified as low quality and deleted from the meta-analysis. Two of the present authors (He and Yang) conducted the quality assessments independently, and resolved any disagreements by discussions.

The study selection, data extraction and quality assessment were performed by two of the present authors (He and Lu), independently. Disagreements were resolved by discussion between the two review authors; if no agreement could be reached, the plan was determined by third author (Yang).

2.5. Statistical analysis

Standard mean difference (SMD) and 95% confidence interval (CI) values were estimated to assess the effects of rTMS on the symptoms of schizophrenia using the Mantel–Haenszel method with a random-effects model. This model assumes different underlying effects, considering both within- and between-study variations, offering the advantage that it accommodates diversity between studies and provides a more conservative estimate of the assessed effect (Lopez-Lopez et al., 2013). The SMD was calculated using Cohen’s *d*. The effect sizes for a single study were calculated using the mean change in symptom severity between post- and pretreatment for the separate conditions. If the mean

change or its standard deviations were not supplied, the *t* or *F* values were used to compute the missing value. Another method was to contact the corresponding author of the original article. If all of these methods failed, the final value and the standard deviations of the posttreatment data were used.

The presence of heterogeneity was assessed using Cochran's *Q*-statistic and quantified using the I^2 statistic. A *P* value of Cochran's *Q*-statistic of <0.1 or an I^2 value above 50% indicates the presence of a very high degree of heterogeneity. Sources of heterogeneity were investigated using meta-regression. The covariates included the study design, total stimulation, type of coil, and percentage of the individual MT, since any of these factors could substantially impact the between-study heterogeneity. Subgroup analyses according to study designs were also conducted in the meta-analysis.

Publication bias was analyzed using funnel plots. The absence of obvious publication bias was suggested when the data in a funnel plot were distributed roughly symmetrically, and vice versa. Egger's linear regression was used to test the symmetry of the funnel plot, and a probability value of $P < 0.05$ was considered suggestive of significant asymmetry. When publication bias was present, the nonparametric trim-and-fill method was used to evaluate its influence.

Cumulative meta-analyses according to the sample size or publication year of single studies were used to evaluate the change trends in the results. In addition, the overall robustness of the results was assessed by analyzing the influence of single studies. Because both Cohen's *d* and Hedges' *g* are the algorithms for calculating SMD, we also calculated Hedges' g as a sensitivity analysis to observe whether different algorithms would affect the stability of the results.

All of these statistical analyses were performed using STATA (version 12.0).

2.6. Grading the evidence of meta-analyses

The strength of the meta-analyzed evidence for recommendations was judged by applying the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methods using GRADEPro software proposed by the WHO for producing practice guidelines (Guyatt et al., 2008). In the GRADE evaluation process, randomized controlled studies are basically considered to present high-quality evidence. According to the GRADE handbook (version 3.6) and pragmatic instructions to guide the grading process, judgments on the included studies consider the following five criteria that are known to lower the quality of evidence: risk of bias, inconsistency (heterogeneity of results across studies), indirectness of evidence, imprecision, and publication bias. Studies that are not downgraded for any reason are judged according to the following three factors that increase the quality of evidence: large effect, plausible confounding that would change the effect, and the dose–response gradient.

The grading was done independently by two of the present authors (Zhai and He) and repeated by Gao if there was any disagreement.

3. Results

3.1. Study selection process and overview of the characteristics of the studies

Fig. 1 shows the process of literature screening. The electronic searches of 3 databases yielded 474 potentially relevant studies, of which 114 records were identified as being relevant to the present study. After excluding 84 records that did not meet eligibility criteria, the full texts related to 30 studies were included in the qualitative synthesis. The reported data were insufficient for 10 of the 30 records, and so 20 studies were included in the quantitative synthesis (meta-analysis).

