Published in final edited form as:

Psychiatry Res. 2014 March 30; 215(3): 505–513. doi:10.1016/j.psychres.2013.12.019.

Revisiting the therapeutic effect of rTMS on negative symptoms in schizophrenia: A meta-analysis

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Abstract

This study sought to determine the moderators in the treatment effect of repetitive transcranial magnetic stimulation (rTMS) on negative symptoms in schizophrenia. We performed a meta-analysis of prospective studies on the therapeutic application of rTMS in schizophrenia assessing the effects of both low-frequency and high-frequency rTMS on negative symptoms. Results indicate that rTMS is effective in alleviating negative symptoms in schizophrenia. The effect size was moderate (0.63 and 0.53, respectively). The effect size of rTMS on negative symptoms in sham-controlled trials was 0.80 as measured by the SANS and 0.41 as measured by the PANSS. A longer duration of illness was associated with poorer efficacy of rTMS on negative symptoms. A 10 Hz setting, at least 3 consecutive weeks of treatment, treatment site at the left dorsolateral prefrontal cortex (DLPFC) and a 110% motor threshold (MT) were found to be the best rTMS parameters for the treatment of negative symptoms. The results of our meta-analysis suggest that rTMS is an effective treatment option for negative symptoms in schizophrenia. The moderators of rTMS on negative symptoms included duration of illness, stimulus frequency, duration of illness, position and intensity of treatment as well as the type of outcome measures used.

Keywords

Negative symptoms; Repetitive transcranial magnetic stimulation; Schizophrenia; Intervention; Meta-analysis

1. Introduction

Negative symptoms in schizophrenia constitute a heterogeneous syndrome that comprises flattened affect, poor communication, avolition, apathy, anhedonia, asociality, psychomotor retardation and impaired attention (Blanchard and Cohen, 2006; Moller, 2007). Among these, the two consensus components are affective flattening and diminished motivation (Blanchard and Cohen, 2006; Moller, 2007). Negative symptoms have been found to be the major predictor of functional outcome in patients with schizophrenia (Brune et al., 2011; Gonzalez-Blanch et al., 2010; Rabinowitz et al., 2012; Shamsi et al., 2011; Villalta-Gil et al., 2006) and are important for their ultimate quality of life and functional recovery (Alvarez-Jimenez et al., 2012; Gorecka and Czernikiewicz, 2004).

Treatment of negative symptoms in patients with schizophrenia, however, remains unsatisfactory. Current treatment of negative symptoms is mainly limited to second generation antipsychotics (SGA), which have been found to be better than first generation antipsychotics (FGA) in that SGAs had fewer side effects such as extrapyramidal symptoms and sedation than FGAs. Although SGAs appear to be more effective than placebo in alleviating negative symptoms, the effect sizes are only small to moderate (Buchanan et al., 2010; Erhart et al., 2006; Leucht et al., 2009). Various adjunctive therapies, such as selective serotonin reuptake inhibitors (SSRIs), glutamatergic compounds, oestrogen and acetylcholinesterase inhibitors, have also been used to alleviate negative symptoms, but their efficacies have been unimpressive (Erhart et al., 2006; Moller, 2003).

Recently, repetitive transcranial magnetic stimulation (rTMS) has been used for the treatment of various psychiatric disorders, such as obsessive-compulsive disorder, post-traumatic stress disorder, bipolar disorders, schizophrenia and depression (Rossi et al., 2009). The Food and Drug Administration (FDA) in the United States has recently approved the use of rTMS to treat refractory depression. Repetitive TMS was tested for the treatment of auditory hallucinations and negative symptoms of schizophrenia, while experiences with catatonic symptoms are limited. It has been suggested that negative symptoms in schizophrenia may be related to a lack of dopamine at the prefrontal cortex and hypofrontality (Hill et al., 2004; Remington et al., 2011). It has also been found that high frequency rTMS may be able to increase cortical excitability and modulate dopamine release (Eisenegger et al., 2008; Pell et al., 2011). This has led to the hypothesis that high frequency rTMS applied at the prefrontal cortex may be an effective treatment of negative symptoms in schizophrenia. Apart from this, rTMS could change the expression of glutamic acid decarboxylase, which is the synthetic enzyme of the precursor of γ -aminobutyric acid (GABA). This may be important as negative symptom scores have been found to be inversely related to benzodiazepine receptor binding in the medial frontal region (Busatto et al., 1997; Trippe et al., 2009).

