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Meta-analysis of the effects of repetitive transcranial magnetic stimulation (rTMS) on negative and positive symptoms in schizophrenia

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Abstract

Background—A growing body of evidence suggests that repetitive transcranial magnetic stimulation (rTMS) can alleviate negative and positive symptoms of refractory schizophrenia. However, trials to date have been small and results are mixed.

Methods—We performed meta-analyses of all prospective studies of the therapeutic application of rTMS in refractory schizophrenia assessing the effects of high-frequency rTMS to the left dorsolateral prefrontal cortex (DLPFC) to treat negative symptoms, and low-frequency rTMS to the left temporo-parietal cortex (TPC) to treat auditory hallucinations (AH) and overall positive symptoms.

Results—When analyzing controlled (active arms) and uncontrolled studies together, the effect sizes showed significant and moderate effects of rTMS on negative and positive symptoms (based on PANSS-N or SANS, and PANSS-P or SAPS, respectively). However, the analysis for the sham-controlled studies revealed a small non-significant effect size for negative (0.27, p=0.417) and for positive symptoms (0.17, p=0.129). When specifically analyzing AH (based on AHRS, HCS or SAH), the effect size for the sham-controlled studies was large and significant (1.04; p=0.002).

Conclusions—These meta-analyses support the need for further controlled, larger trials to assess the clinical efficacy of rTMS on negative and positive symptoms of schizophrenia, while suggesting the need for exploration for alternative stimulation protocols.

Keywords

Schizophrenia; rTMS; meta-analysis; negative symptoms; positive symptoms; auditory hallucinations

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Conflicts of interest

We disclose no conflicts of interest.

1. Introduction

Treatment for schizophrenia remains unsatisfactory. Current available antipsychotic drugs leave many symptoms of the illness untreated and cause unacceptable side-effects (Stone and Pilowsky, 2007). Therefore, the search for new antipsychotic drugs and the development of novel treatments for schizophrenia is critical. A growing body of evidence suggests that repetitive transcranial magnetic stimulation (rTMS) can provide alleviation of both positive and negative symptoms of schizophrenia. However, trials to date have been limited to small number of patients and overall results have been mixed. Previous review articles on this topic have elegantly described major findings of rTMS trials and identified the most extensively used and promising stimulation protocols (Cordes et al., 2006; Saba et al., 2006; Haraldsson et al., 2004). Recently, Stanford et al. (2008) contrasted the effects of different rTMS parameters and proposed methods to optimize dosage. Nevertheless, careful meta-analysis of the findings is sparse. Meta-analytic evidence suggests that severity of auditory hallucinations (AH) can be successfully reduced by rTMS (Aleman et al., 2007). However, this meta-analysis computed mean gain effect sizes of sham-controlled studies applying 1Hz rTMS to the left hemisphere, but the specific sites of stimulation varied across the included studies.

Thus, we conducted meta-analyses of all published prospective studies of the therapeutic application of rTMS in refractory schizophrenic patients. We specifically assessed both protocols most extensively used on the distinctive constellations of symptoms: high-frequency rTMS to the left dorsolateral prefrontal cortex (DLPFC) to treat negative symptoms, and low-frequency rTMS to the left temporoparietal cortex (TPC) for the specific treatment of AH. We also further explored the effects of rTMS to the left TPC on overall positive symptoms.

The original rationale supporting these protocols accommodates several lines of evidence from anatomical and functional neuroimaging studies. Indeed, activation of the prefrontal cortex seems to modulate the release of dopamine (Strafella et al., 2001), which may underlie improvement of negative symptoms (Heimer et al., 1997), whereas positive correlations between increased temporal cortical activity and the hallucinating state in schizophrenics have been reported (e.g., Silbersweig et al., 1995; Dierks et al., 1999; Shergill et al., 2000). Furthermore, there is a selective effect of stimulation frequency related to the different neurophysiological mechanisms triggered by low-frequency (≤1Hz) TMS, producing a decrease in cortical excitability, and high-frequency (>1Hz) TMS, generating the opposite effect (Pascual-Leone et al., 1998). Therefore, high-frequency TMS-triggered activation of prefrontal brain regions aims at reducing the severity of negative symptoms in schizophrenics, while low-frequency TMS is intended to relieve AH by decreasing temporal lobe activation. Moreover, further extension of the latter protocol for the treatment of other positive symptoms (delusions) has also been trialed.

2. Methods

2.1. Selection of studies

A systematic search of the literature was conducted using the Web of Science database (until July 2008). The identification of English language articles was based on the following keywords: schizo* and transcranial magnetic stimulation or TMS or rTMS. In addition, reference lists in systematic reviews and retrieved reports were also examined, but no other papers were included.

2.2. Selection criteria for the meta-analyses

Three different analyses were planned: two analyses designed to evaluate rTMS effects on the negative and overall positive symptoms of schizophrenia, and a third analysis to assess

treatment efficacy on AH, architectured according to the symptom-dependent clinical ratings used. Initially, we adopted the following selection criteria: repetitive TMS was performed; study design was open, crossover or parallel; TMS was applied for more than a single session; psychotropic dosages were unchanged for at least 4 weeks before rTMS treatment (and maintained throughout the trial); and when published studies reported overlapping data sets, only the largest sample was included. Studies were excluded when they met at least one of the following criteria: single- or paired-pulse TMS was delivered; case reports; TMS effects were assessed after a single session; patients were on stable medication regimen for less than 4 weeks prior to rTMS. Furthermore, all studies had to report the mean and standard deviation (SD) of the outcome measures before and after treatment or provide other statistical parameters that could be used to deduce these values. For studies that met inclusion criteria but did not report these scores, the authors were contacted to provide these data.

2.2.1. Analyses for negative and overall positive symptoms—For the analysis of rTMS effects in the treatment of negative symptoms, we included papers in which: high-frequency TMS was used; rTMS was applied to the left DLPFC; outcome measures included the Negative symptom subscale of the Positive and Negative Syndrome Scale (PANSS-N) or the Scale for the Assessment of Negative Symptoms (SANS). We excluded studies when low-frequency TMS was used; TMS was applied bilaterally or to the right DLPFC; outcome measures were non-specific for the assessment of negative symptoms.

For the analysis of rTMS efficacy in the treatment of overall positive symptoms, we applied the following inclusion criteria: low-frequency TMS was used; TMS was applied to the left TPC with coil placed halfway between left temporal (T3) and left parietal (P3), according to the International 10/20 EEG electrode position system; outcome measures included the Positive symptom subscale of the PANSS (PANSS-P) or the Scale for the Assessment of Positive Symptoms (SAPS). We excluded reports when high-frequency rTMS to the temporal cortex was used; TMS was applied above other brain sites (not TPC) or over the left TPC concomitantly to other sites without wash-out periods; outcome measures were non-specific for the assessment of positive symptoms.

2.2.2. Analysis for auditory hallucinations—Within the identification of specific potential TMS-triggered benefits on AH, an analysis was carried out in order to estimate the magnitude of the TMS effects in the reduction of AH severity, measured with a composite score of the following measures: Auditory Hallucination Rating Scale (AHRS); Hallucination Change Scale (HCS); or Scale for Auditory Hallucinations (SAH).

2.3. Extraction of the outcome measures

The data were collected using a semi-structured form for each study by one of the authors and checked by another. The following variables were extracted: (1) mean and SD of the elected outcome measure for baseline and after treatment for the active (uncontrolled studies) and sham groups (controlled studies); (2) study design; (3) demographic and clinical characteristics (number of patients, gender, mean age, mean duration of illness, and medication approach during trial); (4) mean and SD of the baseline clinical status; and (5) TMS protocol [number of patients submitted to active/sham stimulation, frequency, intensity (% of motor threshold), number of sessions, total stimuli, type of coil, sham coil position].

