•Systematic review and meta-analysis•

Efficacy towards negative symptoms and safety of repetitive transcranial magnetic stimulation treatment for patients with schizophrenia: a systematic review

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Background: Negative symptoms are one of the most difficult areas in the treatment of schizophrenia because antipsychotics are often less effective towards them. Repetitive transcranial magnetic stimulation (rTMS) is a new technique for cerebral cortex stimulation and is believed to be a safe and promising method for the treatment of mental disorders. As the clinical research and new treatment models have increased in recent years, the efficacy towards negative symptoms and safety evaluation of rTMS treatment should also be updated.

Aims: To explore the efficacy and safety of rTMS in the treatment of negative symptoms for patients with schizophrenia.

Methods: We searched for relevant controlled clinical trials from the following databases: PubMed, EMBASE, the Cochrane Library, EBSCO, Web of Science, China National Knowledge Infrastructure (CNKI), VIP, Wanfang Data, SINOMED, and Airiti Library. The retrieval time went up to January 2, 2017. The research literature was screened according to the predefined inclusion and exclusion criteria. After data extraction, statistical analysis was conducted by using RevMan 5.3 and Stata 14. Quality evaluation was done on the included research articles. The Cochrane risk of bias assessment tool was adopted for assessing risk of bias. The GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system recommendation grading method was used as the reference standard.

Results: A total of 3500 articles were retrieved. In the end, there were 29 articles included in the meta-analysis with a total sample size of 1440. After the meta-analysis, it was found that the use of antipsychotic treatment combined with rTMS could improve the negative symptoms of patients (SMD=-0.40, 95% CI= -0.62~-0.18). Based on the bias of the efficacy evaluation assessed by the Cochrane risk of bias assessment tool, there were 6 studies rated as having “high risk of bias” and the rest were rated as “unable to determine”. According to the assessment, development and evaluation criteria of the GRADE classification, the evidence quality for the efficacy evaluation index was “moderate”. The acceptability of rTMS treatment was better (RR= 0.75, 95% CI= 0.49~1.15, based on the 1492 samples from the 28 studies), however, the patients who received the rTMS treatment had a higher rate of mild adverse effects (RR= 2.20, 95% CI= 1.53~ 3.18, based on the 1296 samples from the 23 studies).

Conclusions: The use of the antipsychotic treatment incorporated with rTMS treatment can slightly improve the negative symptoms of patients with schizophrenia and has better acceptability and fewer adverse effects. Nevertheless, there is publication bias in this study and the heterogeneity of the study is relatively high. Therefore, we need to be cautious when interpreting the results

Key words: repetitive transcranial magnetic stimulation treatment; schizophrenia; negative symptoms; systematic review; meta analysis

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1. Background

Schizophrenia is a serious mental disorder with an unknown etiology and negative symptoms are one of the most difficult areas in the treatment of schizophrenia.[1,2] The classic first generation of antipsychotic drugs has little treatment effect on negative symptoms and the second generation of antipsychotics also fails to show better treatment effect on negative symptoms.[3,4] Recent research has also been looking for a combined medication method such as antidepressants acting on the 5-HT system, anticholinergic drugs, glycine regulatory drugs, antiepileptic drugs and central stimulants, as well as others for treating negative symptoms. However, the research results were inconclusive.[5] Non-drug therapy such as psychotherapy also failed to show efficacy for treating negative symptoms.[6] Repetitive transcranial magnetic stimulation (rTMS) is a new technique of cerebral cortex stimulation developed in recent years. 1.5 ~ 2 Tesla magnetic pulses can pass through the skull without attenuation and produce induction currents in the neural tissues of the superficial layers of the cerebral cortex. This current, as a result, affects the function of the nerve cells (excitatory or inhibitory) and induces therapeutic effect through the changes in neurotransmitter transmission of synaptic, local regional blood flow, nerve repair, and so forth.[7]

In basic research, it is believed that negative symptoms are mainly related to dopamine (DA), reduction of the function of noradrenaline, and the enhancement of the function of 5-hydroxytryptamine (5-HT).[8] The dopamine hypothesis suggested that neural pathways hypofunction of the frontal cortex mediated mainly by the D1 receptor was related to the negative symptoms of patients.[7] Studies have shown that rTMS can cause changes in a variety of neurotransmitters including dopamine, 5-hydroxytryptamine, glutamate, and so forth. For instance, animal and human experiments found that rTMS on the frontal lobe caused an increase in DA release in the basal ganglia and there was obvious influence on a variety of receptors such as 5-hydroxytryptamine as well as the gene expression that regulated neuronal excitability in different brain regions,[9] and it was speculated that the projection fibers (cortex- striatal fibers) from the cortex to basal ganglia could release DA.[10,11] High frequency magnetic stimulation has certain effect on the regulation of cerebral blood flow velocity.[12,13] Based on the results above, some scholars have explored the clinical effect of rTMS on negative symptoms. Cohen and colleagues reported the treatment of rTMS on negative symptoms. The study was a small open sample that showed a significant reduction in negative symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) after 2 weeks of treatment with 20 Hz of rTMS (80% MT).[14] Up to now, there are already multiple parallel randomized controlled trials with relatively large sample sizes in addition to the relevant published systematic reviews, however, the results are still inconclusive. Some research suggested that rTMS failed to improve negative symptoms.[15-17] However, some research suggested that it could improve the efficacy of drug therapy.[18-20] And in the past few years there have been more controlled trials and clinical studies with larger sample sizes done using this new treatment mode.[21-26] Therefore, this study searched for randomized controlled trails (RCTs) that used rTMS for reducing the negative symptoms of patients with schizophrenia in the published Chinese and English literature. Moreover, the results of these studies were systematically reviewed and analyzed by meta-analysis.

2. Methods

2.1 Search strategy

Electronic search: we searched in the following Chinese and English databases: Pubmed, Embase, the Cochrane Library, EBSCO, Web of science, Chinese National Knowledge Infrastructure (CNKI), Wanfang Data, VIP, SINOMED, and Airiti Library. The English keywords used for search were schizophrenia, schizophrenia*, schizophrenic disorders, schizophrenic disorder, dementia praecox, negative symptoms, transcranial magnetic stimulation, TMS, and rTMS. The Chinese keywords were “重复经颅磁刺激”, “磁刺激” “经颅磁刺激”, “跨颅磁刺激”, “精神分裂症”, and“ 阴性症状 ”. The search deadline for the published studies regarding randomized controlled trials of the rTMS treatment for the negative symptoms of patients with schizophrenia was January 2, 2017. In the search process, we modified the search strategy and keywords according to the requirements of different databases.

We hand-searched the reference lists of the included studies for the discovery of further related research. In addition, we consulted experts in this area as to whether there was any ongoing related research.

2.2 Inclusion and exclusion criteria of literature

This study included randomized controlled trials of rTMS treatment for the negative symptoms of patients with schizophrenia, used the means of systematic review, and evaluated the efficacy and safety of rTMS in the treatment of negative symptoms of schizophrenia.

2.2.1 Study type

Inclusion of randomized controlled trials: Mock randomized controlled trial. For instance, there was a high risk of bias when implementation was done every other day. This systematic review would include this kind of study. Yet, sensitivity analysis was performed. With an unknown randomization method, cluster randomized and randomized crossover studies would also be included and sensitivity analysis was performed.

2.2.2 Study participants

Recognized psychiatric diagnostic criteria: (a) The International Classification of Diseases (ICD), (b) the Diagnostic and Statistical Manual of Mental Disorders

(DSM), and (c) the Chinese Classification of Mental Disorder (CCMD), diagnosed as schizophrenia.

2.2.3 Exclusion criteria

The following studies were excluded: (a) non-human studies; (b) narrative review and reporting studies; (c) non-placebo control; (d) research plan; (e) studies of repeated publication.