To date two meta-analyses have been conducted to specifically examine the therapeutic effects of rTMS on negative symptoms in schizophrenia (Dlabac-de Lange et al., 2010; Freitas et al., 2009). However, the results of these two meta-analyses are different due to the inclusion of different number of studies. Freitas et al. (2009) concluded that there were significant and moderate effects of rTMS on negative symptoms when outcome was defined

by comparing the baseline and endpoint negative symptoms scores. However, when the analysis was limited to five sham controlled studies, the results became non-significant, which suggest that placebo effect should be taken into account. On the contrary, by comparing the mean changes of negative symptoms scores in pre- to post-treatment between active and sham controlled groups in nine studies, Dlabac-de Lange et al. (2010) reported a small but significant effect size supporting the efficacy of rTMS in treating negative symptoms. Another meta-analysis reported the efficacy of rTMS in a variety of psychiatric disorders. Only seven of the studies included examined the efficacy of rTMS on negative symptoms in schizophrenia, and the results showed that its effect size was small and non-significant (Slotema et al., 2010).

A number of factors may modulate the efficacy of rTMS on negative symptoms. These include the assessment tool used, baseline psychopathology, duration of illness (DOI), rTMS frequency, motor threshold (MT), stimulus location, total stimulus strength, and duration of stimulus. These factors have not been thoroughly analyzed in the two aforementioned meta-analyses. In addition, the number of studies included in these meta-analyses is small (eight and nine respectively). Because of this, further research taking into account the effect of possible moderators is needed to determine the efficacy of rTMS treatment on negative symptoms in schizophrenia. The present meta-analysis aimed to clarify the effects of rTMS on the treatment of negative symptoms in schizophrenia and to provide a comprehensive review on the possible moderators of rTMS treatment efficacy on negative symptoms in schizophrenia.

2. Methods

2.1. Selection of studies

Four data bases, namely, PubMed, Web of science, Elsevier and EBSCO, were used to identify relevant studies and the search period was from 1st January 1998 to 30th June 2013. The keywords used were: “schizophrenia” and “transcranial magnetic stimulation” or “TMS” or “rTMS”. In addition, reference lists in systematic reviews and meta-analyses were also examined.

2.2. Selection criteria for the meta-analyses

The following inclusion criteria were used to select articles for the present meta-analysis: diagnosis of schizophrenia was ascertained according to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Third Edition-Revision, Fourth Edition, Fourth Edition-Text Revision (DSM-III, III-R, IV or IV-TR) (American Psychiatric Association, 1980, 1987, 1994, 2000) or the 9th and 10th Edition of the International Classification of Diseases (ICD-9 or -10) (World Health Organization, 1978, 1993); Positive and Negative Syndrome Scale (PANSS) or Scale for the Assessment of Negative Symptoms (SANS) were used to assess negative symptoms (Andreasen, 1989; Kay et al., 1987); rTMS was employed as the intervention; study design was open, crossover or parallel; rTMS was applied for more than a single session; psychotropic medication dosages were unchanged for at least 4 weeks before the rTMS treatment and maintained throughout the trial; and when published studies reported overlapping data sets, only the largest sample was included.

Studies were excluded if they met at least one of the following exclusion criteria: single- or paired-pulse was delivered; case reports; rTMS effects were assessed after a single session; clinical outcome was assessed by rating scales that did not include negative symptoms scores; patients were on stable medication regimen for less than 4 weeks prior to rTMS.

Finally, all studies had to report the mean and standard deviation (S.D.) of the outcome measures before and after treatment; or had to provide *t* or *F* test values that could be used to calculate effect size. For studies that met inclusion criteria but did not report these statistics, the authors were contacted for this information.

2.3. Data extraction

For each study, we recorded the following variables with a semi-structured form: (1) name of the first author and year of publication; (2) study design; (3) demographic and clinical characteristics (sample size, sex, mean age, mean DOI, and percentage of use of FGA); (4) means and S.D.s of the selected outcome measure at baseline and after treatment for the active (uncontrolled studies) and sham groups (controlled studies); if means and S.D.s were not available, *t* or *F* test values were collected; (5) means and S.D.s of the baseline clinical status; and (6) TMS protocol [number of patients submitted to active/sham stimulation, frequency, intensity (% of motor threshold), number of sessions, total stimulus strength, sham coil position].