2.4. Effect size calculation

All our analyses were performed using Stata statistical software, version 8.0 (StataCorp, College Station, TX). Effect sizes were computed as the standardized mean difference (Cohen d) based either on 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 the two independent

groups (sham and active rTMS) in the controlled trials, using the means and SDs. For the post-treatment value, we used the evaluation completed immediately after the end of rTMS treatment, since not all studies reported follow-up assessments. An individual effect size for each study was calculated, and a combined (pooled weighted) effect size was obtained through the implementation of random and fixed effect models. The random effect model gives relatively more weight to smaller studies and wider confidence intervals than the fixed effect model. Since some small studies were included in the meta-analyses, and these studies usually have large effect sizes, we evaluated the influence of individual studies by computing the meta-analysis' estimates and omitting one study at a time. Furthermore, we assessed publication bias using the Begg-modified funnel plot (Egger et al., 1997), in which the standardized mean difference from each plot was plotted against the standard error.

3. Results

3.1. Selected studies

Figure 1 provides a flow diagram reflecting the process of selection of studies for the final analyses (figure 1). The initial strategy yielded 283 peer-reviewed papers. During the initial review, we excluded nearly 55% of the articles as they represented review or opinion articles. During the subsequent more detailed screening, we excluded about 38% of reports as TMS was not used as a therapeutic tool. Ultimately our search identified 47 published papers, of which 19 were devoted to rTMS treatment of negative symptoms and 28 to rTMS effects on positive symptoms.

Within the subset of clinical trials aiming at treating negative symptoms, we searched for those that applied high-frequency rTMS to the left DLPFC, thus excluding trials in which bilateral (Geller et al., 1997; also single-pulse TMS), right (Feinsod et al., 1998; Grisaru et al., 1998; Klein et al., 1998), or the "dominant" (Rollnik et al., 2000) DLPFC was probed. We also excluded the study by Huber et al. (2003), since it was a reevaluation of previous data (Rollnik et al., 2000). This last strategy yielded 13 published reports, of which 8 were sham-controlled (6 parallel and 2 crossover) and 5 were open-label (2 case reports) studies. We then excluded case reports (Saba et al., 2002; Prikryl et al., 2007b) and 1 crossover study (Nahas et al., 1999) in which a single rTMS session was performed. Finally, due to lack of data on means and SDs, 2 additional studies (Hajak et al., 2004; Jin et al., 2006) had to be excluded, and thus 8 final trials were entered in the meta-analysis for the negative symptoms (table 1).

Likewise, within the subset of clinical trials addressing treatment effects on positive symptoms, we searched for those that delivered low-frequency rTMS to the left TPC, and excluded all trials probing the primary auditory cortex (D' Alfonso et al., 2002; Langguth et al., 2006; Jardri et al., 2007), Broca's area (Schönfeldt-Lecuona et al., 2004), or the right DLPFC (Schreiber et al., 2002). Regarding Sommer et al.'s (2007) study, in which the coil was placed either by anatomical landmarks or according to functional activation maps, we only used data from the group stimulated according to the former strategy (n=6). Thus, we retrieved 23 papers, of which 14 were sham-controlled (8 parallel and 6 crossover) and 9 were uncontrolled studies. We then excluded 6 case reports (Franck et al., 2003; Fitzgerald et al., 2006; Poulet et al., 2006; Chung et al., 2007; Favalli et al., 2007; Poulet et al., 2008), 2 studies in which samples overlapped with other reports (Hoffman et al., 1999, 2003), 1 study reporting only 1 week of pre-treatment antipsychotic stabilization (Jandl et al., 2006), 1 study in which several sites were probed with no wash-out periods (Hoffman et al., 2007), and 1 study exploring activity in language regions after successful AH treatment with rTMS (Fitzgerald et al., 2007). Therefore, we were able to enter 12 trials into the meta-analysis for the positive symptoms (table 2).

For the analysis on the therapeutic use of rTMS on AH, exclusively, we extracted a subset of 9 studies, from the previously selected 12 reports, excluding 2 trials for not reporting a

composite score for the AHRS (Lee et al., 2005; Rosa et al., 2007), and 1 concerning the treatment of delusions (Saba et al., 2006) (table 2).

3.2. Treatment of negative symptoms

We initially pooled the results of the 8 studies assessing negative symptoms, and compared the results of post-rTMS treatment vs. baseline, using the active arms only for the controlled studies. The random effect model showed a pooled effect size of 0.58 [95% confidence interval (CI): 0.11, 1.04; p=0.014] and the fixed effect model revealed an effect size of 0.49 (95% CI: 0.17, 0.82; p=0.003) (figure 2). The test for heterogeneity failed to show significant heterogeneity between studies (Q7, χ^2=12.64; p=0.081). These results indicate that high-frequency rTMS above the DLPFC induced a significant, although modest-to-moderate, reduction of negative symptoms in patients receiving active treatment.

We evaluated the influence of individual studies by computing the meta-analysis' random effect model estimates and omitting one study at a time (figure 3). The two studies that induced the largest individual difference when removed were those by Prikryl et al. (2007) and Goyal et al. (2007). With their exclusion, the overall estimate decreased to 0.418 (95% CI: −0.02, 0.86) and 0.417 (95% CI: 0.09, 0.75), respectively. The exclusion of Jandl et al.'s (2005) study produced the highest increase of the overall estimate (0.67, 95% CI: 0.11, 1.23). The overall finding of a beneficial effect of rTMS on negative symptoms in schizophrenia remained significant after the exclusion of any single study, except for the exclusion of the study of Prikryl et al. (2007), in which the results are only marginally significant (95% CI: −0.02 to 0.86).

The funnel plot was used to identify whether the results were biased due to exclusion of unpublished, negative studies, which would render an asymmetrical funnel plot. The obtained plot (figure 4) showed that large studies had effect sizes that were near the pooled effects and showed a smaller effect according to our results. In addition, two studies with large standard error (indicative of small sample sizes) (Prikryl et al., 2007;Goyal et al., 2007) showed remarkably positive results, one of them being outside the 95% CI (Goyal et al., 2007). Although the distribution of the funnel plot might be considered somewhat asymmetrical, and the Egger test was significant (p=0.046), the sensitivity analysis showed that the exclusion of these two positive studies did not change our overall conclusions remarkably.

Lastly, we compared the scores between placebo versus active group in the double-blind studies (only 5 studies met this inclusion criterion). The analysis showed a pooled weighted effect size from the random effect model of 0.27 (95% CI: −0.38, 0.92; p=0.417) and from the fixed effect model of 0.21 (95% CI: −0.23, 0.64; p=0.351) (figure 5; table 3). Since in controlled studies the effect is defined as a difference from the control group, any positive effect in the control conditions would be expected to lower the net effect. In addition, effects of chance due to small number of studies are likely and, finally, the non-significant results here might be due the differences in the relative weighting of studies – i.e., because effect sizes are inversely proportional to the variance, small studies have larger variances and therefore smaller effects sizes. The test for heterogeneity failed to show significant heterogeneity across studies (Q4, χ^2=8.65; p=0.07). However, due to low power of this analysis and, in fact, given the limited number of studies included, a p-value of 0.07 might represent indeed a considerable heterogeneity. For this reason, we also calculated the between-studies analysis of variance. This analysis yielded a relatively large value of 0.293, therefore suggesting a significant heterogeneity across these studies..