2.2.4 Intervention measures

(a) Intervention group

The intervention group could be one of the following situations: high frequency (the stimulation frequency higher than 1Hz) or low frequency (the stimulus frequency equal to or lower than 1Hz); the stimuli were placed on the left, right, or bilateral dorsolateral prefrontal cortex; rTMS could be combined with other interventions such as drug therapy, psychotherapy, and so forth.Single TMS pulse intervention or studies that had less than 1 week intervention time were excluded.

(b) Control group

The control group could be one of the following situations: rTMS mock stimulation, electroconvulsive therapy (ECT), drug therapy, psychotherapy, and rTMS treatment with different parameters.

2.3 Literature screening and data extraction

The literature screening process of this study is shown in Figure 1. The literature search was performed independently by two researchers (Junjie Wang, Hong Gan) using the search terms in the electronic databases. All the documents retrieved were managed using EndNote X5 software. The literature was screened by two researchers (Yingqun Zhou, Hong Gan). The first step was to remove repeated studies. The second step was to screen the literature by browsing the literature titles and abstracts according to the inclusion and exclusion criteria. The third step was to read the full text of the selected literature and to confirm included studies by further screening of the literature according to the inclusion criteria and exclusion criteria. If the two search results were different, the two researchers reviewed the literature together and analyzed the reasons for the differences. If the opinions were still inconsistent, a third person (Jiaoyan Pang) would examine and make the final decision. The data extraction table was developed by two researchers (Hui Li, Junjie Wang) for data extraction and verification. The extraction contents included the research publication year, blind method, sample size, age, course of disease, baseline PANSS score evaluation, medication compliance, stimulation site, positioning method, stimulation frequency and intensity, total number of rTMS treatment, control group stimulation model, number of pulses, and the time of follow-up.

2.4 Quality evaluation of literature

Risk of bias evaluation: the RCTs included were assessed by two independent investigators (Yingqun Zhou, Junjie Wang) based on the risk of bias assessment method recommended by the Cochrane manual version 5.3.0. The specific contents included: (a)random sequence generation; (b) allocation concealment; (c) whether to use the blind method (blinding of the subjects and the treatment providers, blinding of the result evaluators); (d) incomplete results data; (e) other potential risks that affected authenticity. When there was discrepancy of options between the 2 researchers, a third person (Hui Li) would make the determination. If the assessment information was lacking, we contacted the corresponding author via e-mail.

Quality of evidence and grades of recommendation: based on the results of the main outcome indicators of the systematic review, the GRADE system recommendation grading method was used to evaluate the quality of evidence. The quality of evidence grades were as follows: (a) high quality: further research was unlikely to affect the reliability of the efficacy evaluation results; (b) medium quality: further research was likely to affect the reliability of the efficacy evaluation results and was very likely to change the outcome of the evaluation; (c) low quality: further research was very likely to affect the reliability of the efficacy evaluation results and the evaluation outcome was very likely to change; (d) extremely low quality: the results of any efficacy evaluation were uncertain.

2.5 Outcome indicators

2.5.1. Main outcome indicators

Effectiveness was defined as improvement in negative symptoms. The final outcome assessment scales included in this study were the Scale for the Assessment of Negative Symptoms (SANS) and the negative subscale of PANSS.[21]

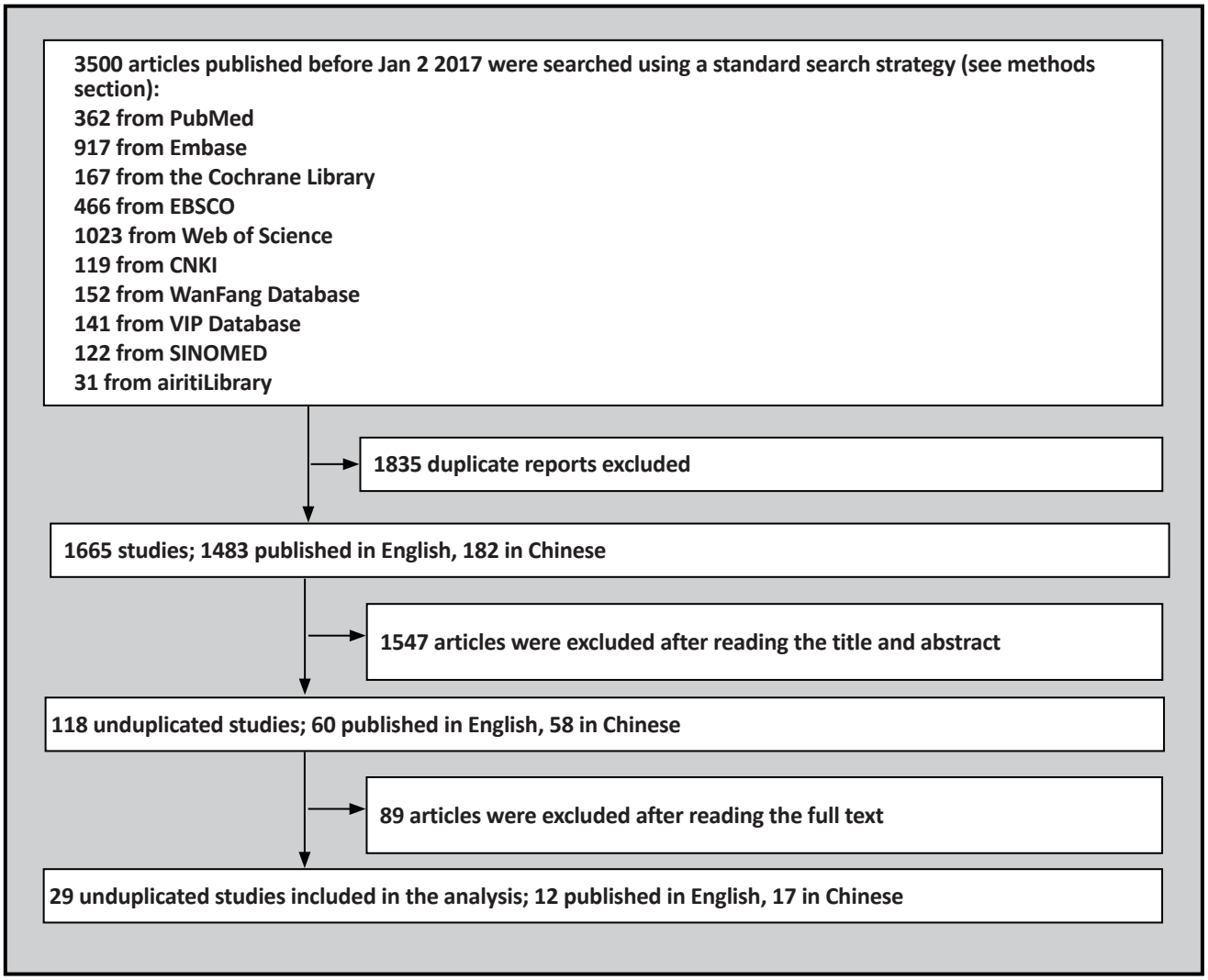
2.5.2. Secondary outcome indicators

a) Acceptability: including any cause of drop-out.
b) Safety of rTMS: the differences of adverse effects between rTMS group and control group were compared including severe adverse effects such as epilepsy and mild adverse effects such as headache, dizziness, insomnia, irritation, discomfort or pain at stimulation site, facial spasm and so forth.