2.4. Effect size calculation

All our analyses were performed using the Comprehensive Meta-Analysis software package (Borenstein et al., 2005). Effect sizes were calculated as Cohen's *d* (Cohen, 1988), which is the difference in group means divided by the pooled standard deviation, based either upon pre- and post-treatment values of one group (active group) within each study or comparison of the mean changes in pre- to post-treatment ratings of two independent groups (sham and active rTMS) in controlled trials, using the means and S.D.s. An individual effect size for each study was calculated and a combined (pool weighted) effect size was obtained using both random and fixed effect models. When means and S.D.s were not reported in a study, *d*-values were computed from the *t* or *F*-values. The random effect model was used in this study because it gives relatively more weight to studies with smaller sample size and wider confidence intervals than the fixed effect model. To test whether the studies could be assumed to reflect a single population of effect sizes, we also calculated a homogeneity statistics, the *Q* statistics. *I*-squared values were also reported. The *Q* statistics tests the null hypothesis that there is no dispersion across effect sizes, and a significant *Q*-statistics indicates heterogeneity of the individual study effect sizes.

To address possible "file-drawer problem" and the possibility of publication bias, a fail-safe statistics estimating the number of non-significant and unpublished studies that would need to be added to the meta-analysis to reduce a mean observed effect to some specified and negligible level was also calculated (Rosenthal, 1979). We set the negligible mean effect at 0.2, which represents a "small" and usually non-significant effect size (Cohen, 1988).

3. Results

Fig. 1 summarizes the process of selection of studies for the meta-analysis. Initially we obtained 117 peer-reviewed papers through PubMed, Web of science, Elsevier, and EBSCO databases. We excluded 37 studies because they were reviews, meta-analyses and abstracts. Through subsequent detailed screening, we further excluded 58 studies which did not focus on negative symptoms or when rTMS was not used as a therapeutic tool. Finally we excluded: three studies which assessed clinical symptoms using a rating scale other than the PANSS or the SANS; one study that was a case report; and one study that used completely different stimulation pattern, which applied rTMS at the left temporoparietal cortex and the left dorsolateral prefrontal cortex at the same time. The study conducted by Jin et al. (2006) was excluded because the results only reported the ANOVA among four groups: alpha TMS, 3 Hz, 20 Hz and sham control, and no data were available to compare the alpha TMS and sham control. In the end, 16 studies fulfilled the inclusion criteria (Barr et al., 2012; Cohen et al., 1999; Cordes et al., 2010; Fitzgerald et al., 2008; Goyal et al., 2007; Hajak et al., 2004; Holli et al., 2004; Jandl et al., 2005; Klein et al., 1999; Mogg et al., 2007; Novak et al., 2006; Oh and Kim, 2011; Prikryl et al., 2007, 2013; Saba et al., 2006; Sachdev et al., 2005; Schneider et al., 2008), of which 13 were included in the pre-post treatment effect analysis and 13 in the shamcontrolled treatment effect analysis (see Table 1). Among the 16 studies, only the study conducted by Novak et al. (2006) included in previous meta-analyses was not included here. This was because it was only available as an abstract online, and we were unable to obtain original data from the author. Information regarding the six excluded studies before the last step is summarized in Table 2 (de Jesus et al., 2011; Huber et al., 2003; Jin et al., 2006; Oh and Kim, 2011; Rollnik et al., 2000; Stanford et al., 2011).

3.1. Pooled effect size of before versus after treatment

We initially analyzed the effects of pre-post rTMS intervention on negative symptoms using three open-label studies. The random effects model showed a pooled effect size of 0.410 [95% confidence interval (CI): -0.056, 0.876; $p = 0.085$]. We then used the active arms of the controlled studies for further analysis. In this part, 10 studies were included. The random effects model showed a pooled effect size of 0.625 [95% confidence interval (CI): 0.228, 1.021; $p = 0.002$] (see Fig. 2). The test for heterogeneity showed significant heterogeneity between studies ($Q_9, \chi^2 = 30.115$, I -squared value = 70.114, $p < 0.001$). The fail-safe number of studies was 41. These results indicated that rTMS induced a significant and moderate reduction in negative symptoms in patients receiving active treatment. To explore the placebo effect, we also analyzed the mean weighted effect size of pre-post sham rTMS using the sham arm in controlled studies. The random effects model showed a pooled effect size of 0.396 (95% CI: 0.158, 0.677; $p = 0.002$). The test for heterogeneity did not show significant heterogeneity between studies ($Q_7, \chi^2 = 10.336$, I -squared value = 32.273, $p = 0.170$). The fail-safe number of studies was 16. These results indicated that there was a small placebo effect of rTMS treatment on negative symptoms.