3.3. Treatment of positive symptoms

We first pooled the results of the 12 studies assessing positive symptoms, and compared the results of post-rTMS treatment vs. baseline, using the active arms solely for the controlled studies. The random effect model showed a pooled effect size of 0.54 (95% CI: 0.32, 0.76; $p<0.001$) and the fixed effect model a pooled effect size of 0.50 (95% CI: 0.31, 0.68; $p<0.001$) (figure 6). The test for heterogeneity failed to show significant heterogeneity (Q11, $\chi^2=14.92$; $p=0.186$). Thus, these results suggest that low-frequency rTMS delivered to the TPC induced a significant, but modest-to-moderate, reduction of overall positive symptoms in patients receiving active treatment.

Next, we assessed the influence of individual studies (figure 7). The two studies that induced the largest individual difference in the pooled effects when excluded were the ones by Hoffman et al. (2005) and Saba et al. (2006). Interestingly, each study had the opposite influence: exclusion of Hoffman et al.'s study increased the overall estimate (0.59, 95% CI: 0.35, 0.84), whereas exclusion of Saba et al.'s trial decreased the overall estimate (0.44, 95% CI: 0.25, 0.62). Yet, the overall finding of a positive effect of TMS on positive symptoms in schizophrenia remained basically unaffected after the exclusion of any single study.

Begg's funnel plot (figure 8) showed that large studies had effect sizes that were near the pooled effects. However, three studies (Saba et al., 2006;Horacek et al., 2007;Rosa et al., 2007) with relatively large standard error showed very positive results, one of them being outside the 95% CI (Saba et al., 2006). Although the distribution of the funnel plot was asymmetrical, and the Egger test was significant ($p=0.008$), the sensitivity analysis showed that the exclusion of these positive studies did not change our overall conclusions.

When assessing only sham-controlled studies and comparing scores between active and sham groups, the pooled weighted effect size from both the random effect model and the fixed effects model was 0.17 (95% CI: −0.05, 0.39; $p=0.129$) (figure 9); no significant heterogeneity was found (Q7, $\chi^2=2.96$; $p=0.966$) (table 3).

3.4. Treatment of auditory hallucinations

Finally, for positive symptoms, we analyzed a subset of studies assessing the effect of rTMS on AH. The pooled effect size, again defined as the pre- versus post-treatment effect within the active arms only for controlled studies, using both the random effect model and the fixed effect model, was of 1.28 (95% CI: 0.89, 1.66; $p<0.001$) and of 1.35 (95% CI: 1.11, 1.58; $p<0.001$), respectively (figure 10). The test for heterogeneity showed that there was a significant heterogeneity across studies (Q8, $\chi^2=19.5$; $p=0.012$). Nevertheless, these results reveal a significant and robust effect of left TPC stimulation on AH in patients receiving active rTMS.

When assessing only sham-controlled studies, the comparison of scores between active versus sham groups showed an effect size from the random effect model of 1.04 (95% CI: 0.38, 1.71; $p=0.002$) and from the fixed effect model of 0.96 (95% CI: 0.65, 1.27; $p<0.001$) (figure 11); significant heterogeneity was found (Q6, $\chi^2=26.85$; $p<0.001$). Thus, the inclusion of controlled studies showed that a significant improvement of severity of AH after treatment was obtained, and the effect was robust (table 3).

4. Discussion

4.1. Summary of findings

Our analyses yielded several clear findings. First, negative symptoms show significant post-treatment improvement across uncontrolled trials but not across controlled studies. When open

trials are included, the effect is modest. The main finding, though, is that there is no statistically significant improvement of this symptom cluster in patients receiving active as compared to sham stimulation. Hence, the treatment of negative symptoms with rTMS as currently performed and measured (PANSS-N or SANS) does not seem to be efficacious. However, the number of sham-controlled studies is small, and two trials with positive results (Hajak et al., 2004; Jin et al., 2006) had to be excluded because of insufficient data. It is possible that inclusion of these studies might have resulted in significant and larger effect sizes. In particular, the study by Jin et al. (2006) clearly showed that the impact of rTMS on negative symptoms, compared to sham stimulation, was statistically significant and relatively impressive. Moreover, their approach suggested that rTMS to the left DLPFC can be beneficial if, in a synergistic fashion, concomitantly tuned with individualized frontal alpha frequency.

Second, positive symptoms, as globally assessed by PANSS-P or SAPS, do not show a statistically significant improvement after rTMS when only sham-controlled studies are analyzed. They do follow the same trend seen for negative symptoms, in the sense that the effect is significant, but modest, when all trials are included. This suggests, however, that overall positive symptoms do not benefit from stimulation of the TPC region, or there was not a sufficient number of studies.

Third, a marked and significant improvement of AH severity is obtained whether controlled or uncontrolled studies are analyzed. Indeed, not only the effect is significant, but it is also large. Thus, these results pinpoint a strong efficacy for the low-frequency rTMS protocol when probing left TPC on AH.

4.2. rTMS treatment of negative symptoms

If all trials are considered, this meta-analysis showed that rTMS to the left DLPFC results in statistically significant effects on negative symptoms in schizophrenia. The effect size was relatively discrete and this raises questions about the clinical relevance of the findings. When a potential placebo effect was considered, the effect of rTMS on negative symptoms was small and non-significant, and, accordingly, this had no clinical impact. Although we did not assess long-lasting effects in our analysis (as only few studies report this assessment), survivorship of effects seems to follow the same trend of poor results. Despite the fact that patients were followed-up in only 3 studies, no improvement was obtained at 2 (Mogg et al., 2007) or 8 weeks post-treatment (Novak et al., 2006). Sachdev et al. (2005) showed, however, that effects can last at least 30 days.

Several possible explanations can be offered for the weak results and divergence across studies. One explanation might be the severity of psychopathology. Indeed, the degree of illness severity (baseline psychopathology, table 1) varied substantially across studies and probably influenced treatment response. For instance, patients in Holi et al. (2004) study, who found no benefit of rTMS, had almost doubled baseline total scores of PANSS as compared to the patients of Prykril et al. (2007) who clearly benefited from rTMS. However, patients in the study by Goyal et al. (2007) were as severely affected as those of Holi et al. but significantly improved after treatment. This differential outcome might be related to the fact that Goyal et al. applied more than twice the number of rTMS stimuli that Holi and colleagues did.

Indeed rTMS parameters appear to be important, though no clear picture emerges. Jin et al. (2006) compared alpha-range (8–13Hz) and 20Hz rTMS, with patients submitted to the former showing significant post-treatment improvement while the latter being no better than sham. This might also justify the negative results of Novak et al. (2006) who used 20Hz rTMS. However, Cohen et al. (1999) found significant improvement after 20Hz rTMS, even though the number of stimuli delivered in their trial was less than half (8,000) of Novak et al.'s trial (20,000). On the other hand, it seems that trials in which a low number of stimuli were delivered

produced negative (4,000; Holi et al., 2004) or worse results (3,500; Jandl et al., 2005) than when total number of stimuli were 10,000 or higher (e.g. 22,500; Prikryl et al., 2007). The highest number of stimuli (36,000) was delivered at 15Hz rTMS in the longest trial (Sachdev et al., 2005), and improvement in negative symptoms was observed, although the sample size was the smallest of all group studies. Therefore, it seems clear that more work is needed to identify optimal rTMS parameters. Ultimately, a multivariate regression analysis including patient characteristics (e.g., age, gender, or baseline psychopathology) as well as TMS parameters (e.g. number of stimuli, stimulation intensity, or number of session) is necessary to assess the contribution of clinical characteristics versus parameters of stimulation.

