# Repetitive Transcranial Magnetic Stimulation for Negative Symptoms of Schizophrenia: Review and Meta-Analysis

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***Background:*** Repetitive transcranial magnetic stimulation (rTMS) has been proposed as a treatment for the negative symptoms of schizophrenia. During the past decade, several trials have reported on the efficacy of rTMS treatment; however, the results were inconsistent.

***Objective:*** To assess the efficacy of prefrontal rTMS for treating negative symptoms of schizophrenia.

***Data Sources:*** A literature search was performed in PubMed, ISI Web of Science, and EMBASE for the years 1985 through July 2008. The search terms used (language not specified) were "*transcranial magnetic stimulation*," "*negative symptoms*," and "*schizophrenia*." A cross-reference search of eligible articles was performed to identify studies not found in the computerized search.

***Study Selection:*** Studies selected were randomized controlled trials assessing the therapeutic efficacy of prefrontal rTMS for negative symptoms in schizophrenia.

***Data Extraction:*** Effect sizes (Cohen *d*) of each study were calculated. The overall standardized mean difference was calculated under a random effects model with 95% confidence intervals.

***Data Synthesis:*** Nine trials, involving 213 patients, were included in the meta-analysis. The overall mean weighted effect size for rTMS versus sham was in the small-to-medium range and statistically significant ($d = 0.43$; 95% CI, 0.05–0.80). When including only the studies using a frequency of stimulation of 10 Hz, the mean effect size increased to 0.63 (95% CI, 0.11–1.15). When including only the studies requiring participants to be on a stable drug regimen before and during the study, the mean weighted effect size decreased to 0.34 (95% CI, 0.01–0.67). Studies with a longer duration of treatment (≥ 3 weeks) had a larger mean effect size when compared to studies with a shorter treatment duration: $d = 0.58$ (95% CI, 0.19–0.97) and $d = 0.32$ (95% CI, −0.3 to 0.95), respectively.

***Conclusions:*** The results of this meta-analysis warrant further study of rTMS as a potential treatment of negative symptoms of schizophrenia.

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Negative symptoms of schizophrenia include blunted affect, apathy, poverty of speech, and social withdrawal. These symptoms predict an unfavorable clinical outcome and are often indicative of poorer social, occupational, and global outcomes.[1–4] Currently, treatment options to improve negative symptoms yield disappointing results. Antipsychotic medication has limited efficacy to improve negative symptoms.[5,6]

Activation of the prefrontal cortex is impaired in people with schizophrenia.[7–12] Negative symptoms appear to be associated with this hypoactivity of the frontal cortex; in particular, the dorsolateral prefrontal cortex (DLPFC) seems to be affected.[13,14] High-frequency repetitive transcranial magnetic stimulation (rTMS) (≥ 5 Hz) can increase cortical excitability.[15,16] Thus, increasing brain activity in the DLPFC by using high frequency rTMS might prove to be an effective treatment of negative symptoms in schizophrenia. In addition, there is evidence that decreased dopamine release in the prefrontal cortex results in negative symptoms.[17–20] Several studies in animals and humans found that prefrontal rTMS can induce mesolimbic and mesostriatal dopamine release via excitatory corticostriatal projections.[21–27] The mesolimbic pathway and the ventral striatal pathway are involved in feelings of reward (motivation) and reinforcement. The negative symptoms of schizophrenia include lack of motivation. Thus, in addition to high-frequency prefrontal rTMS increasing prefrontal cortical excitability, prefrontal rTMS may also modulate the dopaminergic regulation in the brain of schizophrenic patients, which may prove to be effective in the treatment of negative symptoms in schizophrenia. In the past decade, several studies have focused on finding a possible treatment for negative symptoms of schizophrenia by using prefrontal rTMS. Some studies reported a significant improvement,[28–36] but others failed to prove a therapeutic effect of rTMS.[37–41] Given the importance of negative symptoms for the outcome of schizophrenia, and given the fact that current treatment strategies have not yielded substantial improvement, it is of interest to examine the efficacy of novel treatment options. This meta-analysis aims to provide a quantitative review of studies on the efficacy of rTMS treatment of negative symptoms in schizophrenia.