3.2. Pooled effect size of placebo versus active treatment

The mean weighted effect size was 0.532 (95% CI: 0.191, 0.874; $p = 0.002$) when we compared mean changes between active rTMS and sham treatment using the random effects

model (see Fig. 3). The test for heterogeneity showed significant heterogeneity between studies ($Q_{12} = 24.600$, I^2 -squared value = 51.220, $p = 0.017$). The fail-safe number was 41. These results indicated that active rTMS, compared with sham rTMS, induced a significant and moderate improvement in negative symptoms.

3.3. Moderators of the treatment effect of rTMS

Due to the small number of studies, we were unable to run meta-regressions to examine the effects of possible moderators, such as assessment tools, baseline PANSS score, baseline severity of negative symptoms, DOI, medication, rTMS frequency, motor threshold (MT), location, total stimulus strength and duration of stimulus. Nevertheless, we divided the sham-controlled studies into subgroups according to these moderators (see Table 3). A PANSS total score of ≥ 70 and a PANSS negative symptoms subscale score of ≥ 20 or a SANS score of ≥ 35 have commonly been used as arbitrary cutoffs for treatment studies (Findling et al., 2008; Mogg et al., 2007; Schneider et al., 2008). We have therefore used these cutoffs to define the subgroups in our analysis. Since no evidence suggests that demographic variables such as sex, age and education could be moderators of the treatment effect of rTMS on negative symptoms in schizophrenia, we did not analyze these factors in this meta-analysis. Finally, a 10 Hz frequency, stimulation at the left DLPFC and a 110% MT are the most common rTMS treatment parameters reported (Cordes et al., 2010; Goyal et al., 2007; Hajak et al., 2004; Mogg et al., 2007; Prikryl et al., 2007, 2013), and as a result, we have used these parameters to define our subgroups. Previous meta-analyses have shown that 3 weeks was the minimal duration of treatment for rTMS to be effective (Dlabac-de Lange et al., 2010). We have also employed this criterion to test this hypothesis. Finally, we arbitrarily used 8 years as a cutoff for DOI in our subgroup analysis to examine the moderating effect of DOI.

We found that all the studies were heterogeneous. The subgroups defined by the level of negative symptoms evaluated by the SANS, a shorter DOI (< 8 years), a higher baseline negative symptoms level (PANSS negative symptoms subscale score of ≥ 20 or SANS score of ≥ 35), a longer duration of rTMS treatment (≥ 3 weeks), a 10 Hz frequency, stimulation at the left DLPFC and a 110% MT all had larger and significant effect sizes than their corresponding subgroups. However, subgroups defined by different medication dosages did not show any difference in effect size.

4. Discussion

Our study yielded several findings. First, meta-analysis results from sham-controlled trials indicate that rTMS is effective in treating negative symptoms in schizophrenia, with a moderate effect size. Our results also revealed larger effect sizes for rTMS treatment effect on negative symptoms when the SANS rather than the PANSS was used as the assessment tool. In addition, the severity of negative symptoms at baseline predicted response to rTMS. Patients with more prominent negative symptoms at baseline tended to be more responsive to rTMS. Secondly, we found that a number of moderators may influence the effect of rTMS on negative symptoms. The effect of rTMS on negative symptoms tended to be poorer in patients with a longer DOI. Furthermore, at least 3 consecutive weeks of treatment, a

stimulus frequency of 10 Hz, using a 110% MT and application of rTMS at the left DLPFC appeared to be the best rTMS parameters for the treatment of negative symptoms in these patients.