Another potential explanation regards the outcome measures that are currently being used as main assessments to target changes, and even the underlying definition of negative symptoms. In most studies, cognitive and functional outcome measures (assessing the impact of potential benefits in key outcome areas such as social behavior, work performance, and activities of daily living) were scarcely used, but retrieved interesting results. For example, Mogg et al. (2007)'s study found significant improvement of verbal learning (delayed recall) at 2-week follow-up, although none of the patients met criterion for response (20% reduction from baseline in PANSS-N). In Cohen et al. (1999)'s study, where positive results were achieved, there was a trend for general cognitive improvement, and significance was achieved for delayed visual memory. These two domains of cognition are among those identified by the NIMH-MATRICS project as important for schizophrenia (Green and Nuechterlein, 2004; Green et al., 2004). Sachdev et al. (2005) showed significant improvement of functional level (around 33%), while Fitzgerald et al. (2005)'s negative study found improvement in global function but no difference between groups. Thus, consideration of specific cognitive deficits might be valuable, though Novak et al. (2006) did not find any improvement of cognitive deficits.

Also important to consider is the site of stimulation, the left DLPFC. Evidence from anatomical and functional neuroimaging studies has pointed out several sources of dysfunction in schizophrenia patients. With respect to negative symptoms, structural and functional deficits have been shown in medial frontal areas (Koutsouleris et al., 2008; Siegel et al., 1993) and anterior cingulate (Fujimoto et al., 2007; Haznedar et al., 1997), as well as in posterior cortical parietal cortex (Zetzsche et al., 2008), including the inferior parietal lobule (for review, Torrey, 2007), and occipital regions (Onitsuka et al., 2007). The cerebellum has also been strongly related to schizophrenia. Indeed, Andreasen and Pierson (2008) extensively reviewed several lines of evidence for cerebellar abnormalities in schizophrenia and argued its role in the modulation of higher cognitive processes, largely impaired in schizophrenics. Moreover, the DLPFC is a region of the "task-related network" and, at least theoretically, more prone to cognitive enhancement than to core negative symptom improvement. Thus, it is possible that other brain sites would respond better to rTMS and should thus be carefully judged as potential stimulation targets for the treatment of negative symptoms of schizophrenia.

Finally, the total number of patients included in this meta-analysis is limited. Indeed, our sample was of 107 patients and only 63 received active treatment. Of these, almost half (n=27) were included in three studies (Holi et al., 2004; Novak et al., 2006; Mogg et al., 2007) showing negative results. Although we might have been underpowered in our analysis, the effect size of sham-controlled studies was small. Nevertheless, further controlled studies with larger sample sizes using designs shown to induce positive results [as, for instance, the design used by Jin et al. (2006)] seem to be of major importance at this point.

4.3. rTMS treatment of overall positive symptoms

As shown by this meta-analysis, low-frequency rTMS to the left TPC does not seem to be a suitable protocol for the treatment of positive symptoms other than AH. When placebo was concomitantly used, the effect size was small and non-significant. Moreover, these results are

in agreement with previously reported meta-analytic findings of absence of significant improvement in overall positive symptoms (Aleman et al., 2007).

Probably, a major reason for such poor outcome is the targeted site. Positive psychotic symptoms, other than hallucinations, have been associated with dysfunctions in the orbitofrontal cortex (OFC) (Premkumar et al., 2008; Baas et al., 2008). Furthermore, altered distribution of OFC sulco-gyral pattern in schizophrenics and a smaller left middle orbital gyrus, strongly associated with worse positive formal thought disorder, were recently described (Nakamura et al., 2007; 2008). A role for the medial temporal lobe in positive psychotic symptoms was also suggested, while the lateral temporal cortex is involved in hallucinations (Whalley et al., 2007). White matter (WM) changes detected in diffusion tensor imaging studies have also been seen as one source of the illness and seem to be detectable in the early phases (Karlsgodt et al., 2008). Specifically, their functional impact on psychopathology and cognition is unraveling: for instance, frontal WM reduction is correlated with prefrontal alterations in working memory (Schlösser et al., 2007), whereas parietal and cerebellar WM abnormalities may contribute to the emergence of psychotic symptoms in early-onset schizophrenia (Kyriakopoulos et al., 2008). Moreover, cerebellar activation has been associated with delusions and suspiciousness/persecution (Whalley et al., 2007). This suggests that positive psychotic symptoms, such as delusions, might be better addressed if brain regions other than the TPC are targeted.

4.4. rTMS treatment of auditory hallucinations

Confirming prior studies, our meta-analysis demonstrates that rTMS to the left TPC results in robust therapeutic effects on AH. Indeed, even when only considering sham-controlled studies, the obtained effect size remained large and significant. In fact, this effect size was higher than the one obtained by Aleman et al. (2007)'s meta-analytic approach on this topic (d=0.76), in which different stimulation sites were analyzed together. Thus, the fact that we narrowed down our analysis to a single brain location and observed a larger effect size seems to indicate that the temporal association cortex plays a crucial role in the pathophysiology of AHs and offers a promising target for neuromodulatory therapeutic approaches. In this regard, the study by Hoffman and colleagues (2007) was particularly important, since it clearly showed an elevated response rate for rTMS to this region, as compared with rTMS to anterior temporal, frontal or right temporal areas.

Nevertheless, the treatment of AH deserves a few comments directed at possible ways for enhancing outcome. A critical finding of Hoffman et al. (2007)'s study concerned the discrepancy between the fMRI-guided TPC sites used in their trial and the standard TP3 site, which had little to no overlap. Moreover, in Sommer et al. (2007)'s study, 5 of the 7 patients undergoing functional-guided rTMS had predominant right-sided hallucinatory activity, and were therefore stimulated over the right TPC. Hence, this strongly suggests the need for individual assessment of the functional anatomy of hallucinations, so that the use of hallucination-activation maps, obtained either by PET or fMRI, might enhance TMS efficacy. Furthermore, it was recently showed that highest precision is achieved with individual, or even probabilistic, fMRI-guided stimulation (Sparing et al., 2008), as compared to other, less sophisticated approaches including coil position using the International 10/20 EEG electrode system.

Although global results are convincing, not all features of AHS seem to equally and adequately respond to rTMS. For instance, Hoffman et al. (2005) and Lee et al. (2005) found that frequency of AH was subject to significant treatment effects, while Fitzgerald et al. (2005) found a significant effect for loudness of voices. In contrast, Rosa et al. (2007) showed significant improvement after active rTMS in six of the seven AHRS items (except loudness), and maintenance of significant changes in four AH features at one-month follow-up. Yet, results

are still mixed and further work focusing on the impact of rTMS on specific characteristics of AH is needed.

Another relevant finding by Hoffman et al. (2007) relates to the optimal number of sessions: only after the fourth site was probed (about 12 sessions) was there a significant improvement, regardless of the region being stimulated. Thus, the number of sessions might also impact on rTMS efficacy and outcome, and by far the majority of studies included in our analysis included a protocol with a maximum of 10 sessions. In other words, greater efficacy might be obtained if the number of sessions is expanded.

Finally, it is worth noting that only 5 out of the 12 studies entered in this meta-analysis included follow-up analysis. Hoffman et al. (2005) found that mean duration of survivorship was 13 weeks and close to 20 weeks among patients achieving responder status. In the study by Poulet et al. (2005), 50% of patients were still responders when they were followed up to 8 weeks. Chibbaro et al. (2005) found a delayed effect of rTMS on reduction of AH distinguishable from that of the sham group only at 3 weeks post-treatment and thereafter until week 8. In Sommer et al.'s study (2007) severity of AH was still significantly lower than baseline 10 weeks after the last treatment. Lastly, in Rosa et al.'s trial (2007) some AH features were still significantly improved at 6 weeks follow-up. However, further work on the duration of the effects of rTMS on AH is critically needed to assess the practical significance of this treatment. In this respect, modified parameters of rTMS that lead to longer-lasting cortical modulation, such as theta-burst stimulation (Huang and Rothwell, 2004), would seem worth testing.