**Table 1. Studies Included in the Meta-Analysis**

| Study | N | Rating Scale | Treatment Settings | Location | Total No. of Pulses | Duration, days | Effect Size, PANSS | Effect Size, SANS | Effect Size | Study Design | Randomly Assigned |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Schneider et al (2008)[33] | 51 | SANS | 20 trains/d, 5 sec of 1 Hz at 110% MT, 15-sec intertrain interval | Left DLPFC | 2,000 | 20 | | 0.28 | 0.28 | Parallel | Yes |
| | | | 20 trains/d, 5 sec of 10 Hz at 110% MT, 15-sec intertrain interval | | 20,000 | | | 0.58 | 0.58 | | |
| Fitzgerald et al (2008)[37] | 20 | SANS, PANSS | 20 trains/d/DLPFC, 5 sec of 10 Hz at 110% MT, 25-sec intertrain interval | Bilateral DLPFC | 30,000 (15,000 per side) | 15 | 0.19 | 0.89 | 0.54 | Parallel | Yes |
| Goyal et al (2007)[29] | 10 | PANSS | 20 trains/d, 4.9 sec of 10 Hz at 110% MT, 30-sec intertrain interval | Left DLPFC | 9,800 | 10 | 2.22 | | 2.22 | Parallel | Yes |
| Prikryl et al (2007)[34] | 22 | SANS, PANSS | 15 trains/d, 10 sec of 10 Hz at 110% MT, 30-sec intertrain interval | Left DLPFC | 22,500 | 15 | 0.8 | 1.39 | 1.1 | Parallel | Yes |
| Mogg et al (2007)[40] | 17 | PANSS | 20 trains/d, 10 sec of 10 Hz at 110% MT, 50-sec intertrain interval | Left DLPFC | 20,000 | 10 | 0.22 | | 0.22 | Parallel | Yes |
| Novak et al (2006)[41] | 16 | PANSS | 40 trains/d, 2.5 sec of 20 Hz at 90% MT, 30-sec intertrain interval | Left DLPFC | 20,000 | 10 | −0.29 | | −0.29 | Parallel | Yes |
| Hajak et al (2004)[30] | 20 | PANSS | 20 trains/d, 5 sec of 10 Hz at 110% MT | Left DLPFC | 10,000 | 10 | 1.05 | | 1.05 | Parallel | Yes |
| Holi et al (2004)[38] | 22 | PANSS | 20 trains/d, 5 sec of 10 Hz at 100% MT, 30-sec intertrain interval | Left DLPFC | 10,000 | 10 | −0.47 | | −0.47 | Parallel | Yes |
| Klein et al (1999)[39] | 35 | PANSS | 2 trains/d, 60 sec of 1 Hz at 110% MT, 180-sec intertrain interval | Right PFC | 1,200 | 10 | 0.1 | | 0.1 | Parallel | Yes |

Abbreviations: DLPFC = dorsolateral prefrontal cortex, MT = motor threshold, PANSS = Positive and Negative Syndrome Scale, PFC = prefrontal cortex, SANS = Scale for the Assessment of Negative Symptoms.

## METHOD

### Literature Search and Study Selection

Studies were found by performing a literature search in PubMed, ISI Web of Science, and EMBASE for the years 1985 through July 2008 and by conducting a cross-reference search of the eligible articles to identify additional studies not found in the electronic search. The search terms used (language not specified) were "*transcranial magnetic stimulation*," "*negative symptoms*," and "*schizophrenia*." The main outcome measure was reduction of negative symptoms as measured with the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS), or the negative symptom subscale of the Positive and Negative Syndrome Scale (PANSS). Criteria for inclusion in the meta-analysis were a parallel or crossover design with sham control in patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder. However, in 2 studies, statistically significant improvement of negative symptoms after rTMS was maintained at 4-week follow-up.[27,28] Therefore, crossover trials with a wash-out phase of less than 4 weeks were excluded. Only studies using rTMS of the prefrontal cortex were included. If there was insufficient information in the article to calculate the effect size, the corresponding author was contacted. Cohort studies without sham control and studies that did not provide sufficient data to permit calculation of effect sizes were excluded from the meta-analysis.