2.6 Statistical analysis

Rev Man 5.3 and Stata 14.0 statistical software were used for meta-analysis. For the extracted continuous and categorical variable data, the simple criteria for statistical analysis of parameters were used based on whether the variables are consistent with normal distribution. When the minimum value was 0, the mean

Figure 1. Flowchart of the literature search and screening



value was larger than twice the standard deviation; if the minimum value was greater than 0, a normal distribution was determined when subtraction of the minimum value from the mean value[27] was larger than twice the standard deviation. The measurement data were expressed by the adoption of the combined effect as the standardized mean differences (SMD). Count data were shown by using relative risk (RR). The results of the combined calculation were shown in the forest plot. Heterogeneity test was done first. Studies with I^2 (variation statistics of the effect size caused by heterogeneity) < 50% and $p \geq 0.1$ in Q test were regarded as having homogeneity; therefore, the fixed effects model was used. When $I^2 > 50\%$ or $p < 0.1$ in Q test, it explained that actual heterogeneity existed in the study; therefore, the random effects model was used and the source of heterogeneity was analyzed. This study adopted the Cochrane risk of bias assessment tool to evaluate different risk of biases. Subgroup analysis and meta regression analysis were used to explore the sources of heterogeneity based on the factors that might influence heterogeneity in the study. Funnel plot was used to analyze publication bias.

3. Results

3.1 Basic characteristics of the included literature

See figure 1 for the process of study inclusion. There were a total of 3500 articles retrieved using relevant search strategies in 5 English databases and 5 Chinese databases, where the articles were published before January 2, 2017. 1835 duplicate studies were removed at first with 1665 articles remaining. During the title and abstract screening phase an additional 1547 articles were removed. Finally, after reading the full text of the remaining 118 articles, we removed 86 of them and were left with 32 articles. However, because the study

by Goyal and colleagues [28] merely provided the mean value, not the standard deviation, it was excluded as well. In addition, two studies by Hajak (2004) and Cordes (2010) were both excluded for providing change-from-baseline PANSS scores but not final scores. In the end, 29 articles [15-17, 21-26, 30-49] were included in this study for data analysis.

See table 1 for the characteristics of all final included studies. According to the PANSS, the judging standard was a score of 20 or higher on the symptoms

Table 1. The basic characteristics of the included studies

Studies	Blinded Method	Sample size TMS group Control group	Age Mean (SD) TMS group Control group	Course of disease Mean (SD) TMS group Control group	Baseline PANSS Mean (SD) TMS group Control group	Stimulation site[abde], Positioning method	Stimulation frequency Stimulation intensity	Treatment frequency, Number of pulses each time
Klein 1999[29]	Double blind	18 17	30.2 (10.0) 29.5 (9.3)	7.9 (8.6) 7.9 (8.7)	16.5(5.6) 14.1(5.0)	R-PFC -	1Hz 110%	10 times -
Holi 2004[15]	Single blind	11 11	38.5(10.2) 34.8(9.8)	13.5(8.9) 12.9(12)	28.9(11.5) 31.0(7.7)	L-DLPFC -	10Hz 100%	10 times -
Novak 2006[16]	Double blind	9 9	35(9.2) 32.8(6.3)	13.1(8.1) 9.9(4.1)	20 (5.9) 20.5(3.3)	L-DLPFC -	20Hz 90%	10 times 2000 pulses
Xu 2006[36]	Double blind	frontal lobe 21,22 parietal lobe 12,12	36.2(13.7) 37.6(14.6) 34.3(10.6) 45.6(14.1)	12.1(10.1) 12.0(10.2) 13.3(9.9) 21.0(11.8)	22.3(7.8) 22.1(5.8) 23.1(6.7) 23.6(7.6)	B-DLPFC Bilateral parietal lobe	Confirmation of frequency according to the main frequency of EEG, 80%	10 times -
Mogg 2007[17]	Double blind	8 9	50.8 (14.5) 33.6 (9.8)	25 (16.7) 9 (7.9)	29.8 (3.0) 29.1 (2.6)	L-DLPFC -	10Hz 110%	10 times 2000 pulses
Fitzgerald 2008[30]	Double blind	12 8	37.2(10.4) 33.2(9.8)	Not provided	16.8(3.5) 18.6(6.4)	L-DLPF MC moves forward 5CM	10Hz 110%	15 times 2000 pulses
Liu 2008[37]	Double blind	13 12	34.5(13.0) 34.4(8.2)	5.10(4.15) 7.83(5.3)	24.9(7.3) 20.6(8.1)	L-DLPFC -	10Hz 110%	20 times 1500 items
Zhang 2010[38]	Double blind	15 15	37(11) 39(14)	16(12.6) 12(8.7)	25.7(3.1) 26.9(2.9)	L-DLPFC -	TBS mode 80%	20 times 2400 pulses
Ren 2011[40]	Double blind	12 11	31(7) 37.7(12.3)	8.2(3.8) 8.9(4.2)	28.2(6.8) 23.7(6.2)	B-DLPFC F3,F4	20Hz 80%	10 times 800 items
Chen 2011[39]	Double blind	24 22	37.4(11.8) 39.7(13.3)	17(12.6) 13(12.6)	25.9(3.2) 26.9(2.5)	L-DLPFC -	iTBS mode 80%	20 times 2400 pulses
Barr 2012[32]	Double blind	13 12	40.5(12.2) 47.9(12.8)	18.6(11.3) 27.3(16.4)	14.9(6.4) 15.5(6.3)	L-DLPFC Neuronavigation technique	20Hz 90%	20 times 750 pulses
Zheng 2012[21]	Double blind	TBS 18 10 Hz19 20Hz 19 17	56.4(9.3) 56.5(7.4) 56.8(5.4) 55.6(5.8)	-	23.6(5.4) 23.3(4.9) 23.7(5.4) 22.8(5.1)	L-DLPFC -	TBS mode 10Hz 20 Each groups was 80%	10Hz and 20Hz group: 5 times /1200 pulses TBS group: 5times/400 pulses
Prikryl 2013[33]	Double blind	23 17	31.6 (8.0) 33.9(10.0)	4.9 (5.1) 5.9 (7.9)	-	L-DLPFC MC moves forward 5CM	10Hz 110%	15 times 2000 pulses

Table 1. The basic characteristics of the included studies (continuted)

