Factors Modifying the Efficacy of Transcranial Magnetic Stimulation in the Treatment of Depression: A Review

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Objective: So far no convincing answer has emerged to the question of whether transcranial magnetic stimulation (TMS) can make a clinically useful contribution to the treatment of depression. Here we examine whether multiple sensitivity analyses can highlight parameters that predict a favorable treatment response.

Data Sources: Medline, Embase, and the Cochrane database for controlled trials were searched for relevant randomized controlled trials using the expression (*transcranial magnetic stimulation* or *TMS*) and *depression*.

Study Selection: Thirty-three studies were identified and included in the random-effects meta-analysis, and between 17 and 31 studies were included in the secondary analyses comparing outcome of studies with different parameters.

Data Extraction: Study data were extracted with a standardized data sheet. A meta-analysis based on Cohen d effect size measure was done for all studies and various subsets. Regression analysis of effect sizes with study parameters was done in 24 studies.

Data Synthesis: Active TMS treatment was more effective than sham, but variability was too great to take any single study design as paradigmatic. No significant predictors of study effect size were found. Mean effect sizes were reduced, although still significant, in studies with stimulation intensity below 90% of motor threshold and new medication starting within 7 days before to 7 days after start of TMS.

Conclusions: The absence of significant outcome predictors in the presence of significant variability of outcome measures can be interpreted in 2 ways: either study sizes and numbers and designs are insufficient to afford the power necessary to detect such predictors or TMS has a nonspecific effect on depression that is not influenced by study parameters. Large-scale comparative trials are necessary to decide between these interpretations.

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Transcranial magnetic stimulation (TMS) has now been licensed in a number of countries for the treatment of depression. In other countries, it is available as a privately funded treatment. In spite of this, the initial enthusiasm that greeted its arrival as a replacement of drugs or even electroconvulsive therapy has been waning under the influence of recent negative trials[1–4] and reviews.[5] TMS is labor intensive and hence, expensive. As a result, the available publicly funded trials have generally been underpowered, so that at this stage only meta-analyses can provide convincingly large data sets to demonstrate its efficacy. There have been a number of negative meta-analyses, notably the Cochrane review by Martin and colleagues[6] and the recent review by Couturier,[5] which also used the Cochrane methodology. The latter review only used 8 out of 19 then published trials that met its inclusion criteria. These criteria were arguably too restrictive; for example, only the 21-item Hamilton Rating Scale for Depression (HAM-D) was allowed as an outcome measure, although one of the advantages of meta-analyses is that they can compare effect sizes rather than requiring commensurate scales between studies. The present review attempts to include as many randomized double-blind controlled data as possible. At the same time, we recorded potential confounder variables and carried out multiple sensitivity analyses to examine their likely impact on treatment efficacy.

METHOD

Data Sources

Randomized controlled trials were identified by entering the expression (*transcranial magnetic stimulation*

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or *TMS*) and *depression* into the search engines of Medline and Embase. In addition, the Cochrane database of controlled trials was searched for relevant studies using the same phrase and reference lists.

Study Selection

Prospective studies investigating the effects of repetitive TMS (rTMS) on depressive symptoms in patients with depression were included. For this purpose, the following inclusion criteria had to be met: Studies had to be of randomized parallel or crossover design with sham control with both patients and investigators unaware of whether patients were receiving real or sham rTMS. Moreover, patients were required to have a diagnosis of depression, i.e., major depressive disorder or bipolar disorder. Studies included were required to report their findings using either the HAM-D[7] or the Montgomery-Asberg Depression Rating Scale (MADRS).[8] Furthermore, the data required for the meta-analysis (i.e., baseline and follow-up depression scores and their standard deviations before and after the intervention) had to be available. If these data were not available, studies were included only if other data were provided from which these values could be derived.[9]

Data Extraction

The following variables were recorded in a structured fashion: (1) mean and standard deviation of the outcome measure before and after treatment, (2) sample characteristics, (3) study design, and (4) treatment parameters (stimulation frequency and intensity, type of coil used, number of treatment sessions). In crossover studies, only data from the first stage of the study were used, so that possible carryover effects between study phases could be excluded.[6] In studies with more than 1 experimental group, only 1 of the groups was included. When the experimental groups did not significantly differ in terms of efficacy, they were pooled.