In this study, we did not specify rTMS parameters when selecting studies for meta-analysis. As a result, we have included studies that used different stimulus frequencies (1 Hz, 10 Hz, 15 Hz and 20 Hz), stimulus locations (left DLPFC, right DLPFC, bilateral DLPFC, PFC and left TPC), MT (80–110%), and duration of treatment (5–20 days). A total 16 papers and 348 participants were included. To the best of our knowledge, this is the largest meta-analysis that examines the treatment effect of rTMS on negative symptoms in schizophrenia patients. Irrespective of whether negative symptoms were assessed using the PANSS or the SANS, the overall effect of rTMS on these symptoms was significant. The effect sizes (pre- vs post-treatment) were slightly larger than those reported by Freitas et al. (2009) (0.63 vs. 0.58) when the PANSS was used to assess negative symptoms. Freitas et al. (2009) found that the effect of rTMS on negative symptoms was small and non-significant when a potential placebo effect was considered. It has been reported that there is a large placebo response in the treatment effect of rTMS on depression (Brunoni et al., 2009). Similarly we have found a small placebo effect in the treatment effect of rTMS on negative symptoms in schizophrenia. However, we did find a moderate effect on negative symptoms even after the placebo effect was considered (0.53), which is higher than those reported by Dlabac-de Lange et al. (2010) (0.53 vs. 0.43). It should be noted that most of the studies included did not provide breakdown scores of individual negative symptoms, which precluded the opportunity to analyze the efficacy of rTMS on individual negative symptoms.

The moderators which influence the effect of rTMS on negative symptoms have never been systematically explored previously. Possible moderators include clinical variables such as baseline psychopathology, DOI, medication types and dosage; rTMS parameters such as rTMS frequency, location, intensity, and duration of treatment; or instruments used to evaluate outcome. In this study, we have examined many of these moderators.

Although various scales for assessing negative symptoms, like the Schedule for the Deficit Syndrome (SDS), the 16-item Negative Symptoms Assessment (NSA-16) scale and the Clinical Assessment Interview for Negative Symptoms (CAINS) are available (Alphs et al., 1989; Horan et al., 2011; Kirkpatrick et al., 1989), the PANSS and the SANS remain the two most commonly used scales to assess negative symptoms in rTMS intervention studies, probably because both possess good reliability and validity (Andreasen, 1982; Peralta and Cuesta, 1994). However, there are significant differences between these two rating scales. The SANS contains a larger number of items (20 originally, 19 in the current version) when compared with the PANSS (only seven negative symptom items). Thus the SANS provides more detailed information and may be more sensitive to changes in negative symptoms than the negative symptom subscale of the PANSS. Indeed, we found that the effect size generated from studies using the SANS was consistently larger than the effect size generated from studies using the PANSS in both pre-post (0.98 vs. 0.43) and sham-active (0.80 vs. 0.41) comparison of rTMS treatment. Furthermore, three studies (Prikryl et al., 2007; Fitzgerald et al., 2008; Barr et al., 2012) included in the analyses used both rating scales (Barr et al., 2012; Fitzgerald et al., 2008; Prikryl et al., 2007). In two of these studies

(Fitzgerald et al., 2008; Prikryl et al., 2007), the treatment effect on negative symptoms measured by the SANS was larger in comparison with the treatment effect measured by the negative symptom subscale of the PANSS in both pre-post and sham-active comparison of rTMS treatment.

Some studies have shown that patients with chronic schizophrenia have more prominent negative symptoms than patients suffering from first-episode schizophrenia (Jaeger et al., 2003; Wang et al., 2013). However other studies have found that patients with first-episode schizophrenia may also present with predominantly negative symptoms (Hovington et al., 2012; Malla et al., 2004). Studies have shown that patients with a higher PANSS total score or positive symptom score at baseline had greater reduction in global symptoms or positive symptoms after antipsychotic treatment (Levine and Rabinowitz, 2010; Walker et al., 2009). Our results showed that rTMS, as an add-on treatment, may be more effective for patients with a higher baseline negative symptoms subscale score rather than a higher baseline PANSS total score. For those with less prominent negative symptoms, rTMS treatment did not show any significant effect, even when controlling for DOI, probably because there is little room for further improvement in patients with low levels of negative symptoms. This may also be the reason why the sham rTMS control group showed a greater reduction in negative symptoms than the active rTMS group in the study by Holli et al. (2004) since the baseline negative symptom subscale score was higher in the sham rTMS control group than the active rTMS group in this study.

Early intervention of negative symptoms may be more effective (Boonstra et al., 2012). We also found that rTMS had no significant effect on negative symptoms in patients with chronic schizophrenia whose DOI were longer than 8 years. On the contrary, rTMS was effective for patients in the early stage of the illness. It is possible that progressive brain changes such as decrease in brain volume, increase in ventricular volume and reduction in frontal gray and white matter and temporal white matter occur in patients with schizophrenia over time and lead to irreversible changes (Cahn et al., 2009; Olabi et al., 2011).