The basic information of the 30 studies is listed in Table 1. The results for the Quality assessment in the 20 studies included in the quantitative synthesis (meta-analysis) are shown in Fig. 2. Overall, most of the trials had a randomized parallel controlled design (87%), with 18 of the studies involving 1-Hz rTMS (Bais et al., 2014; Blumberger et al., 2012; Brunelin et al., 2006; Chibbaro et al., 2005; Loo et al., 2010; de Jesus et al., 2011; Hoffman et al., 2003; Fitzgerald et al., 2005; Hoffman et al., 2005; Jandl et al., 2006; Lee et al., 2005; McIntosh et al., 2004; Poulet et al., 2005; Rosa et al., 2007; Saba et al., 2006; Slotema et al., 2011; Vercammen et al., 2009, 2010) and 483 schizophrenics (247 receiving 1-Hz rTMS and 236 receiving sham), and 12 studies involving 10-Hz rTMS (Cordes et al., 2010; Goyal et al., 2007; Guse et al., 2013; Hajak et al., 2004; Holi et al., 2004; Mogg et al., 2007; Prikryl et al., 2007, 2013; Quan et al., 2015; Schneider et al., 2008; Wobrock et al., 2015; Wolwer et al., 2014) and 518 schizophrenics (288 receiving 10-Hz rTMS and 230 receiving sham). Except for the study of de Jesus et al. (2011), in which there was a significant age difference between the rTMS and sham groups, and the study of Blumberger et al. (2012), in which subjects in the rTMS group had a significantly shorter illness duration than subjects in the sham group, the baseline psychopathological parameters and the neurocognitive characteristics and demographic characteristics did not differ significantly between the rTMS and sham groups. Three of the 30 studies had received support from equipment companies (Cordes et al., 2010; Hoffman et al., 2005; Wolwer et al., 2014). Most of the trials (90%) were carried out in the Americas and Europe. The main side effects in the two study groups were headache and local tingling sensations.

3.2. Pooled effect size of placebo versus active treatment

Thirteen studies provided sufficient data on the effects of 1-Hz rTMS on auditory hallucinations, of which six supplied the mean change from baseline of the outcome measure (Bais et al., 2014; Blumberger et al., 2012; Brunelin et al., 2006; Fitzgerald et al., 2005; Jandl et al., 2006; Poulet et al., 2005), and six provided only the final data for the outcome measure after the treatment (Loo et al., 2010; de Jesus et al., 2011; Lee et al., 2005; McIntosh et al., 2004; Rosa et al., 2007; Saba et al., 2006; Slotema et al., 2011). The SMD was used as the effect size, which overall was −0.29 (95%CI = −0.57 to −0.01), meaning that the symptoms improved more in the rTMS group than in the sham group. The test for heterogeneity showed significant heterogeneity between the studies ($P = 0.06$) (Fig. 3A).

Seven studies provided sufficient data on the effects of 10-Hz rTMS on the negative symptoms of schizophrenia, of which six supplied the mean change in the outcome measure from baseline (Cordes et al., 2010; Holi et al., 2004; Prikryl et al., 2007, 2013; Wobrock et al., 2015; Wolwer et al., 2014) and one provided only the final data for the outcome measure after the treatment (Quan et al., 2015). The overall effect size was −0.41 (95%CI = −1.16 to −0.35), meaning that there was no significant difference in the improvement of symptoms between the real rTMS and sham groups. The test for heterogeneity showed significant heterogeneity between the studies ($P < 0.001$) (Fig. 3B).

3.3. Meta-regression

Because of the small number of included studies (just 13 for 1-Hz rTMS), single covariate meta-regression was used in an attempt to identify the source of heterogeneity. The covariates set in advance according to clinical knowledge included the study design, total stimulation, type of coil, and percentage of the individual MT.