A random-effects meta-analysis was performed on StatsDirect (version 2.4.5; May 30, 2005) using Cohen d as effect size. This method is more appropriate than the fixed-effects model when there is a high degree of heterogeneity.[10] Variability of effects between the studies was investigated using as a test for heterogeneity the Q ("noncombinability" for d+) test. Following the method implemented in StatsDirect, bias indicators were derived from regression of normalized effect versus Precision[11] and Kendall test on standardized effect versus variance.[12] Secular trends were assessed by means of a bivariate correlation between magnitude of effect size and order of publication. To ensure that the mean baseline depression scores of the sham and active groups in studies included in our analysis did not differ, a paired samples t test was carried out. We conducted a similar test for the subset of studies included in Couturier's meta-analysis.[5] We further carried out a simultaneous multiple regression analysis with the aim of determining whether there were any variables that predicted the magnitude of effect sizes in the individual studies. Variables entered as predictors included (1) mean age of all participants, (2) treatment resistance, (3) number of rTMS sessions, (4) type of depressive disorder, (5) potential medication effects, and (6) stimulation intensity. A medication effect was considered possible if patients started taking a new medication within a period of 7 days before to 7 days after the first rTMS treatment.

Table 1. Couturier's (2005) Criteria for rTMS Trial Quality[a]

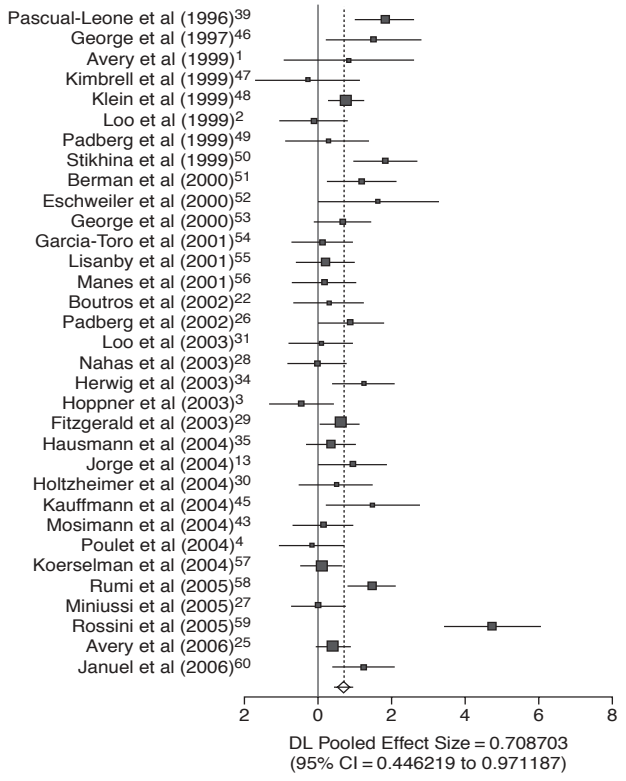
1. Randomized parallel or crossover design with sham control
2. Evidence of allocation concealment
3. Double blinding
4. Presence of intent-to-treat analysis
5. Absence of a carryover effect (if applicable)
6. Diagnosis of DSM-IV major depressive disorder
7. rTMS frequency of ≥ 10 Hz
8. Left DLPFC stimulation
9. 5 to 10 Treatment sessions
10. rTMS intensity of ≥ 80%
11. Sham coil angled between 45 and 90 degrees from the scalp
12. Clear presentation of the data
13. 21-Item HAM-D as primary outcome measure
14. Closed trial
15. Patients without primarily psychotic disorders, major depressive episodes with psychotic features, or other psychiatric illnesses
16. Nonspecific populations
17. Absence of a possible medication effect

[a]Based on Couturier.[5]
Abbreviations: DLPFC = dorsolateral prefrontal cortex, HAM-D = Hamilton Rating Scale for Depression, rTMS = repetitive transcranial magnetic stimulation.