The number of sessions of rTMS treatment delivered varied from 1 to 20 sessions across the studies included in our meta-analysis. We excluded the study that applied rTMS for a single session such that the smallest number of session delivered was five (Jandl et al., 2005). From a clinical practice point of view, fewer sessions would be preferred if the efficacy of treatment is similar. In our meta-analysis, it appears that at least 15 sessions (in 3 consecutive weeks) was sufficient to generate significant short-term therapeutic effects and rTMS treatment for less than 15 sessions did not show any significant effect on negative symptoms. This is consistent with results reported by Dlabac-de Lange et al. (2010). Nevertheless, it should be pointed out that the long-term effect of rTMS on negative symptoms has not been established and as a consequence, the number of sessions required to achieve long term effects is unclear.

The mean effect size increased from 0.53 to 0.79 when the meta-analysis was limited to studies which used an rTMS frequency of 10 Hz. This is higher than the mean effect size (0.63) reported by Dlabac-de Lange et al. (2010), with an increase from 0.43 to 0.63 when

only studies that used an rTMS frequency of 10 Hz were included. These results support that 10 Hz is the rTMS frequency with the best efficacy.

In our meta-analysis, except for one study which applied rTMS at the left temporoparietal cortex (LTPC), all the other 15 studies applied rTMS at the prefrontal cortex. It is well established that hypofrontality is associated with negative symptoms (Semkovska et al., 2001; Weinberger et al., 1988). Since high-frequency (HF) rTMS (< 5 Hz) may increase cortical excitability and modulate dopamine release (Eisenegger et al., 2008; Pell et al., 2011), the application of HF rTMS to the PFC seems to be logical and appropriate for the treatment of negative symptoms. However, there is no consensus as to which part of the PFC should be stimulated. In our meta-analysis, nine studies applied stimulation at the left DLPFC, two at bilateral DLPFC, one at the right DLPFC and one at the LTPC. Overall, the mean effect size for studies stimulating the left DLPFC was moderate and significant, whereas the mean effect size for studies stimulating other locations was small and non-significant. This is consistent with the results of Cho et al.'s study (Cho and Strafella, 2009), which demonstrated that rTMS applied at the left DLPFC but not the right DLPFC could modulate dopamine release in brain regions related to negative symptoms.

Fifty percent MT is the minimal intensity required to elicit an EMG response at 50 μ V (Rossini et al., 1994). A higher MT% would increase the risk of side effects such as seizure and pain. The intensity of rTMS stimulation usually ranges from 90% to 130% MT (Rossi et al., 2009). Among the studies included in our meta-analysis, the intensity of rTMS ranged from 80% to 110% MT and we found that 110% MT had the best efficacy on negative symptoms.

Previous studies did not show that negative symptoms are more responsive to rTMS when patients are on SGA (Erhart et al., 2006; Salimi et al., 2009). The results of our study is consistent with this finding in that the type of antipsychotics did not have an impact on the efficacy of rTMS on negative symptoms when rTMS was used as an add-on treatment. Moreover, because few studies included in our meta-analysis provided medication dosages, we did not have sufficient data to analyze the effect of medication dosage on negative symptoms responsiveness to rTMS.

There are several limitations in the present meta-analysis. First, the total number of studies (viz., 16) and participants (viz., 348) included were relatively small, especially for studies that used the SANS as outcome measure. Only five studies used the SANS to assess negative symptoms of schizophrenia. Moreover, none of the studies included patients with a DOI of less than 5 years. Secondly, the SANS and other instruments that measure negative symptoms such as the SDS and the 16-item Negative Symptoms NSA-16 or the CAINS should be applied to find the most sensitive and appropriate scale to detect changes in negative symptoms in rTMS treatment. Sub-components of negative symptoms should also be analyzed to see if there is a differential effect of rTMS treatment on these components. Thirdly, neurocognitive functions (e.g., attention, memory, executive functions) should be systematically evaluated to clarify if they have any moderating effect on the efficacy of rTMS on negative symptoms.

Despite these limitations, our study provides strong evidence to support that rTMS is an efficacious add-on treatment for negative symptoms in schizophrenia, especially for individuals with early stage schizophrenia. The optimal parameters appear to be a frequency of 10 Hz, stimulation at the left DLPFC, a 110% MT and at least 3 consecutive weeks of treatment. Further studies should be conducted to clarify if these parameters are more effective for schizophrenia patients with predominant negative symptoms.