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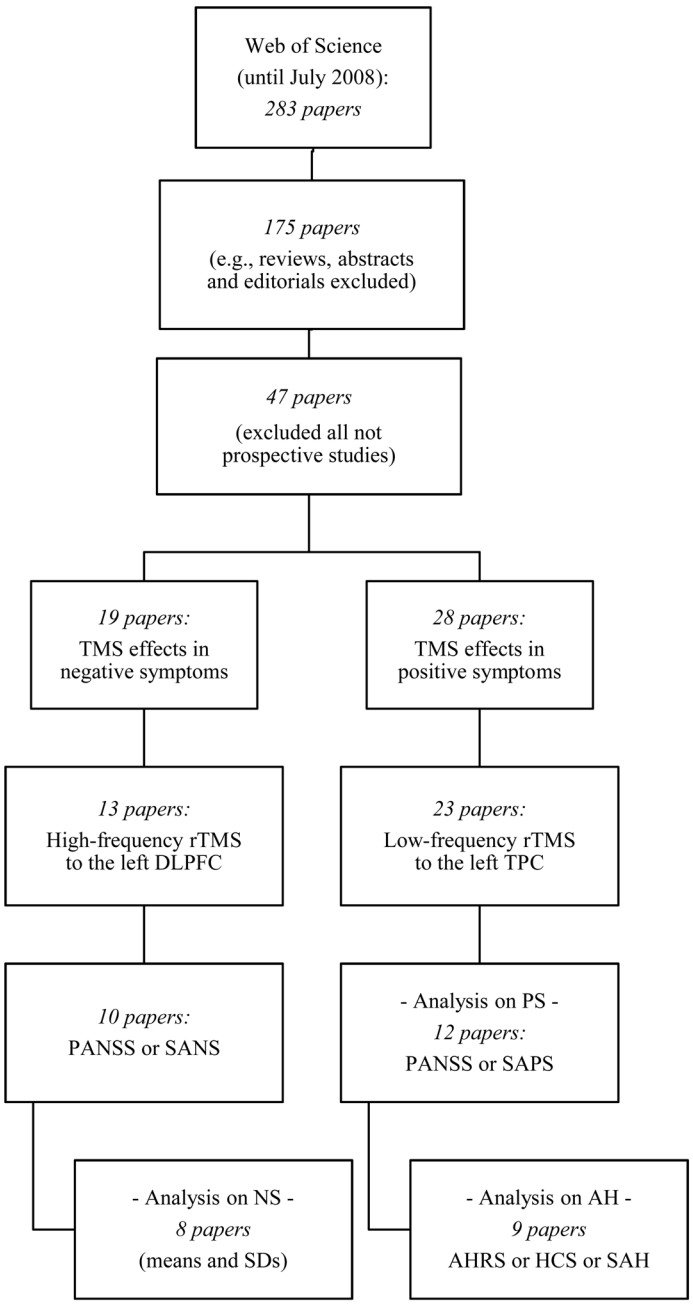

Figure 1.
Flow diagram of the selection process of peer-reviewed articles for main analyses (negative and positive symptoms) and additional analysis (auditory hallucinations).

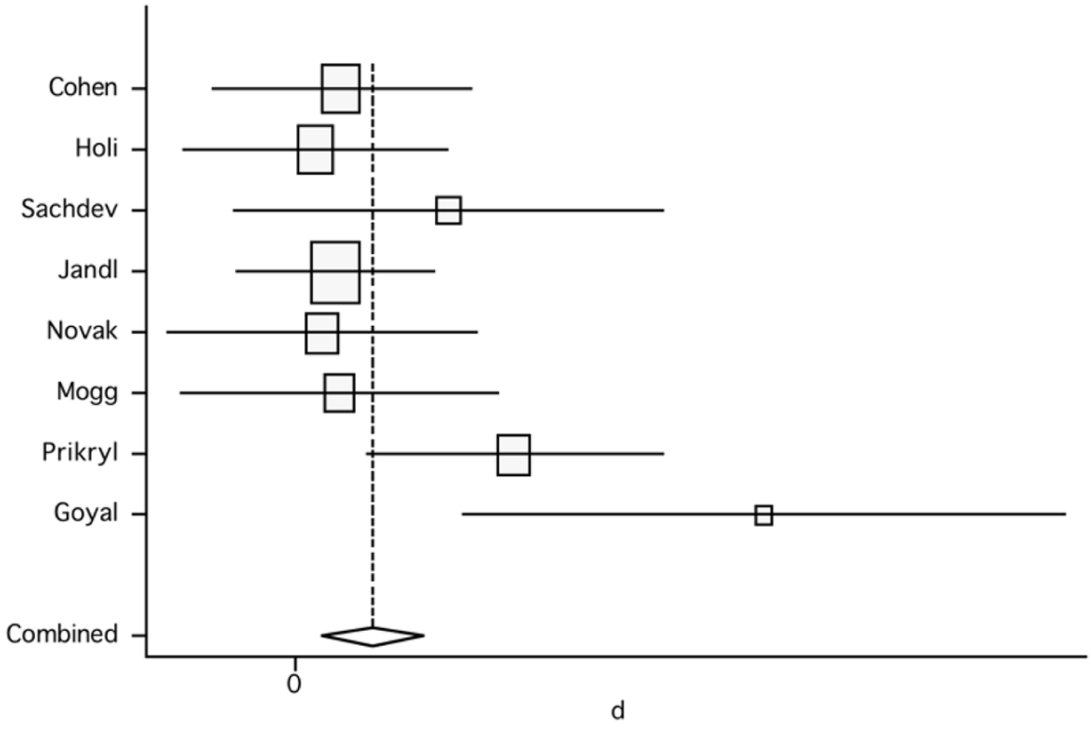

Figure 2.
Pooled effect size (before *versus* after treatment) for studies of rTMS effects on negative symptoms (random effect model).

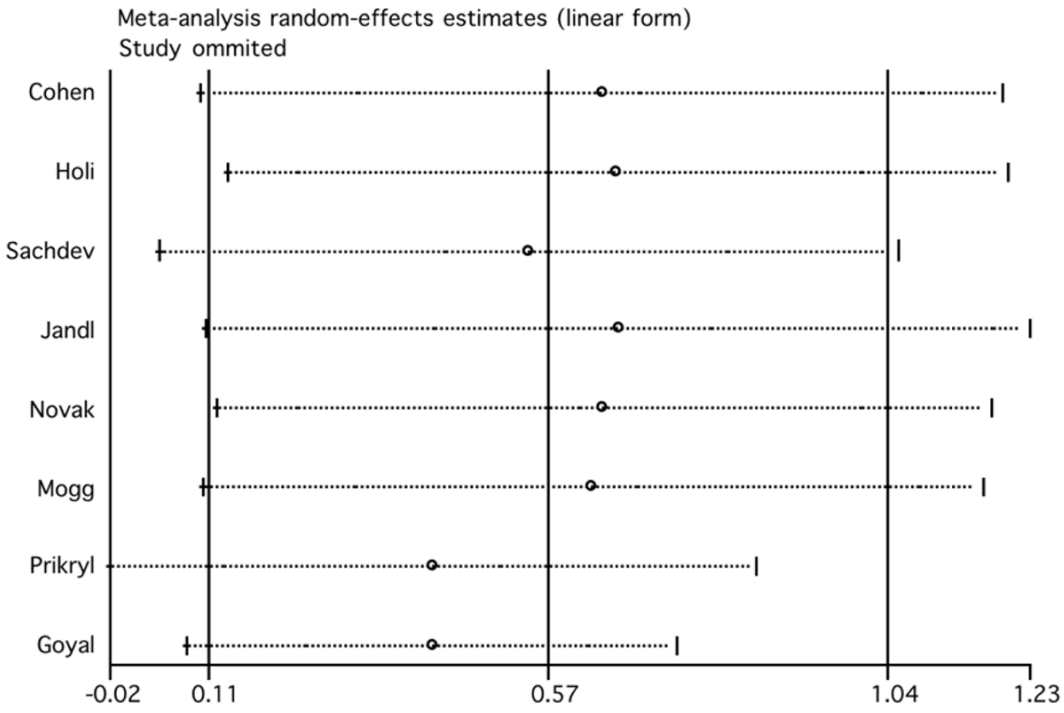

Figure 3.
Estimates of the random effect model omitting one study at a time (rTMS effects on negative symptoms).