Studies	Blinded Method	Sample size TMS group Control group	Age Mean (SD) TMS group Control group	Course of disease Mean (SD) TMS group Control group	Baseline PANSS Mean (SD) TMS group Control group	Stimulation site[abde], Positioning method	Stimulation frequency Stimulation intensity	Treatment frequency, Number of pulses each time
Duan 2013[41]	Double blind	21 20	26.6(7.2) 27.3(8.5)	4.8(2.5) 4.5(2.6)	22.3(3.1) 22.6(3)	L-DLPFC F3 of 10/20	10Hz 100%	20 times -
Gan 2014a[22]	Double blind	20 21	26(8) 27(7)	5.4(2.7) 4.8(2.5)	22.9(3.6) 22.3(3.1)	L-DLPFC F3 of 10/20	TBS mode 100%	20
Gan 2014b[42]	Single blind	38 37	27.4(8.6) 26.9(7.5)	5.1(2.3) 4.7(2.1)	22.8(6.6) 22.3(6.8)	L-DLPFC F3 of 10/20	10Hz 100%	20
Rabany 2014[34]	Double blind	20 10	33.1(11.3) 35.9(11.0)	-	22.7(8.4) 20.1(3.6)	L-DLPFC MC moves forward 5CM	20Hz 120%	20 times 1680 pulses
Zhao 2014[43]	Single blind	TBS 24 10Hz 24 20Hz 23 22	47.7(11.8) 48(12.2) 49.1(10.6) 46.7(13.1)	-	38.7(7.4) 37.6(5.1) 36.2(8.8) 38.6.7(2.1)	L-DLPFC -	10Hz(80-110%) 20Hz(80-110%) TBS(80%)	10 and 20 Hz groups: 20 times /1500; TBS group: 20 times /2400 pulses
Quan 2015[24]	Double blind	78 39	46.9 (7.9) 46.9 (9.1)	20.5(11.0) 18.0(11.0)	26.2(3.6) 27.0(4.4)	L-DLPFC MC moves forward 5CM	10Hz 80%	10 times 800 pulses
Lange 2015[35]	Double blind	16 16	41.8(11.6) 32.3(9.7)	15.6(10.1) 9.92(8.9)	20.6(3.7) 19.7(5.4)	Bilateral DLPFC F3 and F4	10Hz 90%	30 times 2000 pulses
Xu 2015[23]	evaluator blind	5Hz 30 10Hz 30 30	44.4(6.2) 46.8(6.7) 44.7(4.3)	11.8(3.6) 11.6(3.7) 12.8(3.5)	26.0(3.2) 25.33(2.6) 25.2(2.7)	L-DLPFC -	5Hz 10Hz Both groups were 80%	10 times 2500 pulses
Bai 2015[44]	Single blind	36 35	35.4(7.1) 34.6(6.3)	25.4(7.3) 27.1(4.2)	28.8(4.0） 29.3(3.9）	L-DLPFC -	10Hz 100%	20 times 800 pulses
Gan 2015[49]	Single blind	32 35	28(9) 29(9)	4.5(2.9) 4.9(2.9)	22(6) 25.2(2.7) 22(6) 25.2(2.7)	L-DLPFC -	10Hz 100%	20 times 4000 pulses
Wang 2015[45]	Double blind	41 42	42.5(5.6) 42.0(5.9)	5.9(2.4) 6.2(2.7)	26.6(4.1) 26.8(3.3)	L-DLPFC -	10Hz 110%	20 times 2400 pulses
Zhang 2015[46]	Single blind	35 34	40.7(9.8) 39.1(8.8)	5.2(3.0) 5.89(3.1)	29.4(2.1) 28.5(2.3)	L-DLPFC -	10Hz -	20 times 800 pulses
Tikka 2016[26]	evaluator blind	10 10	28.4(2.9) 25.5(5.0)	3.6(1.2) 3.5(1.1)	17.5(5.6) 17.1(5.5)	R-IPL[e] MRI navigation	cTBS 5Hz 120%	10 times 900 pulses
Garg 2016[25]	Double blind	20 20	32.4(8.4) 37.2(7.9)	7.2(7.5) 6.1(5.6)	25.3(8.0) 20.6(9.2)	Below occipital protuberance 1CM	TBS 100%	10 times 600 pulses
Li 2016[47]	Double blind	25 22	45.2(10.2) 44.9(10.6)	19.7(2.2) 19.9(2.3)	27.2(7.6) 25.9(7.2)	L-DLPFC -	10Hz 110%	20 times -
Ma 2016[48]	Double blind	58 60	-	-	19.6(3.8) 20.9(4.7)	L-DLPFC -	10Hz 90%	20 times 1000 pulses

a.F3 and F4: Electrode placement location of the International 10–20 system
b. L-DLPFC: left dorsolateral prefrontal cortex; R-DLPFC: right dorsolateral prefrontal cortex; B-DLPFC: bilateral right dorsolateral prefrontal cortex
c. cTBS: continuous theta burst stimulation; iTBS: intermittent theta burst stimulation
d. MC: motor cortex; e. R-IPL: inferior parietal lobule; f. SD: standard deviation; g. no data or not described

subcale. Except for 7 of the studies, [16,26,29,30,32,35,48] the included patients with schizophrenia in most of the studies mainly had negative symptoms. Patients took antipsychotics before treatment and the original drug treatment was unchanged during the treatment process. Therefore, all the studies were combined with rTMS as a synergistic treatment. The time for follow-up was mostly 2 weeks after treatment. The smallest study sample size was 17 cases; [17] the largest was 117 cases. [24] The smallest mean age was 26 years[22] and the oldest was 56.[21]

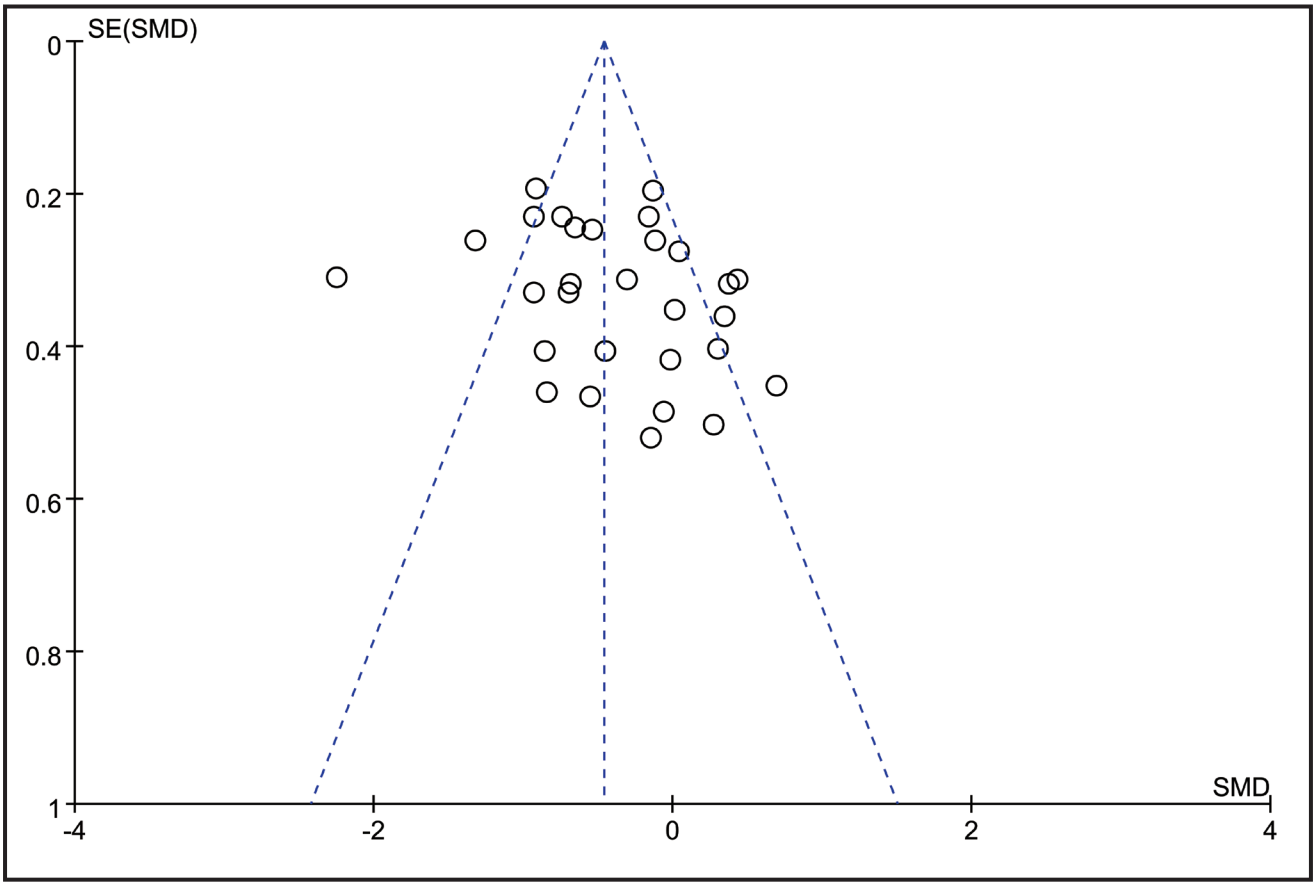
In terms of treatment parameters, the stimulation sites were the following: other than 2 studies, most of the studies used high frequency stimulation on the left dorsolateral prefrontal cortex. The stimulation site of the study of Garg and colleagues was the speech function in the cerebellum. Frequency of stimulation: most used high frequency stimulation, however, there were 5 studies [21,22,26,38,39] using transcranial magnetic stimulation with thet a burst stimulation. The course of treatment: 2 weeks, 3 weeks, or 4 weeks; other than Lange 2015[50] there was one study that had stimulation treatment daily. Except for the 2 studies by Gan,[22, 42] other control groups used mock stimulation as the control study. Nevertheless, there were differences in method of mock stimulation. Most of them chose a mock stimulus coil or flipped the magnetic coil.