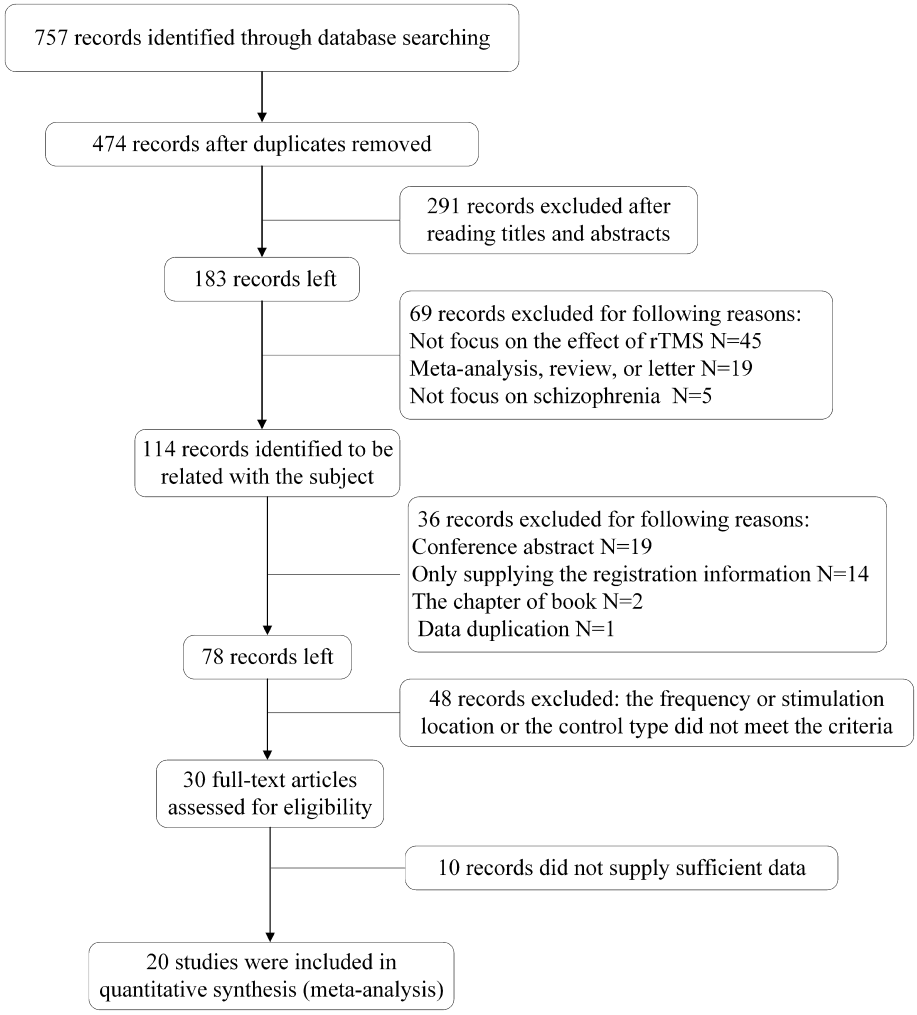

Fig. 1. Flow chat of study selection.

The single covariate meta-regression did not identify the source of heterogeneity.

3.4. Subgroup meta-analysis

Subgroup analysis by the study design showed that 1-Hz rTMS did not significantly affect auditory hallucinations in the parallel control group or in the crossover group compared with sham.

3.5. Sensitivity analysis

For 1 Hz rTMS, sensitivity analysis by analyzing the influence of single studies showed that the total pooled effect size was greatly affected by the studies of McIntosh et al. (2004), Fitzgerald et al. (2005), Poulet et al. (2005), Brunelin et al. (2006), Jandl et al. (2006), and Rosa et al. (2007). Excluding any of these studies resulted in the loss of significant better effects of real 1-Hz rTMS on auditory hallucinations (Fig. 4).

Hedges' g for 1-Hz and 10 Hz were −0.28 (95%CI = −0.55 to −0.01) and -0.38 (95%CI = −1.11 to 0.35), respectively, which suggested that different algorithms did not change the trend of pooled results.

3.6. Cumulative analysis

A cumulative analysis of 1-Hz rTMS by publication date showed no stable temporal trend, while one by sample size demonstrated that the effects of 1-Hz rTMS on auditory hallucinations increased gradually and became positive as small-sample studies were included (Fig. 5). Cumulative analyses of 10-Hz rTMS by publication date and sample size did not show any stable trends.

3.7. Publication bias

The evaluation of publication bias using funnel plots found evidence of obvious asymmetry for 1-Hz rTMS. The results were further verified by Egger's test, which yielded $P = 0.051$, which indicates a marginal asymmetry. The trim-and-fill method was applied to adjust this bias and calculate the number of unpublished studies that could lead to asymmetry (Fig. 6). This analysis suggested that two studies were missing, and the SMD adjusted by the trim-and-fill method was opposite to the original estimate (SMD = 0.684, 95%CI = 0.523–0.894), indicating that our analyses were not stable, and moreover that future new research is very likely to change the results. No publication bias was evident for 10-Hz rTMS (P-value for Egger's test = 0.673).

3.8. Grading of meta-analysis

Following the GRADE algorithm, we downgraded the quality of the evidence of studies investigating the effects of rTMS on auditory hallucinations compared with sham from high to low for both inconsistency and publication bias. The inconsistency mainly referred to heterogeneity between studies that was not explained

Table 1
Characteristic of included studies.