In order to illustrate such potentially confounding effects, studies were classified in the following fashion: (1) mean age of all participants ≤ 50 years versus > 50 years, (2) treatment resistance (yes/no), (3) number of rTMS sessions (5 sessions, 10 sessions, or > 10 sessions), (4) type of depressive disorder (major depressive disorder/bipolar depression), (5) medication (stable/unstable), (6) stimulation intensity (80%, 90%, 100%, or > 100% of motor threshold), (7) left dorsolateral prefrontal cortex (DLPFC) stimulation frequency (< 15 Hz or ≥ 15 Hz), (8) psychotic features (present/absent), and (9) inclusion in Couturier's study (yes/no).[5] Separate meta-analyses for each of these subgroups were performed in lieu of a sensitivity analysis, and confidence intervals of weighted effect sizes were determined as above. The presence of a significant difference in effect size between high-frequency stimulation of the left DLPFC and low-frequency stimulation of the right DLPFC was investigated by means of an independent samples t test.

Finally, in order to assess whether trial quality was related to rTMS efficacy, we rated each trial in terms of trial quality according to Couturier's criteria[5] (Table 1) and used these ratings to perform a bivariate correlation between trial quality and magnitude of the effect size.

Figure 1. Forest Plot of 33 Transcranial Magnetic Stimulation Treatment Studies in Depression[a]



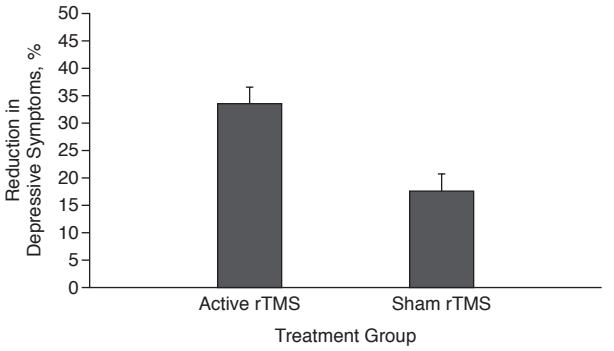
[a]Effect size meta-analysis plot (random effects).
Abbreviation: DL = DerSimonian-Laird.

Table 2. Sample Characteristics of 33 Studies Included in Meta-Analysis

Characteristic	No. of Studies	Active TMS	Sham TMS
No. of patients		475	402
Age, mean (SD), y	27	49.14 (8.19)	48.85 (7.24)
Duration of current episode, mean (SD), mo	16	16.08 (19.61)	17.76 (23.98)
Baseline HAM-D score, mean (SD)	26	27.05 (5.49)	25.86 (5.45)

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, TMS = transcranial magnetic stimulation.

Figure 2. Mean Reduction (%) in Depressive Symptoms for Active and Sham Repetitive Transcranial Magnetic Stimulation (rTMS)



Data Synthesis

Thirty-three studies were found that met the criteria for inclusion (Figure 1). Sample characteristics are displayed in Table 2. A paired-samples t test indicated that there was no significant difference between sham and control groups in terms of baseline depression scores ($t = 1.98$, $df = 27$; $p > .05$). However, for the subset of studies included in Couturier's meta-analysis,[5] a significant difference was found ($t = 3.7$, $df = 5$; $p < .05$), with a mean score of 22.7 ± 2.5 on the HAM-D for the sham group and a mean score of 27 ± 3.4 for the active treatment group. This indicates that, at baseline, participants in the sham group were significantly less depressed than participants in the active treatment group.