### Statistical Analysis

Individual effect sizes (Cohen *d*) of each study were calculated with reported significance values using the effect size program developed by Wilson.[42] When data on different scales rating the same effect were available, the data were summarized, calculating a standardized mean difference. If no standard deviations were reported, we used the mean standard deviation of all the other studies as an estimate (this procedure was necessary for only 1 study[33]). A random effects model was used, and the mean weighted effect size was calculated by using Review Manager 5.0, developed by The Cochrane Collaboration.[43] Individual effect sizes were weighted by the standard error of the estimate. Heterogeneity refers to variability among studies in a systematic review, which may be caused by clinical and methodological diversity. Significant heterogeneity limits a reliable interpretation of the results. Heterogeneity was assessed by using $\tau^2$, $\chi^2$, and $I^2$ tests. Potential publication bias was assessed by using a funnel plot.

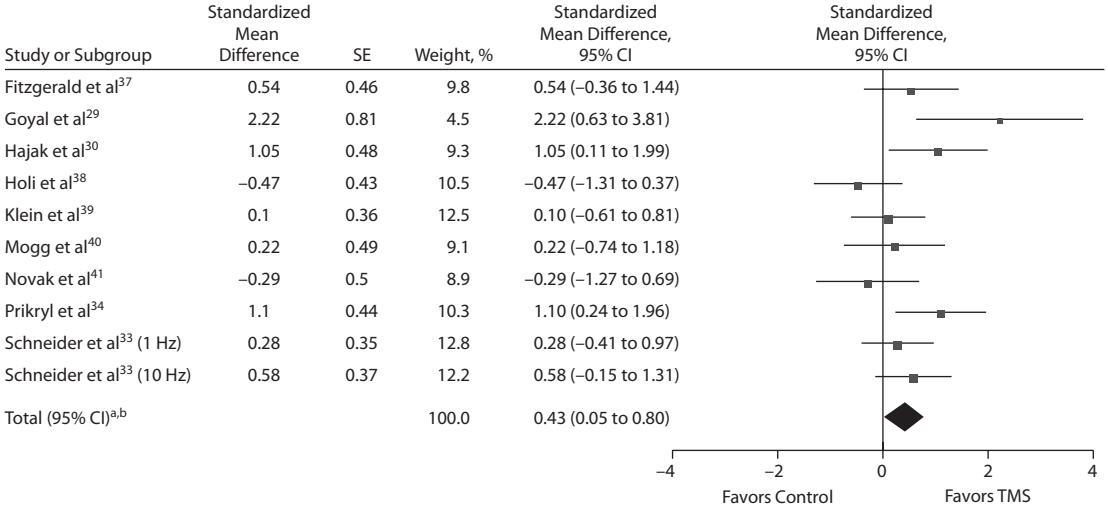
   

**Table 2. Studies Excluded From the Meta-Analysis**

| Study | N | Rating Scale | Treatment Settings | Duration, days | Reason for Exclusion | Study Design | Randomly Assigned |
|---|---|---|---|---|---|---|---|
| Jin et al (2006)[36] | 27 | PANSS | α (8–13 Hz), 3 or 20 Hz at 80% MT bilaterally over the DLPFC | 10 | Wash-out phase < 4 weeks | Crossover | Yes |
| Stanford et al (2006)[44] | 5 | No data | 20 Hz at 100% MT over the left DLPFC | No data | No control condition | Open label | No |
| Sachdev et al (2005)[32] | 4 | PANSS | 15 Hz at 90% MT over the left DLPFC | 20 | No control condition | Open label | No |
| Jandl et al (2005)[35] | 10 | SANS | 10 Hz at 100% MT over the left DLPFC | 5 | No control condition | Open label | No |
| Langguth et al (2003)[31] | 10 | PANSS | 10 Hz at 110% MT over the left DLPFC | 10 | Overlap with Hajak et al[30] | Double-blind, sham-controlled | Yes |
| Rollnik et al (2000)[45] | 12 | BPRS | 20 Hz at 80% MT over the DLPFC of the dominant hemisphere | 10 | No data available on negative symptom cluster of the BPRS; wash-out phase < 4 weeks | Crossover | Yes |
| Cohen et al (1999)[28] | 6 | PANSS | 20 Hz at 80% MT over the PFC | 10 | No control condition | Open label | No |

Abbreviations: BPRS = Brief Psychiatric Rating Scale, DLPFC = dorsolateral prefrontal cortex, MT = motor threshold, PANSS = Positive and Negative Syndrome Scale, PFC = prefrontal cortex, SANS = Scale for the Assessment of Negative Symptoms.