Study	Year	Design	Country	*N*		Hertz	Location	% MT	No. of sessions	Total stimuli	Sham	Questionnaires
				Active	Sham							
Hoffman	2003	Par	USA	11	10	1	T3P3	90	9	NA	45°	HCS/AHRS/ PANSS/ CGI
McIntosh	2004	Cro	UK	16	16	1	T3P3	80	4	2400	45	PANSS
Chibbaro	2005	Par	Italy	8	8	1	T3P3	90	4	3600	45	SAPS/SANS/SAH
Fitzgerald	2005	Par	Canada	17	16	1	T3P3	90	10	9000	45	HCS/PSYRATS/PANSS
Hoffman	2005	Par	USA	27	23	1	T3P3	90	10	9000	45	HCS/CGI/AHRS/PANSS
Lee	2005	Par	Korea	13	14	1	T3P3	100	10	16,000	90	AHRS/PANSS/CGI
Poulet	2005	Cro	France	10	10	1	T3P3	90	10	10,000	Sham coil	AHRS/SAPS
Brunelin	2005	Par	France	14	10	1	T3P3	90	10	10,000	Sham coil	AHRS/SAPS
Jandl	2006	Cro	UK	14	14	1	T3P3	100	5	900	45	PSYRATS/ SAPS/ SANS
Saba	2006	Par	France	9	9	1	T3P3	80	10	3000	Sham coil	PANSS/CGI
Rosa	2007	Par	Brazil	6	5	1	T3P3	90%	10	9600	Sham coil	AHRS/PANSS/CGI
Vercammen	2009	Par	Netherlands	12	12	1	T3P3	90	12	14,400	Sham coil	AHRS/PANSS/PANAS
Loo	2010	Cro	Australia.	18	18	1	T3P3	110	3	720–1440	Vertex	AHRS/MADRS
Vercammen	2010	Par	Netherlands	9	9	1	T3P3	90	12	14,400	Sham coil	PANSS、AVH
de Jesus	2011	Par	Brazil	8	9	1	T3P3	80	20	24,000	45	BRPS/CGI/AHRS
Slotema	2011	Par	Netherlands	22	20	1	T3P3	90	15	18,000	90	AHRS/PANSS/ PSYRATS
Blumberger	2012	Par	Canada	17	17	1	Left primary auditory cortex	115	20	24,000	90° single wing	PANSS/PSYRATS/HCS/ AHRS
Bais	2014	Par	Netherlands	16	16	1	T3P3	90	12	14,400	Sham coil	PANSS/AHRS
Hajak	2004	Par	German	10	10	10	LDLPFC	110	10	10,000	Sham coil	PANSS
Holi	2004	Par	Finland	11	11	10	LDLPFC	100	10	10,000	90	PANSS
Goyal	2007	Par	India	5	5	10	LDLPFC	110	10	9800	45	PANSS/CGI
Mogg	2007	Par	UK	8	9	10	LDLPFC	110	10	20,000	Sham coil	PANSS
Prikryl	2007	Par	Czech	11	11	10	LDLPFC	110	15	22,500	90	PANSS/SANS/SAPS
Schneider	2008	Par	Canada	17	17	10	LDLPFC	110	20	20,000	NA	SANS/BPRS
Cordes	2010	Par	Germany	18	14	10	LDLPFC	110	10	10,000	Sham coil	CGI/ (PANSS/GAF
Guse	2013	Par	Germany	13	12	10	LDLPFC	110	15	15,000	45° single wing	n-back working memory task
Prikryl	2013	Par	Czech	23	7	10	LDLPFC	110	15	30,000	Sham coil	SANS/SAPS/MADRS/ CDSS
Wolwer	2014	Par	Germany	18	14	10	LDLPFC	110	10	10,000	Sham coil	CGI/PANSS
Quan	2015	Par	China	78	39	10	LDLPFC	80	10	8000	90	PANSS/SANS/CGI
Wobrock	2015	Par	Germany	76	81	10	LDLPFC	110	15	15,000	45° single wing	PANSS/CDSS

Abbreviations: Par, parallel; Cro, crossover; T3P3, located between T3 and P3 electrode position; LDLPFC, left dorsolateral prefrontal cortex; NA, not available; HCS, Hallucination Change Scale; AHRS, Auditory Hallucination Rating Scale; PANSS, Positive And Negative Syndrome Scale; CGI, Clinical Global Impression Severity of Illness Rating; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; SAH, Scale for Auditory Hallucinations; PSYRATS, Psychotic Symptoms Rating Scale; PANAS, Positive and Negative Affect Scale; BPRS, Brief Psychiatric Rating Scale; GAF, Assessment of Functioning Scale; MADRS, Montgomery – Åsberg Depression Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia.