For the active rTMS group, reductions in depressive symptoms (as indicated by reductions in scores on the HAM-D and MDRS) ranged from –10.4% to 59.4%, with a mean of 33.6% (Figure 2). For the sham rTMS group, reductions ranged from –15% to 54%, with a mean of 17.4%. The pooled estimate of the effect size (d+) was 0.65 (95% CI = 0.51 to 0.79), indicating a clinically significant effect of rTMS. However, the test for heterogeneity was highly significant ($Q = 100.9$, $df = 32$; $p < .0001$), indicating that the variability in outcome measures between the studies exceeded that expected by chance. There was no significant bias: the intercept in the regression of normalized effect versus precision was 1.43 (approximate 95% CI = –0.78 to 3.65; $p = .2$). The Kendall test on standardized effect versus variance gave a τ of 0.13 ($p = .29$).

A bivariate correlation between order of publication and magnitude of the effect size did not reach significance, indicating that there was no secular trend (Kendall $\tau = –0.08$; $p > .05$; Spearman $\rho = –.08$; $p > .05$). The multiple regression analysis with effect size as dependent measure and age, treatment resistance, number of rTMS sessions, type of depressive disorder, presence of medication effect, and stimulation intensity entered as predictors did not yield any significant predictors of effect size. A comparison of the weighted mean effect sizes and their confidence intervals for each of these categories is displayed in Table 3. An independent samples t test indicated the absence of a significant difference in effectiveness between high-frequency left prefrontal cortex stimulation and low-frequency right prefrontal cortex stimulation.

Several of Couturier's criteria[5] were relatively uninformative with respect to study quality. All of the studies included in our analysis were closed (criterion 14),

Table 3. Univariate Comparisons of Effect Sizes in Relation to Study Parameters (not controlled for potential confounds)

Variable	No. of Studies	Weighted Effect Sizes	95% Confidence Interval
Total	33	0.65	0.51 to 0.79
Age (mean [SD] age of study sample)	27		
≤ 50 y (43.9 [0.7])	16	0.73	0.53 to 0.93
> 50 y (56.4 [1.4])	11	0.51	0.27 to 0.75
Treatment-resistant sample	30		
Yes	18	0.66	0.47 to 0.86
No	12	0.61	0.38 to 0.83
No. of sessions	31		
5	5	1.28	0.83 to 1.72
10	22	0.53	0.35 to 0.70
> 10	4	0.78	0.46 to 1.11
Type of depression	30		
Unipolar	17	0.56	0.36 to 0.75
Mixed unipolar/bipolar	13	0.75	0.52 to 0.98
Medication	30		
Stable	25	0.65	0.49 to 0.81
Unstable	5	0.27	0.09 to 0.63
Stimulation intensity	29		
80%	7	0.37	0.02 to 0.73
90%	7	0.66	0.31 to 1.01
100%	5	0.89	0.54 to 1.24
> 100%	10	0.66	0.44 to 0.89
Left DLPFC stimulation frequency	26		
< 15 Hz	13	0.66	0.43 to 0.89
≥ 15 Hz	13	0.55	0.32 to 0.77
Psychotic patients excluded	31		
Yes	12	0.73	0.49 to 0.97
No (or doubtful)	19	0.57	0.38 to 0.75
Included in Couturier's (2005) study[5]	17		
Yes	6	0.73	0.24 to 1.22
No	11	0.63	0.38 to 0.87
Individualized location of the PFC	28		
Yes	4	0.61	0.28 to 0.95
No	24	0.68	0.51 to 0.85

Abbreviations: DLPFC = dorsolateral prefrontal cortex, PFC = prefrontal cortex.

randomized sham-controlled studies (criterion 1), with data displayed in a clear manner (criterion 12). Furthermore, a randomized design with sham control usually requires adequate allocation concealment (criterion 2), double blinding (criterion 3), and intention-to-treat (criterion 4). Very few studies addressed these issues individually. In fact, only 3 studies addressed the issue of allocation concealment, while only 5 studies explicitly addressed the issue of intention-to-treat analysis. Due to word limits of publications, a failure to address these criteria may reflect quality of reporting rather than study quality itself. We therefore decided to remove these criteria from our analysis.