**Figure 1. Meta-Analysis of Randomized Trials of Repetitive Transcranial Magnetic Stimulation for Negative Symptoms of Schizophrenia**



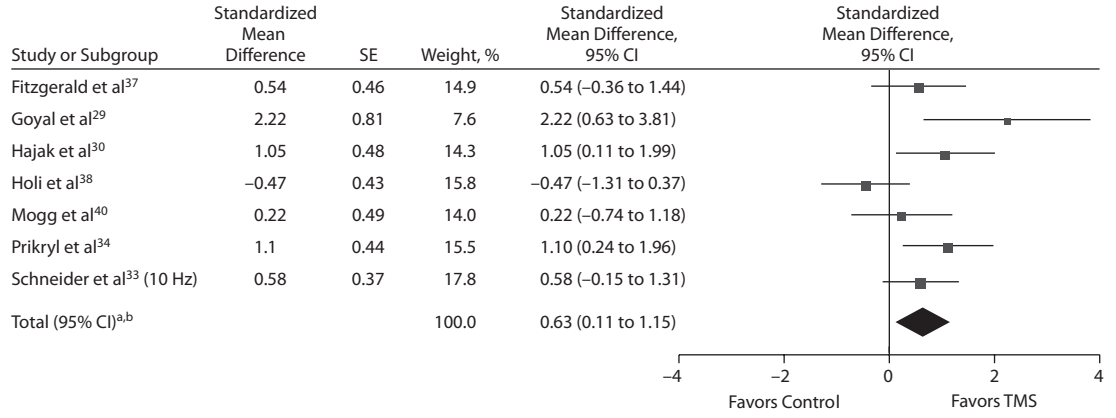

[a]Heterogeneity: $\tau^2 = 0.17$; $\chi^2_9 = 16.69$, $P = .05$; $I^2 = 46\%$.
[b]Test for overall effect: $Z = 2.23$, $P = .03$.
Abbreviation: TMS = transcranial magnetic stimulation.

## RESULTS

Sixteen studies were found that reported empirical data regarding prefrontal rTMS treatment of schizophrenia.[28–41,44,45] Nine studies fulfilled the inclusion criteria and were included in the treatment effect analysis.[29,30,33,34,37–41] The study by Langguth et al[31] was excluded because it reported on the same sample as Hajak et al,[30] the latter including the largest sample size. The study by Rollnik et al[45] was excluded because, although information was given concerning changes of the total BPRS after prefrontal rTMS, specific data about changes of the negative symptom cluster of the BPRS were not available. The study by Jin et al[36] was excluded because the wash-out phase was 2 weeks.

The included studies all had a parallel design and used the PANSS negative subscale or the SANS, or both, to measure pretreatment and posttreatment change. Information regarding the included studies is given in Table 1, and information regarding the excluded studies is given in Table 2. The studies included in the meta-analysis involved 213 patients, of whom 198 were diagnosed with schizophrenia and 15 with schizoaffective disorder. The mean weighted effect size for rTMS compared to sham treatment was 0.43 (95% CI, 0.05–0.80) (Figure 1). There was, however, significant heterogeneity among individual effect sizes ($\chi^2_9 = 16.69$, $P = .05$). Visual assessment of the funnel plot showed asymmetry. The study by Goyal et al[29] had a different research method compared to the other studies. This small study conducted among 10 patients

**Figure 2. Meta-Analysis of Randomized Trials of 10-Hz Repetitive Transcranial Magnetic Stimulation for Negative Symptoms of Schizophrenia**




[a]Heterogeneity: $\tau^2 = 0.25$; $\chi^2_6 = 12.96$, $P = .04$; $I^2 = 54\%$.
[b]Test for overall effect: $Z = 2.39$, $P = .02$.
Abbreviation: TMS = transcranial magnetic stimulation.

found a large treatment effect after rTMS. Patients entering the study were drug-free or drug-naive. After entering the study, patients were started on antipsychotic medication. The other studies included in the analyses required participants taking antipsychotic medication to be on a stable drug regimen before entering the study and for the duration of the study. When excluding the study by Goyal et al[29] from the analyses, the mean weighted effect size decreased to 0.34 (95% CI, 0.01–0.67) but remained significant. Furthermore, the heterogeneity disappeared and the funnel plot was symmetrical.