3.2 Research quality

The results of the quality assessment are shown in figure 2 and table 2. Only 7 out of the 29 studies did not describe the random sequence generation in detail resulting in a rating of "unable to determine".[15-17, 22,29,32,34] The method of random sequence generation was provided in 22 studies resulting in a rating of "low risk". There were 15 studies[17,26,36,42,51] that described the specific implementation process of the blinded method for participants. Except the 3 studies[22, 34, 46] that did not describe the blinding of the evaluators, the evaluation of the negative symptom outcome indicators were assessed by the evaluators using the blind method in all other studies. The loss to follow-up bias in one study[26] was rated as "high risk" because the drop-out rate of this study was larger than 20% and the intention-to-treat analysis was not implemented. There were 5 studies[15,16,29,30,42] that reported incomplete data due to drop-out and adverse effects.

See figure 2 for the funnel plot of the main treatment efficacy outcome indicators given by the 29

Figure 2. Funnel plot of potential publication bias of the efficacy of antipsychotics combined with rTMS in the treatment of the negative symptoms of schizophrenia



studies. The asymmetry of the funnel plot asymmetry may be due to publication bias, but there may also be other factors leading to the asymmetry.

3.3 Treatment effect

In the 29 studies, only 1 study assessed the efficacy of the negative symptoms with the SANS scale.[33] The

Table 2. Risk of bias assessment based on the Cochrane risk of bias assessment tool for the 29 included studies

Studies	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Klein 1999[29]	Unclear	Unclear	Unclear	Low	Unclear	High	Low
Holi 2004[15]	Unclear	Low	Unclear	Low	Unclear	High	Unclear
Novak 2006[16]	Unclear	Unclear	Unclear	Low	Unclear	High	Low
Xu 2006[36]	Low	Unclear	Low	Low	Low	Low	Low
Mogg 2007[17]	Unclear	Low	Unclear	Low	Low	Low	Low
Fitzgerald 2008[30]	Low	Low	Unclear	Low	Unclear	Low	Unclear
Liu 2008[37]	Low	Unclear	Low	Low	Low	Low	Low
Zhang 2010[38]	Low	Unclear	Low	Low	Low	Low	Low
Ren 2011[40]	Low	Unclear	Low	Low	Low	Low	Low
Chen 2011[39]	Low	Unclear	Low	Low	Low	Low	Low
Barr 2012[32]	Unclear	Unclear	Unclear	Low	Low	Low	Low
Zheng 2012[21]	Low	Unclear	Low	Low	Low	Low	Low
Prikryl 2013[33]	Low	Unclear	Low	Low	Unclear	Unclear	Low
Duan 2013[41]	Low	Unclear	Low	Low	Low	Low	Low
Gan 2014a[22]	Unclear	Unclear	Unclear	Unclear	Low	High	Low
Gan 2014b[42]	Low	Low	Unclear	Low	Low	Low	Low
Rabany 2014[34]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Zhao 2014[43]	Low	Unclear	Low	Low	Low	Low	Low
Quan 2015[24]	Low	Unclear	Low	Low	Unclear	Unclear	Low
Lange 2015[35]	Low	Low	Unclear	Low	Unclear	Low	Low
Xu 2015[23]	Low	Unclear	Low	Low	Low	Low	Low
Bai 2015[44]	Low	Unclear	Unclear	Low	Low	Low	Low
Gan 2015[49]	Low	Unclear	Unclear	Low	Low	Low	Low
Wang 2015[45]	Low	Unclear	Low	Low	Low	Low	Low
Zhang 2015[46]	Low	Unclear	Unclear	Unclear	Low	Low	Unclear
Tikka 2016[26]	Low	Low	Low	Low	Low	Low	Low
Garg 2016[25]	Low	Unclear	Unclear	Low	Low	Low	Low
Li 2016[47]	Low	Unclear	Low	Low	Low	Low	Low
Ma 2016[48]	Low	Unclear	Low	Low	Low	Low	Low

[a] Other biases considered included the bias of the study specificity and false research results
[b] If these 7 items were evaluated as "low", the overall bias was evaluated as a "low risk of bias "; If there was at least one "Unclear" and the rest were "low", this study was "unable to evaluate the risk of bias"; If there was any aspect evaluated as "high", this study was "high risk of bias"

rest of the studies provided data from the PANSS-negative subscale, which included 1400 participants. The heterogeneity of the included studies was high. The random effect model was used when I^2 was 73%, SMD= -0.40, and 95%CI= -0.62~-0.18. As shown in figure 3, the efficacy of the synergistic rTMS treatment on negative symptoms in schizophrenia had a weak effect. According to the GRADE evaluation criteria, the overall evidence quality level for the primary outcome indicator, which was the improvement of negative symptoms at the end of the rTMS treatment, was "moderate". See table 3.

Heterogeneity of results may be due to differences across studies in patients' negative symptom severity

Figure 3. Forest plot of efficacy of antipsychotic drugs combined with rTMS in treatment of negative symptoms in schizophrenia

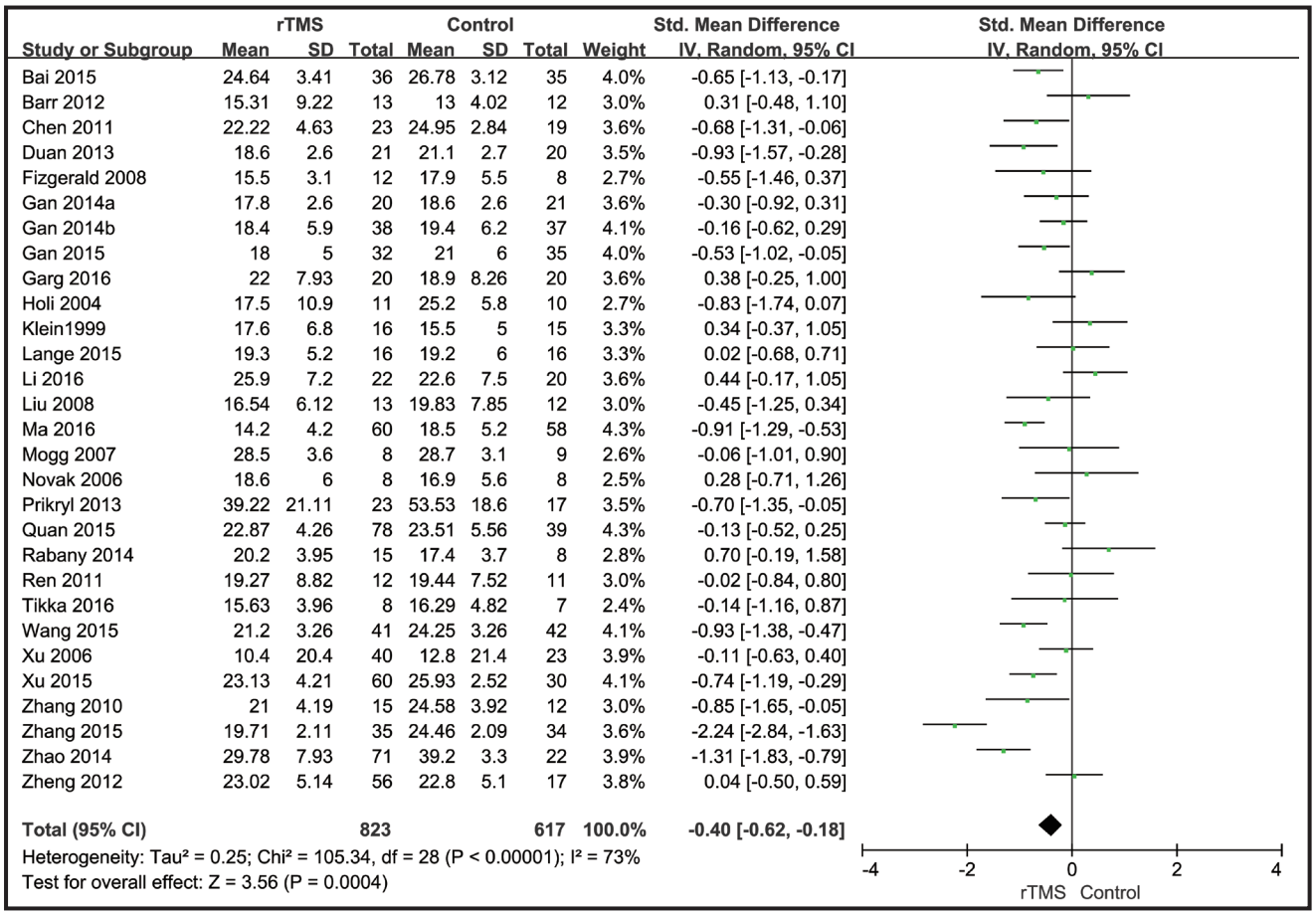


Table 3. Summary of the quality GRADE rating of different outcome indicators in randomized controlled trials and the meta analysis results of antipsychotic drugs combined with rTMS in the treatment of negative symptoms of schizophrenia