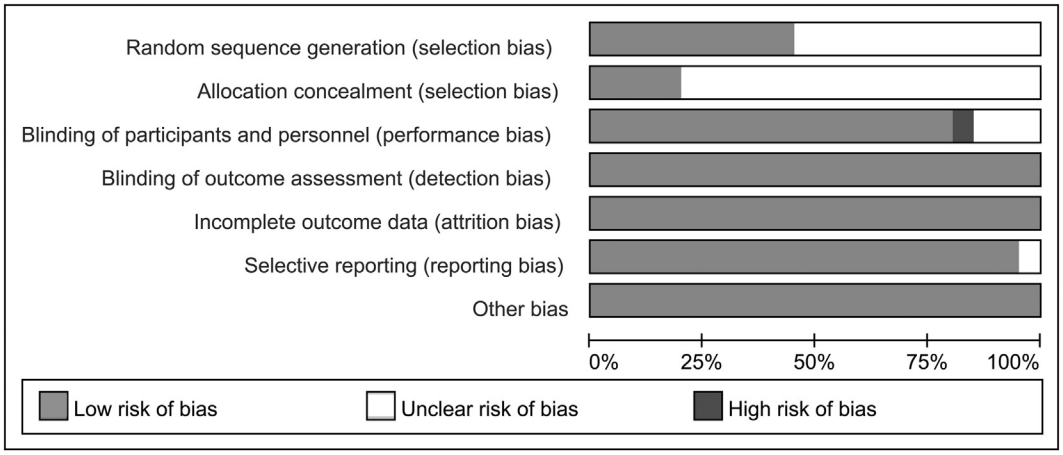

Fig. 2. The assessment of bias risk in the 20 studies included in the quantitative synthesis.

by the study design, total stimulation, type of coil, or percentage of the individual MT. We downgraded the meta-analysis of the effects of 10-Hz rTMS on the negative symptoms of schizophrenia due to serious inconsistency and imprecision. The grading of the quality of the epidemiological evidence as low or very low thus classifies any estimate of effect as uncertain, with further research likely to have an important impact on the confidence in the estimates.

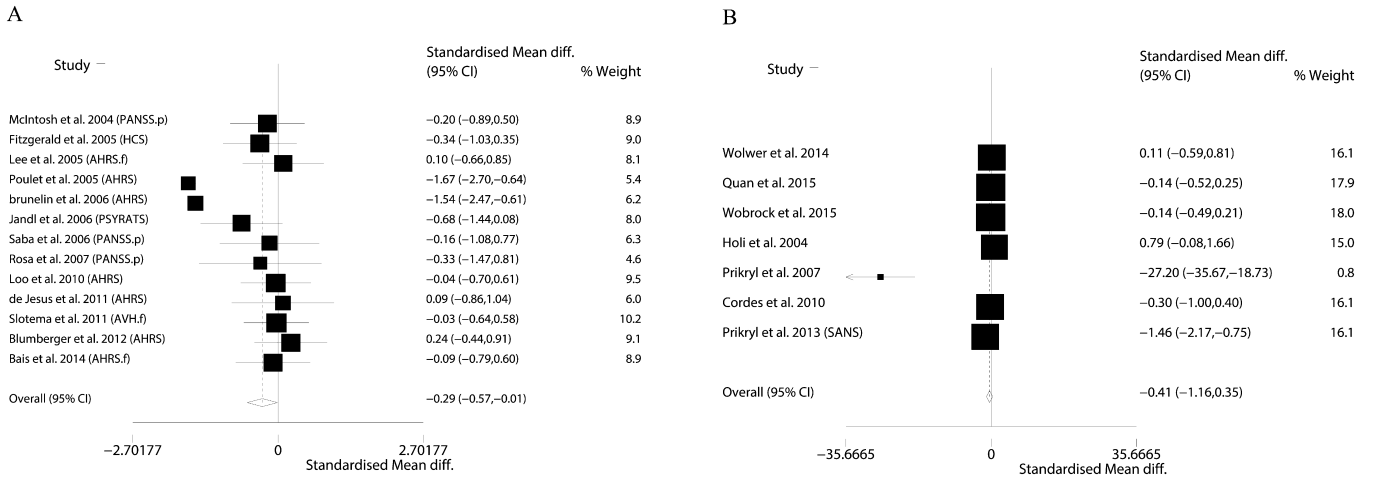

Fig. 3. (A) Pooled effect size for studies of 1-Hz rTMS effect on auditory hallucinations of schizophrenia; (B) pooled effect size for studies of 10-Hz rTMS effect on negative symptoms of schizophrenia.