In order to discover whether the frequency of stimulation had influence on the effect size, we calculated the mean effect size of the 7 studies that used a frequency of stimulation of 10 Hz. The mean effect size increased to 0.63 (95% CI, 0.11–1.15), but the heterogeneity was significant ($\chi^2_6 = 12.96$, $P = .04$) (Figure 2). When excluding the study by Goyal et al[29] from the analyses, the mean weighted effect size was 0.5 (95% CI, 0.03–0.96), and, again, the heterogeneity disappeared. We also compared studies with a duration of treatment of less than 3 weeks (6 studies) to those applying treatment for 3 weeks or longer (3 studies). The mean effect sizes were 0.32 (95% CI, −0.3 to 0.95) and 0.58 (95% CI, 0.19–0.97), respectively.

To assess the influence of the rating scale used, we calculated the mean weighted effect size as measured by the negative subscale of the PANSS and the SANS separately. The mean weighted effect size as measured by the negative subscale of the PANSS was 0.35 (95% CI, −0.12 to 0.82; $K = 8$, N = 172). When excluding the study by Goyal et al[29] from the analyses, the mean weighted effect size was 0.22 (95% CI, −0.17 to 0.61; $K = 7$, N = 162). The mean weighted effect size as measured by the SANS was 0.73 (95% CI, 0.26–1.19; $K = 3$, N = 93).

## DISCUSSION

The results of this meta-analysis provide evidence that high-frequency rTMS of the DLPFC may be beneficial in the treatment of negative symptoms in schizophrenia. Although the overall treatment effect size of 0.43 was small, it did approach the medium range according to the nomenclature of Cohen,[46] in which $d = 0.2$ is considered a small effect size and $d = 0.5$ is considered a medium effect size. The effect size was smaller than that reported for a meta-analysis of 10 studies regarding 1 Hz rTMS over the left temporoparietal cortex for reducing auditory hallucinations in schizophrenia, which was 0.76.[47] In general, other treatments, such as antipsychotics, have also been more successful in targeting positive than negative symptoms of schizophrenia. There was significant heterogeneity, and the funnel plot was asymmetric. When excluding the study applying a research method different from the other studies, the overall treatment effect decreased to 0.34 and the heterogeneity disappeared. The funnel plot was then symmetrical. An important question is how the mean effect size for TMS compares to the effect of antipsychotics. A meta-analysis on the treatment of negative symptoms with antipsychotic medication found antipsychotics to be more effective than placebo. However, all the effect sizes found were small, the mean effect sizes as measured by the Pearson correlation coefficients ranging between 0.17 and 0.21.[48] When considering the working mechanism of TMS, this differs from antipsychotics. Specifically, rTMS might address neurobiologic mechanisms relevant for negative symptoms that have not been targeted by antipsychotics. High-frequency rTMS (≥ 5 Hz) can increase cortical excitability and thereby increase brain activity in the DLPFC and, in addition, may induce mesolimbic and mesostriatal dopamine release.[15]

It is important to note that an advantage of rTMS above antipsychotic medication might be the mild side effects of rTMS. Adverse effects of rTMS are mainly limited to discomfort due to twitches of scalp muscles during stimulation in some people and headache up to several hours after stimulation (which can be treated with acetaminophen). This suggests that rTMS might be more effective than current antipsychotic medication. However, caution is needed when interpreting these results as the evidence base (number of published studies) for antipsychotics is large, but the evidence base for rTMS still rather limited.