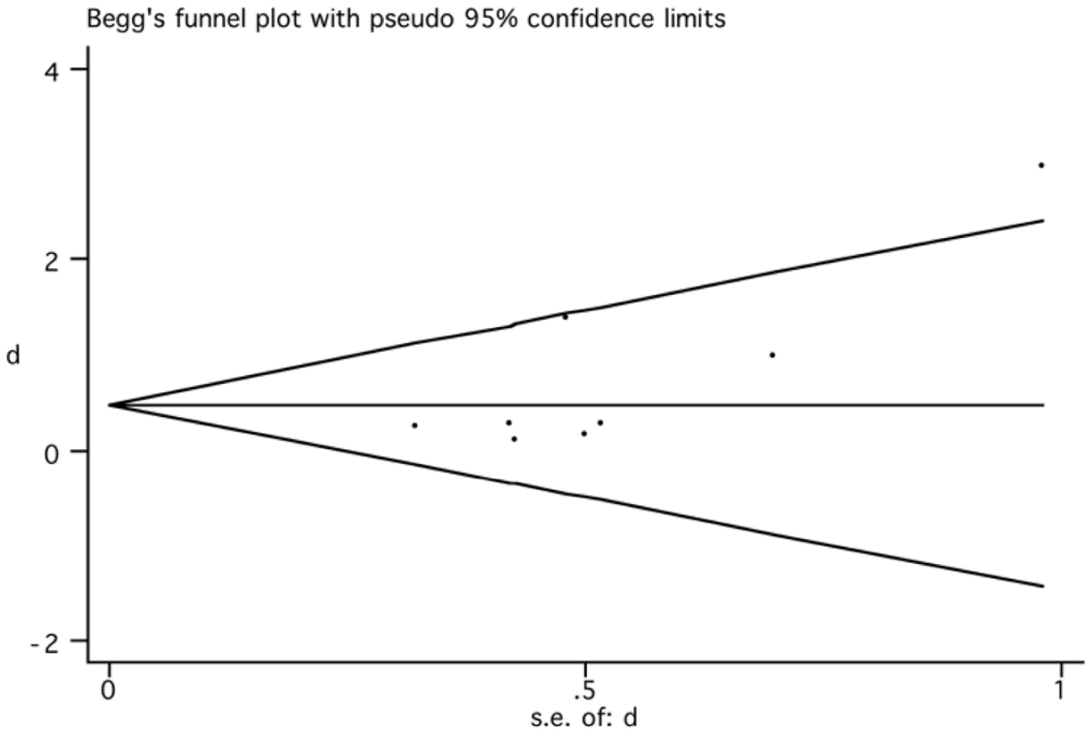

Figure 4.
Begg's funnel plot (95% CI) (rTMS effects on negative symptoms).

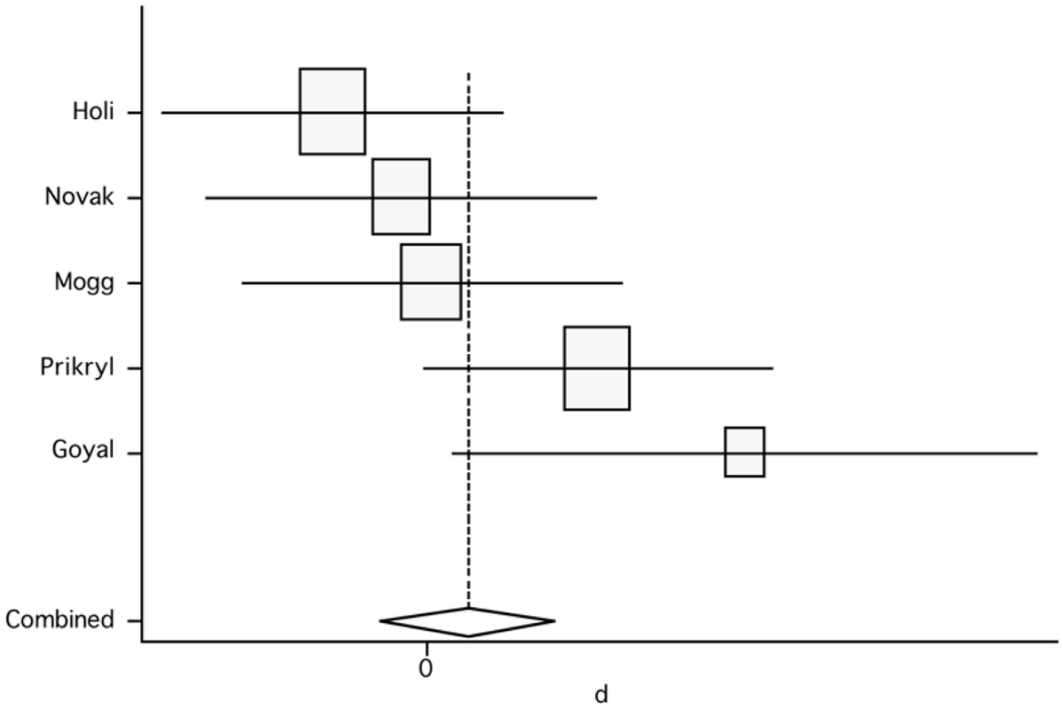

Figure 5.
Pooled effect size (placebo *versus* active treatment) for studies of rTMS effects on negative symptoms (random effect model).

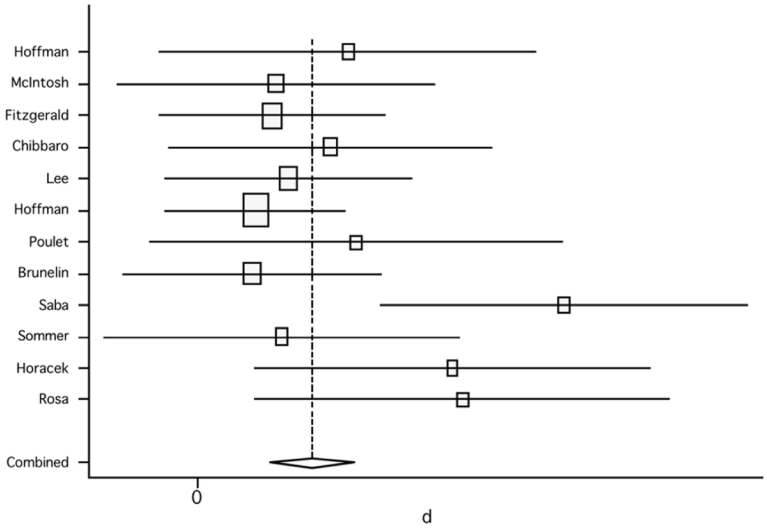

Figure 6.
Pooled effect size (before *versus* after treatment) for studies of rRMS effects on positive symptoms (random effect model).