Outcome	Number of Study (including sample size)	Heterogeneity test		Analysis model	Group effect test		Estimated value[a]	95% CI of the estimated value	GRADE [b]
		I^2	*p*		*z*	*p*			
Clinical efficacy	1440	73%	<0.001	Random effect	3.56	<0.001	-0.40 (SMD)	-0.62, -0.18	Medium
Drop-out situation	1492	0%	0.98	Fixed effect	1.32	0.19	0.75 (RR)	0.49, 1.15	Low
Adverse effect	1296	0%	0.73	Fixed effect	4.23	<0.001	2.20(RR)	1.53, 3.18	Low

[a]Standardized mean difference was used in the comparison of continuous variables; Risk ratios of categorical variables (RR)
[b]The use of Grades of Recommendation Assessment Development and Evaluation to rate each result's evidence quality

and differences in stimulation methods. Therefore, we used meta-regression to assess the relationship between the above factors and the source of heterogeneity. In addition, we also included age and course of disease as possible regulatory variables into the meta-regression model to analyze the effects of these two factors on heterogeneity. The results showed that, conducting separate meta-regression analysis on the above mentioned 4 factors, the regression model of the treatment efficacy and the baseline PANSS negative symptom score found that t=-2.23, p=0.035, indicating the severity of the negative symptoms were one of the sources of heterogeneity. After putting the severity of the negative symptoms into the meta regression model, the variance component of the study was reduced from 0.26 to 0.25, showing that 3.85% of the source of heterogeneity could be explained. The regression models of treatment efficacy, rTMS method, course of disease, and age respectively found t=0.89, p=0.381; t=1.20, p=0.245, and t=-0.38, p=0.709, indicating that the association of these 3 factors and heterogeneity among the studies were not statistically significant. After placing the four factors into the meta-regression model simultaneously, the variance component of the study was reduced from 0.26 to 0.19, showing that 26.92% of the source of heterogeneity could be explained. Figure 4 was the meta-regression analysis of the standardized mean difference (SMD) of the rTMS combined with antipsychotic drugs for the treatment of negative symptoms and the baseline PANSS negative symptom score.

3.4 Acceptability

There were 28 studies that reported dropouts and the total sample size was 1492 cases. The heterogeneity of the studies was low. Fixed effect model was selected because I^2 was 0%. The analysis results showed that RR= 0.75, 95%CI= 0.49~1.15. As the group that used synergistic treatment for the negative symptoms of schizophrenia, rTMS had no difference in the acceptability to the control group, as shown in figure 5. In addition, the GRADE evidence quality of the outcome indicator was rated as “low level”, as shown in table 3.

Figure 4. Meta-regression analysis of the standardized mean difference (SMD) of the TMS combined with antipsychotic drugs for the treatment of negative symptoms and the baseline PANSS negative symptom score

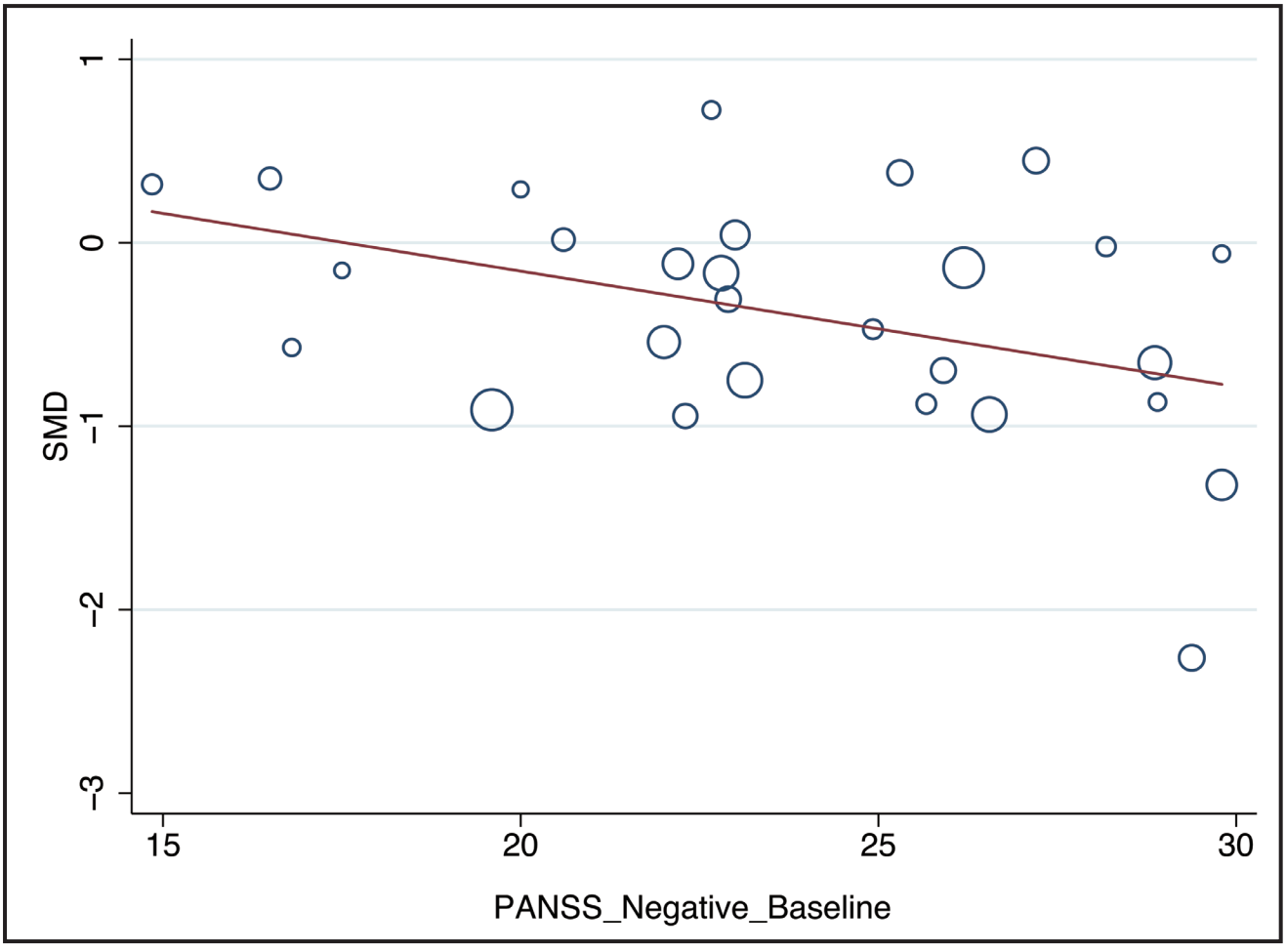
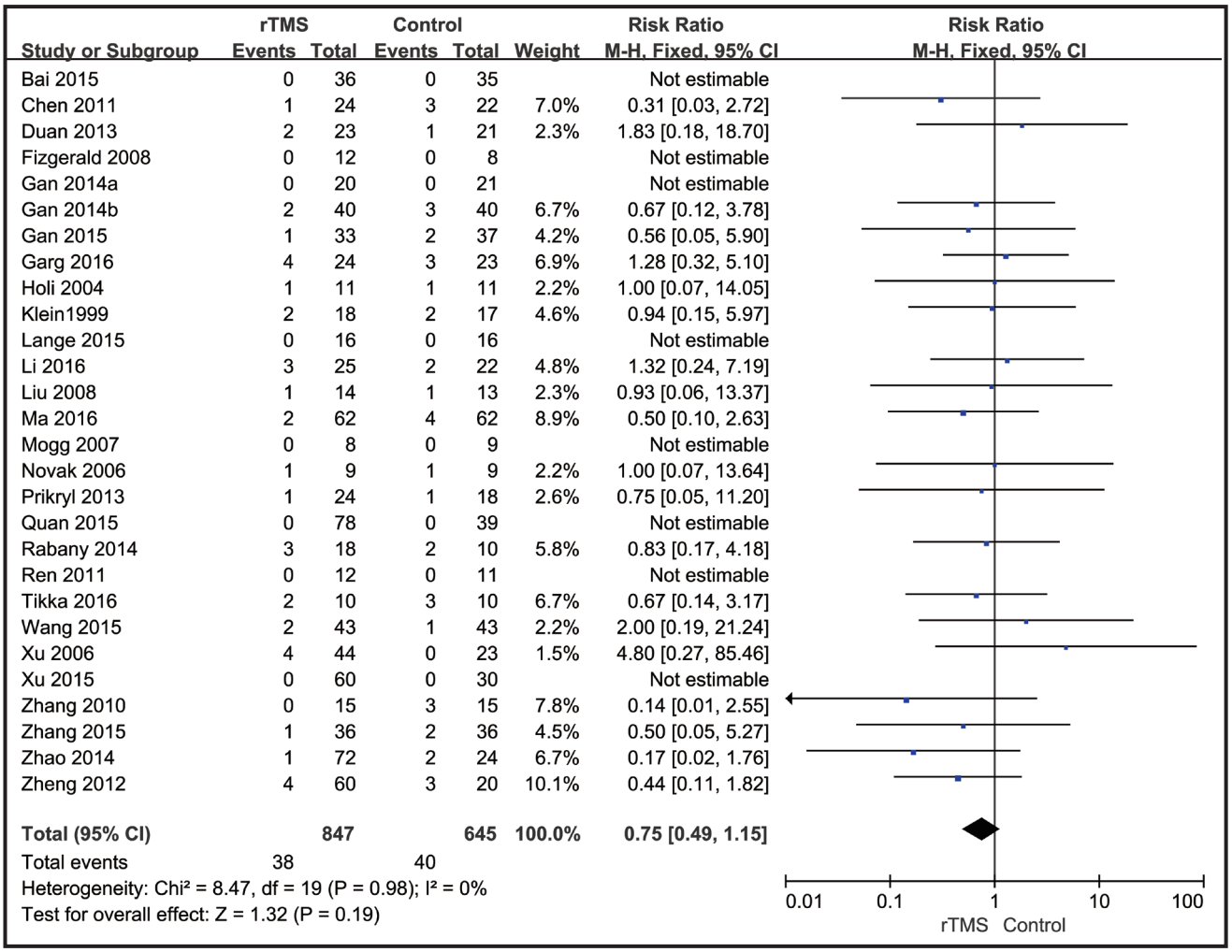