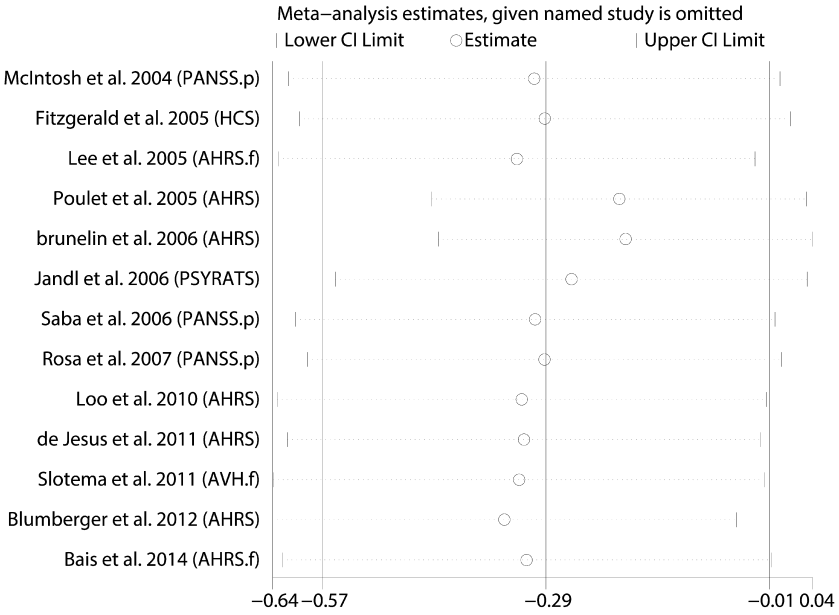

Fig. 4. The relative influence of each individual dataset on the pooled effect size for 1-Hz rTMS effect on auditory hallucinations of schizophrenia.

4. Discussion

A new meta-analysis was conducted in this study to evaluate the effects of rTMS versus sham in the treatment of the negative and positive symptoms of schizophrenia. Unlike previous meta-analyses (Aleman et al., 2007; Freitas et al., 2009; Otani et al., 2015; Shi et al., 2014; Slotema et al., 2012, 2010; Tranulis et al., 2008), the present meta-analysis also searched for the source of heterogeneity, evaluated the stability of the results, analyzed the influence of publication bias, and graded the level of evidence. The relevance of the current study was mainly based on the quality of the elected data based on the use of both GRADE algorithm and the Cochrane Collaboration's tool for assessing the risk of bias. Overall, the studies of 1-Hz rTMS that targeted the left temporoparietal cortex had a moderate effect size. The heterogeneity among these studies was high, but meta-regression did not identify the source of the heterogeneity. The results were not very stable due to the substantial impact of single studies and publication bias. The quality of the evidence was graded low, and so we do not recommend that this evidence is utilized for clinical practice. The effect size of 10-Hz rTMS targeting left DLPFC was not significant.

The mean change in outcome measures from baseline could not be obtained despite contacting the authors of some of the articles, and so the final value after treatment was used. The bias in this situation was very low because the baseline values in these studies was balanced between the real rTMS and sham groups. The mean weighted effect size of the studies that targeted the left temporoparietal cortex in the current meta-analysis was −0.29. Because the mean change was determined as the final value after treatment minus the baseline value, which was opposite to the previous meta-analysis (using the baseline value minus the post-treatment value), our results are consistent with previous research results. However, the effect size was smaller than in previous studies, in which it was between 0.44 and 1.0 (Aleman et al., 2007; Freitas et al., 2009; Slotema et al., 2012, 2010; Tranulis et al., 2008), which may be due to differences in the numbers of included studies and the outcome measures used.