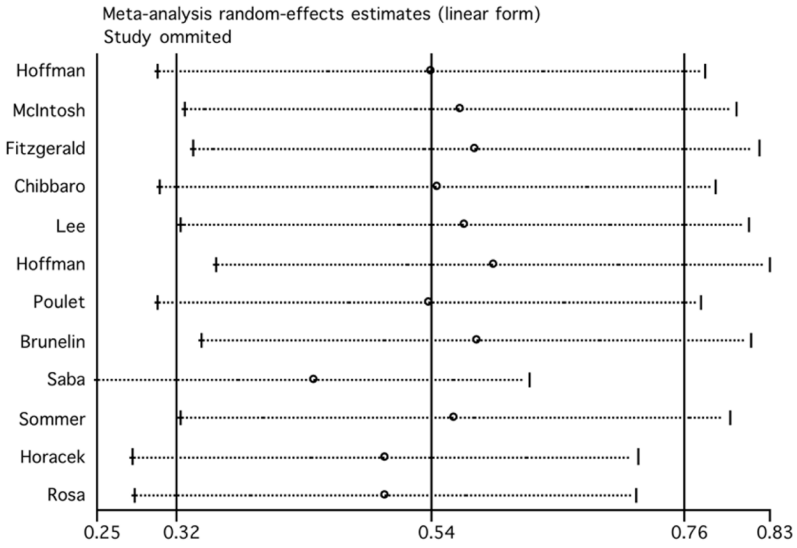

Figure 7.
Estimates of the random effect model omitting one study at a time (rTMS effects on positive symptoms).

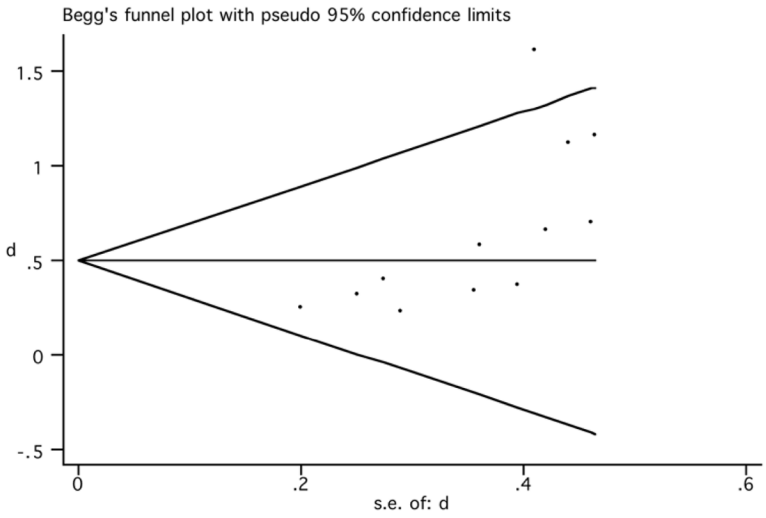

Figure 8.
Begg's funnel plot (95% CI) (rTMS effects on overall positive symptoms).

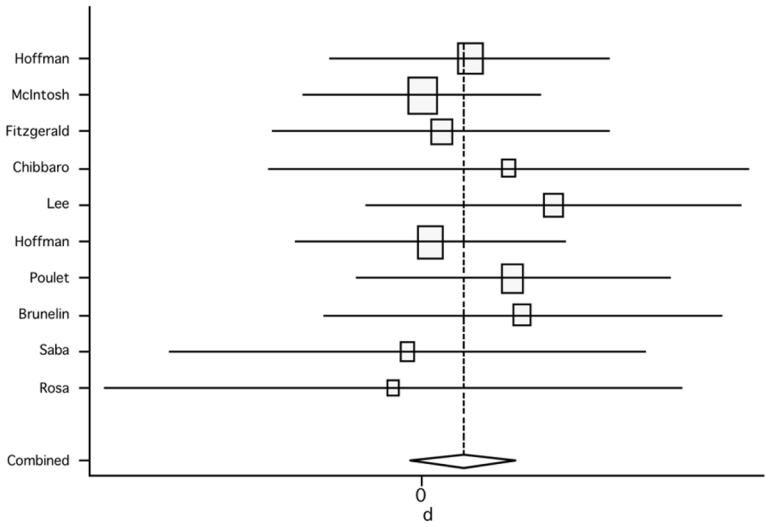

Figure 9.
Pooled effect size (placebo *versus* active treatment) for studies of rTMS effect on overall positive symptoms (random effect model).

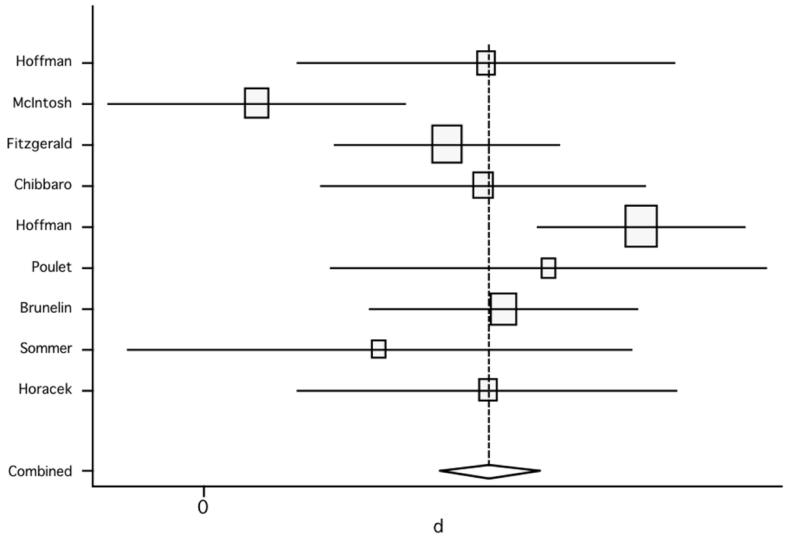

Figure 10.
Pooled effect size (before *versus* after treatment) for studies of rTMS effects on auditory hallucinations (random effect model).

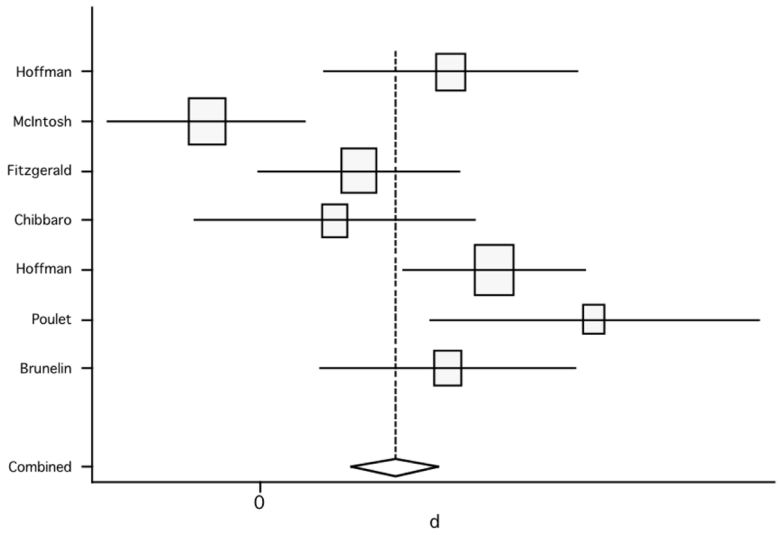

Figure 11.
Pooled effect size (placebo *versus* active treatment) for studies of rTMS effects on auditory hallucinations (random effect model).