Figure 5. Efficacy of antipsychotic drugs combined with rTMS in the treatment of negative symptoms of schizophrenia: drop outs



3.5 Adverse effects

There was no report of severe adverse events in all included studies. There were 19 studies which had mild adverse effect induced by rTMS. There were reports on the specific adverse effects of 1296 schizophrenic patients in addition to the reports on the total number of cases with adverse effects. The adverse effects reported included headache, dizziness, pain in the stimulated area, facial spasm, and insomnia. The meta-analysis of the results showed that rTMS for the treatment of negative symptoms had a higher incidence of adverse effects: RR= 2.20, 95%CI= 1.53~ 3.18. Moreover, the heterogeneity was low (I^2 =0), as shown in figure 6. However, the evidence quality of these studies was rated as "low level" (table 3).

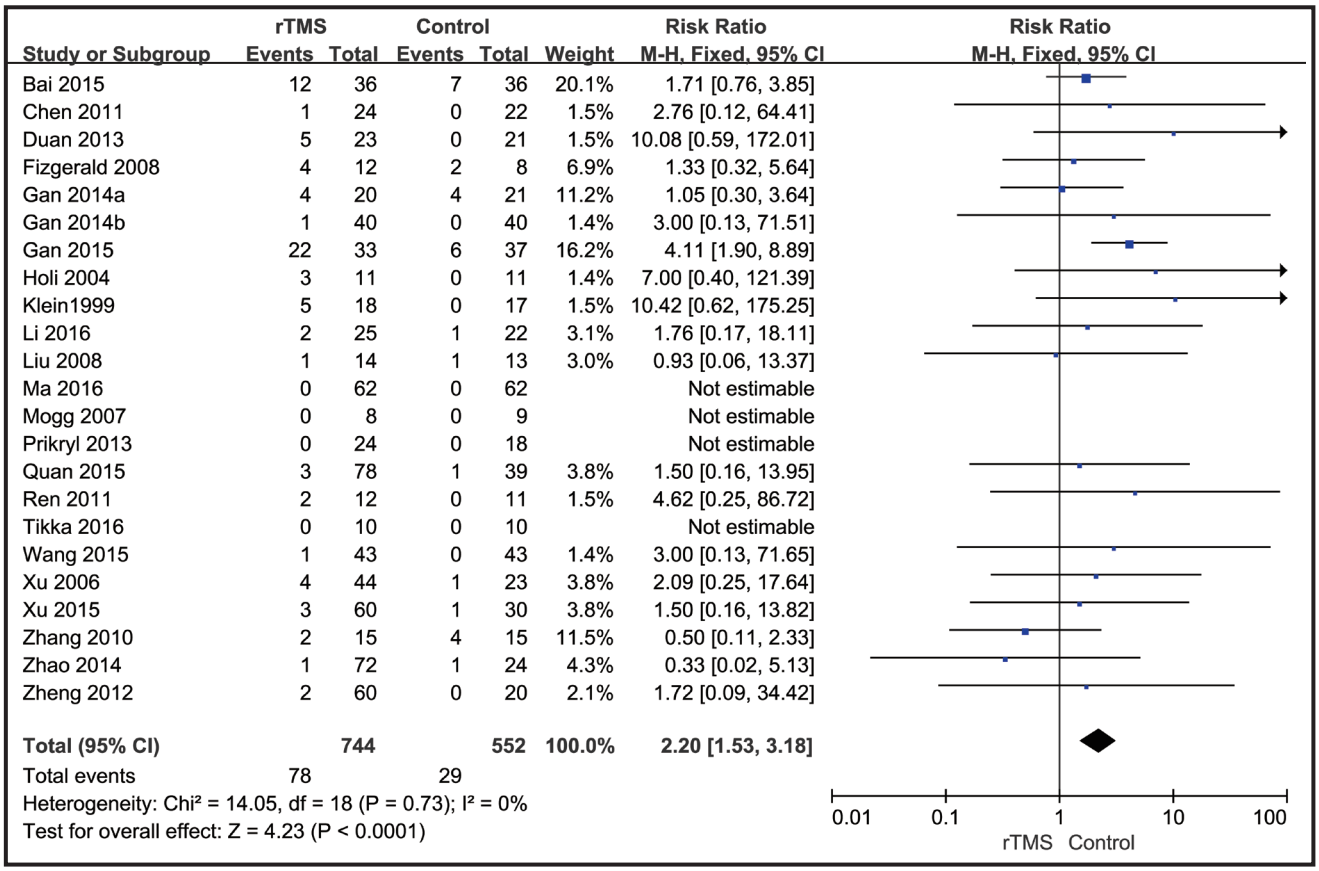
4. Discussion

4.1 Main findings

There were less treatment options for the negative symptoms of patients with schizophrenia. Although there have been several systematic reviews that assessed the efficacy of rTMS treatment, the development of new treatment paradigms in recent years and the increase of studies with large sample sizes may have supplemented or changed the conclusions of the previous systematic reviews. The aim of this study was to evaluate and update the efficacy and safety of the rTMS treatment on negative symptoms of schizophrenia.