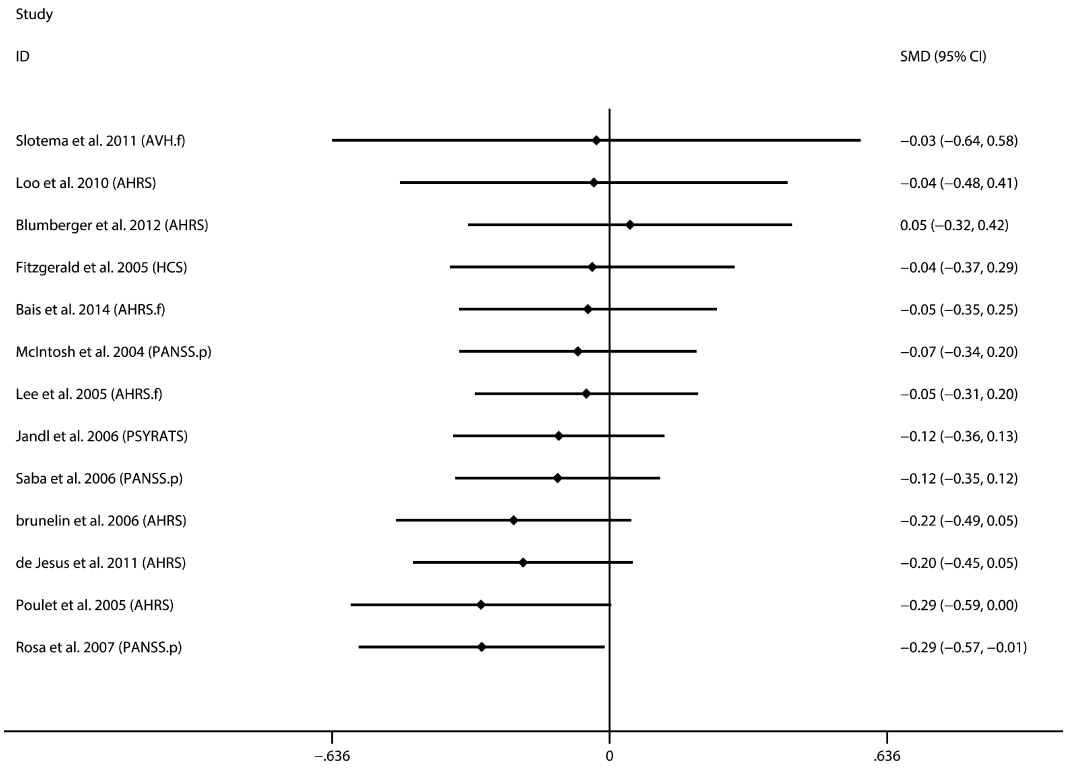

Fig. 5. Cumulative meta-analyses according to sample size for 1-Hz rTMS effect on auditory hallucinations of schizophrenia.

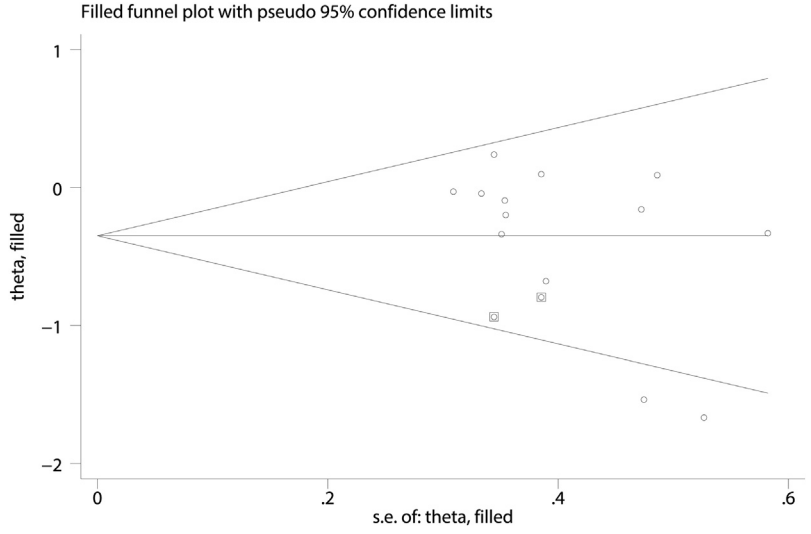

Fig. 6. Funnel plot of publication bias test for 1-Hz rTMS effect on auditory hallucinations of schizophrenia after trim-and-fill method.