Table 1

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

Study		Demographic and clinical characteristics				TMS parameters							Baseline psychopathology					
Authors	Design	N	Gender (% M)	Mean age (y)	Mean duration SCZ (y)	Active N	Sham N	Frequency	% MT	No. of sessions	Total stimuli	Sham coil position	Type of coil	Rating scale	Active Mean	Active SD	Sham Mean	Sham SD
Cohen *et al*., 1999	Open-label	6	33.3%	39.00	.	6	.	20 Hz	80%	10	8000	.	Fig. 8	PANSS-G	37.67	11.15	.	.
Holi *et al*., 2004	Parallel	22	86.4%	36.70	13.20	11	11	10 Hz	100%	10	4000	90°	Fig. 8	PANSS-T	105.20	41.20	110.30	20.20
Sachdev *et al*., 2005	Open-label	4	100%	34.50	13.75	4	.	15 Hz	90%	20	36000	.	Fig. 8	.	.	.	.	.
Jandl *et al*., 2005	Open-label	10	50.0%	42.70	18.10	10	.	10 Hz	100%	5	3500	.	Circul	BPRS	36.90	8.10	.	.
Novak *et al*., 2006	Parallel	16	75.0%	34.10	11.50	8	8	20 Hz	90%	10	20000	90°	Fig. 8	PANSS-T	65.50	19.70	61.10	16.90
Mogg *et al*., 2007	Parallel	17	94.1%	41.70	16.53	8	9	10 Hz	110%	10	20000	Placebo coil	Fig. 8	PANSS-T	86.00	9.75	86.00	10.09
Prikryl *et al*., 2007a	Parallel	22	100%	33.90	6.73	11	11	10 Hz	110%	15	22500	90°	Fig. 8	PANSS-T	57.73	8.40	64.00	13.10
Goyal *et al*., 2007	Parallel	10	100%	28.00	.	5	5	10 Hz	110%	10	9800	45°	Fig. 8	PANSS-T	104.20	8.16	103.20	12.40
Total	.	107	.	.	.	63	44	.	.	.	.	.	.	.	.	.	.	.

TMS: Transcranial magnetic stimulation; M = Male; SCZ = Schizophrenia; MT = Motor threshold; Fig 8 = Figure-of-eight coil; Circul = Circular coil; PANSS-G = General psychopathology subscale of the Positive and Negative Syndrome Scale; PANSS-T = Total score of PANSS; BPRS = Brief Psychiatric Rating Scale; . = data not available or not applicable.

Table 2

Selected peer-reviewed articles for meta-analysis of rTMS effects on auditory hallucinations (*) and for meta-analysis of rTMS effects on overall positive symptoms of schizophrenia.

Study		Demographic and clinical characteristics				TMS parameters							Baseline psychopathology					
Authors	Design	N	Gender (% M)	Mean age (y)	Mean duration SCZ (y)	Active	Sham	Frequency	% MT	No. of sessions	Total stimuli	Sham coil position	Type of coil	Rating scale	Active		Sham	
						N	N								Mean	SD	Mean	SD
* Hoffman *et al.*, 2000	Crossover	12	83.3%	41.80	.	12	12	1 Hz	80%	4	2400	45°	Fig. 8	PANSS-G	38.33	7.69	38.75	11.85
* McIntosh *et al.*, 2004	Crossover	16	43.8%	35.90	11.60	16	16	1 Hz	80%	4	2400	45°	Fig. 8	PANSS-G	36.00	6.80	33.90	8.40
* Fitzgerald *et al.*, 2005	Parallel	32	53.1%	36.03	14.31	17	15	1 Hz	90%	10	9000	45°	Fig. 8	PANSS-G	38.12	6.33	41.27	6.63
* Chibbaro *et al.*, 2005	Parallel	16	68.8%	40.05	8.15	8	8	1 Hz	90%	4	3600	45°	Fig. 8	.	.	.	.	.
Lee *et al.*, 2005	Parallel	27	59.0%	40.57	.	13	14	1 Hz	100%	10	12000	90°	Fig. 8	PANSS-G	42.46	14.04	43.93	11.06
* Hoffman *et al.*, 2005	Parallel	50	66.0%	35.28	24.07	27	23	1 Hz	90%	9	7920	45°	Fig. 8	PANSS-G	31.06	8.66	31.89	11.19
* Poulet *et al.*, 2005	Crossover	10	70.0%	34.90	10.60	10	10	1 Hz	90%	10	10000	Placebo coil	Fig. 8	.	.	.	.	.
* Brunelin *et al.*, 2006	Parallel	24	66.7%	34.53	9.33	14	10	1 Hz	90%	10	10000	Placebo coil	Fig. 8	PANSS-T	81.40	11.40	79.60	11.50
Saba et al., 2006	Parallel	16	81.3%	30.65	7.95	8	8	1 Hz	80%	10	3000	Placebo coil	Fig. 8	PANSS-G	42.25	5.73	48.38	7.47
* Sommer *et al.*, 2007	Open-label	6	100%	38.83	14.00	6	.	1 Hz	90%	15	18000	.	Fig. 8	PANSS-G	38.00	7.32	.	.
* Horacek *et al.*, 2007	Open-label	12	58.3%	34.40	6.36	12	.	0.9 Hz	100%	10	10800	.	Fig. 8	PANSS-T	72.83	17.89	.	.
Rosa *et al.*, 2007	Parallel	11	54.6%	31.27	7.03	6	5	1 Hz	90%	10	9600	Placebo coil	Fig. 8	PANSS-G	52.17	9.37	52.20	5.89
Total	.	232	.	.	.	149	121	.	.	.	.	.	.	.	.	.	.	.

*: Selected peer-reviewed articles for analysis of rTMS effects on AH; TMS: Transcranial magnetic stimulation; M = Male; SCZ = Schizophrenia; MT = Motor threshold; Fig 8 = Figure-of-eight coil; Circul = Circular coil; PANSS-G = General psychopathology subscale of the Positive and Negative Syndrome Scale; PANSS-T = Total score of PANSS; . = data not available or not applicable.

Table 3

Pooled weighted effect sizes for negative symptoms, overall positive symptoms, and auditory hallucinations.

Negative symptoms	**Random effect model**	**95% CI**	**p value**	**Fixed effect model**	**95% CI**	**p value**	**Q statistics**	**p value**
Pooled weighted effect size* (all studies)	0.58	0.11, 1.04	0.014	0.49	0.17, 0.82	0.003	12.64	0.081
Pooled weighted effect size* (controlled studies)	0.27	−0.38, 0.92	0.417	0.21	−0.23, 0.64	0.351	8.65	0.07
Positive symptoms	*Random effect model*	*95% CI*	*p value*	*Fixed effect model*	*95% CI*	*p value*	*Q statistics*	*p value*
Pooled weighted effect size* (all studies)	0.54	0.32, 0.76	<0.001	0.50	0.31, 0.68	<0.001	14.92	0.186
Pooled weighted effect size* (controlled studies)	0.17	−0.05, 0.39	0.129	0.17	−0.05, 0.39	0.129	2.96	0.966
Auditory hallucinations	*Random effect model*	*95% CI*	*p value*	*Fixed effect model*	*95% CI*	*p value*	*Q statistics*	*p value*
Pooled weighted effect size* (all studies)	1.28	0.89,	<0.001	1.35	1.11,	<0.001	19.50	0.012
Pooled weighted effect size* (controlled studies)	1.04	0.38, 1.71	0.002	0.96	0.65, 1.27	<0.001	26.85	<0.001

*Effect size: standardized mean difference. The mean difference was calculated using the change from pre- to post-treatment for the active group. CI: confidence interval.