We screened 29 RCTs studies with major outcome indicators from both English and Chinese databases, including 12 English articles and 17 Chinese articles. The studies that had a large sample size and long course of treatment were mostly Chinese. Based on the meta-analysis results of 1440 cases, antipsychotic treatment combined with the rTMS treatment may improve the negative symptoms of patients with schizophrenia. Based on the risk of bias assessment of a single study, the evidence quality GRADE rating of the primary outcome indicator (efficacy) was "moderate level", meaning that the outcome indicator result was a weak

Figure 6. Adverse effects of antipsychotic drugs combined with the rTMS in treatment of negative symptoms of schizophrenia forest plot



recommendation for supporting the use of rTMS intervention. In terms of acceptability and adverse effects, rTMS had better acceptability and no serious adverse effect.

4.2 Limitations

The quality of the RCT studies included in this systematic review was high. The evaluators were blinded. However, the heterogeneity of our main outcome indicators was high. Further meta regression analysis showed that the severity of negative symptoms when first entered into the group might possibly be the source of heterogeneity. In addition, differences in the rTMS treatment methods in the included studies such as the intensity of stimulation, the total number of pulses, and so forth, may also be a source of heterogeneity.

4.3 Implications

This study conducted evaluation of RCT studies of rTMS combined with antipsychotics in the treatment of the negative symptoms of schizophrenia, discovering that the use of rTMS had a relatively weak effect on the improvement of negative symptoms. Although its use had good acceptability, the treatment might induce adverse effects such as dizziness, headache, and so forth. For patients with schizophrenia who have persistent negative symptoms, the use of rTMS might be considered clinically. However, we should be cautious in the interpretation of the results due to the high heterogeneity of the studies. Further studies are needed to determine the optimal mode of treatment, such as stimulation frequency, stimulation intensity, duration of treatment, and total pulse number.

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Conflict of interest statement

The authors declare no conflict of interest related to this manuscript.

Authors' contributions

Junjie Wang and Hong Gan were responsible for the literature search.

Hong Gan, Yingqun Zhou, and Jiaoyan Pang were responsible for article selection.

Hui Li and Junjie Wang were responsible for data extraction.

Junjie Wang, Yingqun Zhou, and Hui Li were responsible for risk of bias assessment.

Junjie Wang and Hui Li were responsible for statistical analysis.

Hui Li and Junjie Wang were responsible for writing up the article.

Jijun Wang and Chunbo Li were responsible for planning and guidance.

重复经颅磁刺激治疗对精神分裂症患者阴性症状的疗效和安全性：系统综述

王俊杰 周颖群 甘鸿 庞娇艳 李惠 王继军 李春波

背景：阴性症状是精神分裂症治疗的难点之一，抗精神病药物对其疗效较差。重复经颅磁刺激（repetitive transcranial magnetic stimulation, rTMS）是一项新型脑皮质刺激技术，被认为是一项安全而有前景的精神障碍治疗方法，近年来临床研究及新的治疗模式增多，rTMS 治疗阴性症状的疗效和安全性评价需要更新。

目标：探索 rTMS 治疗对精神分裂症患者阴性症状的有效性及安全性。

方法：我们从以下数据库搜索了相关的临床对照试验：PubMed、EMBASE、the Cochrane Library、EBSCO、Web of science、中国知网、维普、万方、中国生物医学文摘数据库、台湾学术文献数据库等数据库，检索时间截止于 2017 年 1 月 2 日。按照预先定好的纳入和排除标准筛选研究文献，提取数据后应用 RevMan 5.3 和 Stata 14.0 对数据进行统计分析。对纳入研究进行质量评价，采用 Cochrane 风险评估偏倚工具评估各种偏倚的风险性。结合 GRADE (Grades of Recommendation, Assessment, Development, and Evaluation, GRADE) 系统推荐分级方法为参照标准，进行主要结局指标证据水平的分级。

结果：总共检索到 3500 篇文献，最终 29 篇文献纳入 meta 分析，合计样本量 1440 例。进行 meta 分析后发现，抗精神病药物治疗合并使用 rTMS 可改善患者的阴性症状（SMD=-0.40，95%CI=-0.62~-0.18）。根据 Cochrane 风险评估偏倚工具对疗效的评估的偏倚进行评估，其中 6 篇研究评价为“高偏倚风险”，其它为“无法判断”。根据 GRADE 分级的评估、制定和评价标准，该疗效评估指标的证据质量是“中等”。rTMS 治疗的可接受性较好（RR=0.75，95%CI=0.49~1.15，基于 28 项研究的 1492 例样本），但接受 rTMS 治疗的患者出现轻微不良反应的比率更高（RR=2.20，95%CI=1.53~3.18，基于 23 项研究的 1296 例样本）。

结论：抗精神病药物治疗合并使用 rTMS 治疗可以一定程度改善精神分裂症患者的阴性症状，可接受性较好，不良反应较轻。但是本研究存在发表性偏倚，且研究的异质性较高，所以对结果进行解释时需要慎重。

关键词: 重复经颅磁刺激治疗; 精神分裂症; 阴性症状; 系统综述；meta 分析

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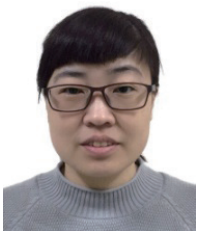

Junjie Wang graduated at Jining Medical University in 1998 with her bachelor's degree in Medicine and graduated from Shanghai Jiaotong University School of Medicine with her master's degree in 2003. In 2014, she was accepted into the Shanghai Jiaotong University School of Medicine and did her doctorate at the Shanghai Mental Health Center with a concentration in psychiatry and mental health. Her main research interests are the pathogenesis and early intervention for schizophrenia.

Notice for soliciting papers for the 14th academic conference of the Chinese Society of Neuroscience & Psychiatry (CSNP)

"The 14th annual academic conference of the Chinese Society of Neuroscience & Psychiatry", which is hosted by CSNP, and undertaken by Mental Health Center of Shanghai Jiao Tong University's medical school and Shandong Mental Health Center, will be held in the Luneng Hilton Hotel in Jinan, Shandong, from 29th June to 1st July, 2017.

The present society welcomes paper submissions and conference participations. The conference affair group accepts abstracts (objectives, methods, results and conclusions) under 1000 words. The website used for paper submissions and registrations is http://61.147.124.137:8088/2017/default.aspx. The academic committee of this conference will review papers and select high quality reports for presentation at the conference. We look forward to your participation and support! The deadline for paper submission is 1st June, 2017.

We welcome colleagues from all over China and abroad to participate in this conference held in scenic Jinan. We are looking forward to a lively discussion on developments in the field.

Dates: 29th June to 1st July, 2017 (check in on 29th June)

Address: Luneng Hilton Hotel in Jinan, Shandong, No.2888 South Erhuan Lu, Central District in Jinan

Cost arrangement: The registration fee, travel fee and accommodation fee are at your own expense. The registration fee is 1000 yuan (Shandong representatives and graduate students with student IDs can pay half of the registration fee). The accommodation fee from 30th June to 1st July 2017 is 500 yuan per standard room.

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Chinese Society of Neuroscience & Psychiatry

4th February 2017