Since we only included the first stage of the crossover in studies of 2 or more parallel crossovers, criterion 5, i.e., the absence of a carryover effect, was equally uninformative. A diagnosis of major depressive disorder (criterion 6) was uninformative, as all studies recruited participants suffering from major depressive disorder, with the exception of Jorge and colleagues[13] whose participants suffered poststroke depression. After the removal of these criteria, 31 out of the 33 studies were assessed for trial quality according to the remaining 9 criteria (Table 4). Trial quality varied from 4 to 9 with a mean of 7.19 criteria satisfied; however, there appeared to be no significant correlation between trial quality and effect size ($r = 0.11$; $p > .05$).

Table 4. Revised Criteria for rTMS Trial Quality

1. rTMS frequency of ≥ 10 Hz
2. Left DLPFC stimulation
3. 5 to 10 Treatment sessions
4. rTMS Intensity of ≥ 80%
5. Sham coil angled between 45 and 90 degrees from the scalp
6. 21-Item HAM-D as primary outcome measure
7. Patients without psychotic features or other psychiatric illnesses
8. Nonspecific populations
9. Absence of a possible medication effect

Abbreviations: DLPFC = dorsolateral prefrontal cortex, HAM-D = Hamilton Rating Scale for Depression, rTMS = repetitive transcranial magnetic stimulation.

DISCUSSION

In summary, we found rTMS to be more effective in the treatment of depression than sham rTMS, with a large effect size of 0.71. This finding is in keeping with the results of some meta-analyses[14–17] but in contradiction to others.[5] In our study, real rTMS decreased depressive symptoms by a mean of 33.6%. This figure is highly consistent with the decrease in HAM-D scores of 34% that was recently reported by Paus and Barrett.[18] Our results are in contrast to a very recent meta-analysis,[5] which failed to find efficacy of rTMS in depression in a small number of selected trials. Couturier's results[5] imply that studies of higher quality and of a more rigid methodological design do not demonstrate clinical efficacy of rTMS in the treatment of depression. However, we found no significant differences in effect sizes between studies included in and excluded from Couturier's meta-analysis.[5] Similarly, the present study did not find a significant correlation between trial quality (measured by Couturier's criteria)[5] and magnitude of the effect size. There was a great variability in the results of the individual trials with regard to clinical effects, yet this did not appear to have any relation to the quality of the studies. Therefore, the exclusion of studies of apparently "lower quality" may not be justified. Equally, the large clinical effect of rTMS found in the present meta-analysis cannot be attributed to the inclusion of studies of lower quality not included in Couturier's meta-analysis.[5]

In contrast to Couturier,[5] we did find a significant effect size in the subset of studies she included in her meta-analysis (Table 4). The discrepancy in effect sizes is most likely because Couturier did not correct for differences in

baseline scores between control and treatment groups, whereas we did. Couturier used the "weighted mean difference measure," which is the absolute difference between the mean scores after treatment in the active and sham rTMS groups. This method is a more conservative approach, which is appropriate for big sample sizes, as it assumes the baseline scores to be normally distributed. However, when the distribution of scores at baseline is skewed, this method is less appropriate, as it ignores the variability of baseline measures and renders the analysis less powerful. In such circumstances, an analysis based on changes from baseline will be more efficient and powerful, as it removes a component of between-person variability from the analysis.[19] Our analyses showed that there was, in fact, a highly significant difference in baseline scores between the control and treatment groups for the studies included in Couturier's meta-analysis.[5] It appears that this skew at baseline, together with an analysis that only focuses on outcome, was responsible for Couturier's failure to detect the significant effect of active treatment as compared with sham treatment.[5]

Problems of Applicability

Since the Q-test for heterogeneity of effect sizes was significant, indicating a greater than chance variability between studies, it is not possible to select from among them a protocol of patient recruitment and treatment procedure that would be predicted to result in the average rTMS efficacy reported here.