Interestingly, the mean effect size increased to 0.63 when including only those studies using a frequency of 10 Hz. The study included in the meta-analyses that used a higher-frequency stimulation of 20 Hz showed a better treatment effect in the placebo group than in the verum group.[41] This difference, however, did not reach significance. The study using lower-frequency stimulation of 1 Hz also found no significant treatment effect.[33,39] Although the study by Jin et al[36] could not be included in the analyses because the wash-out phase was less than 4 weeks, the findings are of interest. Jin et al[36] performed a crossover trial and found that rTMS stimulation set at each patient's peak α frequency EEG, which varies between 8 and 13 Hz, produced a significantly larger therapeutic effect on negative symptoms in schizophrenia when compared to sham rTMS, 3-Hz rTMS, or 20-Hz rTMS. Considering that a frequency of 10 Hz lies within the peak α frequency band, this may explain the larger treatment effect found in the 10-Hz group in comparison with the 1-Hz and 20-Hz groups.

The larger mean effect size found in the group receiving a longer duration of rTMS treatment suggests a possible dose-response relationship. A meta-analysis comparing the recent versus the earlier prefrontal rTMS studies on depression found that the more recent rTMS clinical trials showed larger antidepressant effects than the earlier trials.[49] The recent studies used more rTMS sessions.

Finally, hypoactivity and hypometabolism in the prefrontal cortex have been suggested to underlie cognitive dysfunction in schizophrenia.[13,14] In 5 studies, cognitive assessments were administered before and after rTMS.[28,33,37,40,41] One study found a significant improvement in a delayed visual memory task, and another study found better delayed recall on a test of verbal learning at 2-week follow-up in the rTMS group.[28,40] Three studies did not find any significant improvement in cognitive functioning.[33,37,41] Thus, although the putative beneficial effect of rTMS on cognition remains unclear, it is at least apparent that no adverse effects on cognition were observed.

The underlying working mechanism of rTMS remains unclear. The 2 studies that combined rTMS treatment with Single Photon Emission Computed Tomography (SPECT) scans did not detect any changes in regional cerebral blood flow.[28,30] However, 1 EEG study[50] found a significant cortical activation upon the improvement of negative symptoms. SPECT scanning is not as accurate as positron emission tomography (PET) scanning and functional magnetic resonance imaging (fMRI). The latter offers the best approach to analyze brain activity and to detect changes in brain activity; it has better spatial and temporal resolutions. Considering the above, functional imaging studies using fMRI or PET scanning to assess possible changes in brain activity are needed. Finally, rTMS of the prefrontal cortex has been found to decrease depressive symptoms in patients diagnosed with a depression. Yet, the improvement of negative symptoms could not be accounted for by an antidepressant action of the rTMS.[29,30,33]

The most effective combination of rTMS parameters has not yet been determined. The studies in this meta-analysis differed in rTMS stimulation site (right prefrontal cortex, left prefrontal cortex, and bilateral stimulation), frequency, stimulation intensity, number of trains per session, duration of each train and duration of treatment. Seven studies applied stimulation to the left dorsolateral prefrontal cortex (DLPFC), 1 study stimulated the left and right DLPFC, and 1 study stimulated the right prefrontal cortex. The DLPFC was defined as 5 cm anterior and in a parasagittal plane from the point of maximal stimulation of the abductor pollicis breves. Herwig et al[51] found that this method for locating the DLPFC was not precise anatomically—only in 7 of 22 subjects (12 healthy subjects and 10 depressed patients) was the DLPFC targeted correctly in this manner.[51] Functional targeting by applying navigating procedures to locate the DLPFC takes individual anatomic differences into account and may increase treatment effect. In addition, further research is required to determine the optimal rTMS stimulation site—right, left, or bilateral prefrontal rTMS.[52] Neuroimaging studies have found hypoactivity in both the right and left DLPFC. Most studies applied rTMS to the left DLPFC. One study[37] included in our meta-analysis studied the effect of bilateral rTMS. This study found a trend for a treatment effect in the rTMS group as compared to the placebo group based on SANS data, but this difference did not reach statistical significance. Yet, in an exploratory analysis, a greater reduction in scores on the autistic preoccupation scale of the PANSS in the rTMS group was noted.[37] Finally, it is important to mention that the studies differed in the total number of pulses administered. We suggest that future studies should control for the number of pulses administered.