Acknowledgments

This study was supported by Grants from the Strategic Priority Research Programme (B) of the Chinese Academy of Sciences (XDB02030200), the National Science Fund China (81088001 and 91132701), the Project-Oriented Hundred Talents Programme (07CX031003), a Grant from the Knowledge Innovation Project of the Chinese Academy of Sciences (KSCX2-EW-J-8), the National Key Project of Scientific and Technical Supporting Programs funded by Ministry of Science & Technology of China (No. 2007BAI17B04), the CAS/SAFEA International Partnership Programme for Creative Research Teams (Y2CX131003), Fogarty training Grant in Harvard University (D43TW5809), and the Queensland Smart Futures International Fellowship.

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Fig. 1.
Flow chart of the selection process of peer-reviewed articles for the current meta-analysis.

Fig. 2.

Pooled effect size (before versus after treatment) for studies of rTMS effects on negative symptoms (random effect model).

Fig. 3.
Pooled effect size (placebo versus active treatment) for studies of rTMS effects on negative symptoms (random effect model).

Table 1

Selected peer-reviewed articles for meta-analysis of rTMS effects on negative symptoms of schizophrenia.

Study	Design	N	Gender (%M)	Mean age (year)	Demographic and clinical characteristics		TMS parameters		Location	Frequency	%MT	No. of sessions	Total stimuli	Baseline psychopathology			
					Medication (% FGA)	DOI (year)	Active (N)	Sham (N)						PANSS-T	PANSS-N	PANSS-T	PANSS-N
Cohen et al. (1999)	Open-label	6	33.3%	39.00	–	–	6	–	PFC	20 Hz	80%	10	8,000	86.17	31.67	–	–
Klein et al. (1999)	Parallel	35	37.1%	29.90	88.6%	7.90	18	17	RDLPFC	1 Hz	110%	10	1200	64.40	16.50	54.60	14.10
Hajak et al. (2004)	Parallel	20	30%	39.80	55%	14.5	10	10	LDLPFC	10 Hz	110%	10	10000	82.20	–	82.00	–
Holi et al. (2004)	Parallel	22	86.4%	36.70	0%	13.20	11	11	LDLPFC	10 Hz	100%	10	10000	105.20	28.90	110.30	31.00
Jandl et al. (2005)	Open-label	10	50.0%	42.70	–	18.10	10	–	LDLPFC	10 Hz	100%	5	3500	–	–	–	–
Novak et al. (2006)	Parallel	16	75%	34.00	6.25%	10.50	8	8	LDLPFC	20 Hz	90%	10	20000	63.5	20	61.5	20.5
Sachdev et al. (2005)	Open-label	4	100%	34.50	–	13.75	4	–	LDLPFC	15 Hz	90%	20	36000	–	29.25	–	–
Saba et al. (2006)	Parallel	18	81.3%	30.65	–	7.95	9	9	LTPC	1 Hz	80%	10	3000	88.00	20.62	100.20	25.38
Goyal et al. (2007)	Parallel	10	100%	28.00	–	–	5	5	LDLPFC	10 Hz	110%	10	9800	104.20	32.61	103.20	28.26
Mogg et al. (2007)	Parallel	17	94.1%	41.70	52.9%	16.53	8	9	LDLPFC	10 Hz	110%	10	20000	86.00	29.80	86.00	29.10
Prikryl et al. (2007)	Parallel	22	100%	33.90	–	6.73	11	11	LDLPFC	10 Hz	110%	15	22500	57.73	21.00	64.00	21.82
Fitzgerald et al. (2008)	Parallel	20	80.00%	35.60	5%	10.38	12	8	BDLPFC	10 Hz	110%	15	30000	67.30	16.80	60.50	18.60
Schneider et al. (2008)	Parallel	51	33.3%	41.10	–	18.00	34	17	LDLPFC	1 Hz 10 Hz	110%	20	2000 20000	–	–	–	–
Cordes et al. (2010)	Parallel	32	78.1%	34.34	12.5%	5.66	18	14	LDLPFC	10 Hz	110%	10	10000	79.10	23.70	81.50	26.80
Barr et al. (2012)	Parallel	25	68.0%	44.04	24%	22.79	13	12	BDLPFC	20 Hz	90%	20	30000	–	14.85	–	15.50
Prikryl et al. (2013)	Parallel	40	100%	32.59	2.5%	5.33	23	17	LDLPFC	10 Hz	110%	15	30000	–	–	–	–
Total		342					202	140									

TMS: Transcranial Magnetic Stimulation; M=Male; FGA=First Generation Antipsychotics DOI= Duration of Illness; PANSS=Positive and Negative Syndrome Scale; PANSS-T=Total score of PANSS; PANSS-N=Negative subscale score of PANSS; PFC=Prefrontal Cortex; LDLPFC=Left Dorsolateral Prefrontal Cortex; RDLPFC=Right Dorsolateral Prefrontal Cortex; BDLPFC=Bilateral Dorsolateral Prefrontal Cortex; LTPC=Left Temporoparietal Cortex; –=data not available or not applicable.