According to our clinical knowledge, we believe that the stimulation frequency, stimulation site, the total simulation, MT, the original study design, and the type of coil may be the main factors underlying the different findings among original studies, so we considered them to be possible confounding factors before starting the meta-analysis. Unfortunately, the results of the univariate meta-regression did not demonstrate these factors to be the main sources of heterogeneity between studies. The baseline level of auditory hallucinations could be a source of the heterogeneity, but different articles used different scales to evaluate the severity of auditory hallucinations at baseline. This prevented comparison of baseline symptoms, as a result we were not able to add this important measure as a covariate in the meta-regression before starting the meta-analysis. Tranulis et al. performed a meta-regression in which the total number of stimulations, rTMS intensity, and duration of treatment were treated as confounders, but they found no statistically significant effects (Tranulis et al., 2008). We therefore think that the heterogeneity could be due to a combination of two or more of the above factors. The subgroup analysis by the study design in the meta-analysis of Aleman et al. showed that 1-Hz rTMS was more effective against auditory hallucinations than sham in both parallel studies and crossover studies (Aleman et al., 2007). However, our subgroup analysis showed that the significant effects disappeared in both subgroups. The different

number of included studies may be the main factor causing this difference. From this perspective, our results were generally more reliable when more studies were included.

The statistical analysis indicated a critical level of publication bias in the text, and in order to ensure the reliability of the results, we used the trim-and-fill method to assess the impact of publication bias. Publication bias was also found in the meta-analysis by Slotema et al., with the effect sizes of studies targeting the left temporoparietal area being significantly higher for those published before 2007 than for more recent studies (Slotema et al., 2012). Those authors suggested that this decline over the years could be due to an initial positive outcome or to publication bias. The initial reports on newly introduced treatment strategies tend to include relatively small samples and provide favorable results, while small-sample studies with negative findings are not published. This small-sample effect was also found in the present study, with the trim-and-fill method showing that including newer studies made it more likely for the results of the meta-analysis to be reversed. A cumulative meta-analysis study also found that including literature with a lower precision resulted in the meta-analysis becoming more positive, indicating that the inclusion of lower accuracy studies caused bias.

All of the studies included in the present meta-analysis were high-quality randomized double-blind clinical trials, and the level of original evidence was high. However, the final level of evidence was downgraded to low due to the presence of heterogeneity of unknown origin and publication bias problems when combined with the original data. Therefore, although we found that 1-Hz rTMS had therapeutic effects on the auditory hallucinations of schizophrenia, the level of evidence was too low for recommending this treatment modality in clinical practice. Combining with the meta-analysis performed by Slotema et al. finding that the effects of 1-Hz rTMS on auditory hallucinations were no longer significant at a 1-month follow-up (Slotema et al., 2012), we believe that high-quality randomized controlled trials on this topic are still needed. Although other meta-analyses have found 1-Hz rTMS to be effective against hallucinations, the recommended level of evidence was not reported (Aleman et al., 2007; Freitas et al., 2009; Slotema et al., 2012, 2010; Tranulis et al., 2008), and so it is not possible to deduce its value in clinical applications.

The effects of 10-Hz rTMS on the negative symptoms of schizophrenia did not differ significantly from those of sham. However, Shi et al. found significant effects, with an effect size of 0.532 (Shi et al., 2014). The main reason for this difference in the findings was that the findings for 1 Hz, 10 Hz, and 20 Hz were combined together and the stimulus position was not limited in the study of Shi et al.

The main limitation of the present study is the small number of articles included in the meta-analysis. When the number of included studies or the total sample is small in a meta-analysis, the efficacy of interventions can often be exaggerated due to the presence of random errors. Test sequential analysis (TSA) has often been used to adjust for random errors and to estimate the sample size required for a systematic review or meta-analysis. However, TSA is only suitable for the mean difference, and using the SMD is more appropriate in this study because the outcomes measured by the included studies are inconsistent; TSA could therefore not be used to estimate the required sample size in the present meta-analysis. The small number of included studies could also have hindered the investigation of the long-term effects of rTMS. We were unable to obtain the original data for some of the studies, even though the authors had been contacted successfully, and this may have introduced bias into the results. Another limitation was that we did not research the effect of rTMS with certain location on other specific symptoms. Actually, certain location of rTMS may have wide effects on many symptoms of schizophrenia. For instance, 1 Hz rTMS over left temporoparietal cortex may exert effects not only on auditory hallucinations, but also on negative symptoms of schizophrenia. However, for the effects of certain position of rTMS on other symptoms, the information was not provided in most of studies, we therefore did not study that point.

The results of this study indicate that there may be an effect of applying 1 Hz rTMS to the temporoparietal cortex in patients with schizophrenia. However, since the effect size was moderate and the level of evidence was relatively low, these results need to be confirmed in future large-scale randomized controlled trials before they could be recommended for inclusion in clinical practice.

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