For measurement of the treatment effect, studies applied the PANSS and/or the SANS, both of which are semistructured interviews. Both instruments have adequate construct and concurrent validity, good internal consistency reliability, moderate test-retest reliability, and interrater reliability coefficients ranging from moderate to high.[53–60] However, the rating scales may differ in the amount of information obtained for the negative syndrome and the extent to which cognitive functioning is estimated. For example, the "attentional impairment," "inappropriate affect," and "poverty of content of speech" items of the SANS may be more closely

related to cognitive dysfunction than negative symptoms.[61] The National Institute of Mental Health- Measurement and Treatment Research to Improve Cognition in Schizophrenia (NIMH-MATRICS) consensus statement[62] on negative symptoms agreed that the SANS is preferred to the PANSS in research focusing on negative symptoms because the SANS covers multiple domains and multiple items in each domain.[62] The 6 earliest studies included in our analysis used the negative subscale of the PANSS, 2 more recent studies used both rating scales, and the latest study used the SANS. The mean weighted effect size as measured by the SANS was larger in comparison with the negative subscale of the PANSS. The more recent studies had a better study design and longer treatment duration, partially explaining the difference found. Two studies[34,37] included in the analyses used both rating scales. In both studies the treatment effect as measured by the negative subscale of the PANSS was smaller in comparison with the treatment effect as measured by the SANS. Indeed, it has been suggested that the SANS is more sensitive to change than is the negative subscale of the PANSS.[63]

Another important issue to address is that, in all studies, all or at least a substantial proportion of the patients enrolled were using psychoactive drugs. The study by Holi et al,[38] which had a negative effect size, was carried out on chronically severely ill and hospitalized patients, often using high dosages of medication, including benzodiazepines and anticonvulsant drugs. Anticonvulsant drugs reduce the intracortical excitability and raise the motor threshold.[64,65] This activity may decrease the effect of rTMS treatment in patients using anticonvulsant drugs, corresponding with the results published by Hoffman et al.[66] Antipsychotics block dopamine and may thus interfere with the putative mechanisms of rTMS, ie, to increase mesolimbic and mesostriatal dopamine release.[21–27] Combining prefrontal rTMS with a third-generation antipsychotic such as aripiprazole would be interesting in this regard, as third-generation antipsychotics are partial dopamine agonists. However, one should note that each study titrated the dose according to each individual motor threshold, which may compensate for medically induced changes in cortical excitability.

An important and potentially confounding variable to address is the sham condition. An ideal sham condition in rTMS studies would mimic the clicking sound of the real rTMS coil and cause the same scalp or facial sensation caused by the real rTMS coil but induce no therapeutic effect. The studies in our analysis applied different methods for sham stimulation. In most of the studies, the coil was tilted off the scalp by 45° or 90°, with 1 or 2 wings of the coil touching the scalp. This method may produce similar tactile sensations and the same clicking sounds as the real rTMS treatment. However, this method can stimulate the cortex and, as a consequence, may induce a therapeutic effect.[67,68] Some of the studies used a sham coil system that imitates the clicking sound of the real rTMS coil but does not induce a magnetic field, or it blocks the magnetic field so that it does not pass through the skull. The latter system, however, does not cause scalp or facial sensation, in contrast to the real rTMS coil.

Finally, an important limitation of this meta-analysis is the small number of included studies (9) and total number of subjects (213). Larger randomized controlled trials are needed to further establish the clinical significance of this treatment and to systematically vary the TMS parameters.

In conclusion, this meta-analysis suggests that prefrontal rTMS might be a beneficial treatment for negative symptoms of schizophrenia. A frequency of stimulation of 10 Hz and a duration of treatment of at least 3 weeks enhances the treatment effect. Randomized clinical trials with larger samples are needed to further establish clinical efficacy and to determine the most effective combination of rTMS parameters. In addition, it is important to further optimize the TMS technique by, for example, developing more valid sham conditions and by controlling the coil-to-cortex distance.[69,70] Finally, neuroimaging studies using fMRI or PET scans before and after rTMS treatment may be informative to elucidate underlying mechanisms of action of rTMS treatment.

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