Table 2

Studies excluded from the meta-analysis.

Study Authors	TMS parameters				Reason for exclusion		
	Design	Location	Frequency	%MT	No. of sessions	Total stimuli	
Rollnik et al. (2000)	Parallel	DDL PFC	20 Hz	80%	10	8000	No data available on negative symptom cluster of the BPRS
Huber et al. (2003)	Open-label	DDL PFC	20 Hz	80%	10	8000	The sample is the same as Rollnik et al
Oh et al. (2011)	Open-label	LTPC LDLPFC	1 Hz 10 Hz	100%	15	9000 9000	Completely different stimulation pattern
Jin et al. (2006)	Parallel	BDLPFC	8–13 Hz	80%	10	–	Results reported the ANOVA among four groups: alpha TMS, 3 Hz, 20 Hz and sham control, no data available comparing the alpha TMS and sham control.
Stanford et al. (2011)	Open-label	LDLPFC	20 Hz	100%	20	32,000	Case report
de Jesus et al. (2011)	Parallel	LTPC	1 Hz	80%	20	23,040	No data available on negative symptom cluster of the BPRS

BPRS=Brief Psychiatric Rating Scale; PANSS = Positive and Negative Syndrome Scale; LDLPFC= Left Dorsolateral Prefrontal Cortex; DDL PFC=Dorsolateral Prefrontal Cortex of Dominant Hemisphere; BDL PFC=Bilateral Dorsolateral Prefrontal Cortex; LTPC=Left Temporoparietal Cortex; –=data not available or not applicable.

Table 3

Effect size of subgroups grouped by moderators.

Subgroup by confounders	No of studies	<i>I</i> -squared values	Effect size (Cohen's <i>d</i>) Random effect model	95% confidence interval	<i>p</i>
^a Assessment tools		49.199*			
SANS	5		0.796	0.324 to 1.268	0.001
PANSS	11		0.411	0.039 to 0.782	0.03
^a DOI		57.553*			
<8 years	6		0.823	0.283 to 1.364	0.003
8 years	7		0.357	-0.144 to 0.857	0.162
^a rTMS duration		57.553*			
<3 weeks	8		0.418	-0.096 to 0.933	0.069
3 weeks	5		0.796	0.324 to 1.268	0.001
^a rTMS frequency		57.553*			
10 Hz	9		0.791	0.329 to 1.254	0.001
Other Hz	4		0.103	-0.314 to 0.519	0.629
^a rTMS location		57.553*			
Left DLPFC	9		0.666	0.165 to 1.167	0.009
Other location	4		0.359	-0.103 to 0.820	0.128
^a rTMS intensity		57.553*			
110% MT%	9		0.821	0.425 to 1.217	<0.001
Other MT%	4		-0.036	-0.532 to 0.459	0.885
^b Baseline PANSS score		60.856*			
<70	4		0.513	-0.225 to 1.251	0.173
70	6		0.653	0.035 to 1.306	0.063
^b Baseline negative symptom		54.706			
PANSS-N score <20 or	3		0.192	-0.262 to 0.646	0.407
SANS <35	9		0.514	0.087 to 0.942	0.018
PANSS-N score ≥ 20 or					
SANS ≥ 35					
^a % of FGA		59.168*			
<50%	6		0.302	-0.246 to 0.850	0.281
>50%	3		0.589	-0.278 to 1.455	0.183

SANS=Scale for the Assessment of Negative Symptoms; PANSS=Positive and Negative Syndrome Scale; PANSS-N=Negative Subscale Score of PANSS; FGA=First Generation Antipsychotics; DOI=Duration of Illness; rTMS = repetitive Transcranial Magnetic Stimulation; DLPFC=Dorsolateral Prefrontal Cortex; MT=Motor Threshold.

* $p < 0.05$.

^a include studies measured by SANS and PANSS.

^b include studies measured by PANSS only.