Variability in Parameters

Variability of effect sizes between studies is likely to reflect significant variability in study parameters[20–23] such as age, depression type and chronicity, presence of psychotic symptoms, duration and severity of illness, number of rTMS trains delivered per session, inter-train interval, and number of stimuli in each stimulation train. Moreover, a high proportion of patients were taking nonstandardized antidepressant medication. All these factors may have confounded treatment effects and may have biased the outcome of individual studies. However, from the results of the present analysis, it appears that there are no variables that clearly predict rTMS efficacy. This is in contrast with a recent descriptive review of rTMS efficacy, which concluded that several patient factors and treatment parameters predict rTMS responsiveness.[24] It has been argued that stimulation intensity may play an important role in treatment outcome,[2,25] with an increase in intensity resulting in higher efficacy.[26] Similarly, greater stimulus frequency[27] and a greater number of rTMS sessions[6,22,28–30] have been associated with increased rTMS efficacy.

Surprisingly, the present meta-analysis appears to be the first to have attempted to quantify whether rTMS efficacy systematically varies with study parameters. We included 33 individual trials, resulting in an impressive sample size of 877 patients. This may have removed any spurious associations found in smaller studies but may possibly also have missed significant effects by adding uncontrolled confounding variability. From the present results, the best prediction that can be made is that studies enrolling participants taking unstable medication and studies using stimulation intensities of less than 90% of motor threshold may result in smaller levels of rTMS efficacy (Table 4). As the overlap in confidence intervals of the mean effect sizes demonstrates, though, this prediction will be associated with a considerable (false positive) error rate. Unfortunately, both the absence of strong predictors of treatment response and the emergence of weak predictors that either are independent of the experimental treatment (confounding medication) or are related to the ease of discriminating active and sham treatment (stimulus strength) are consistent with a placebo mechanism for the TMS antidepressant effect.

Site of rTMS Stimulation

We found high frequency stimulation of the left DLPFC and low frequency stimulation of the right DLPFC to be equally efficacious. However, this finding should be regarded with caution, as these results are based on 24 studies that targeted the left DLPFC but only 3 studies that targeted the right DLPFC. The finding of equal efficacy may be viewed as indirect, albeit preliminary, support for the notion that depression is characterized by left-right asymmetry that can be reversed both by increasing left frontal and by decreasing right frontal cortical activity.

It has been suggested that simultaneous stimulation of the left and right DLPFC may be more effective in the treatment of depression. Until now, only 1 study has investigated the efficacy of rTMS applied to the left and right DLPFC simultaneously.[31] That study found a significant improvement in depressive symptoms after bilateral rTMS stimulation, which, however, was not significantly different from the improvement in depressive symptoms after sham stimulation.

Failure to locate the DLPFC accurately may have been responsible for the low clinical efficacy of rTMS that was documented in many studies.[32] In most rTMS studies, the site of stimulation (i.e., the DLPFC) is located by identifying a point 5 cm anterior to the motor cortex (positioning method). This method does not allow for variability in head size and shape[33] or individual cortical morphology[34] so that direct stimulation of the DLPFC may not be guaranteed. Several recent studies have employed neuronavigational techniques and neuroimaging to locate the DLPFC.[13,25,34,35] Apart from Hausmann et al.,[35] all reported relatively positive results, but their mean effect size does not appear to differ from that of studies using conventional localization of the stimulation area.

Some authors have argued that the DLPFC may not be the best target for the application of rTMS altogether.[36]

Other areas of the brain may respond more rapidly to rTMS,[36] for example, both the cerebellum and the parietal cortex, which are part of the complex network involved in the regulation of mood and emotion disrupted in depression,[37,38] but there are as yet insufficient treatment data.

Length of Remission After rTMS Treatment

We only examined the efficacy of rTMS immediately after treatment and did not examine its efficacy at follow-up. Several studies have indicated, on the basis of follow-up data, that the beneficial effects of rTMS are not long lasting.[1,22,39] Consistent with this, a meta-analysis by Martin et al.[16] indicated that rTMS may be more efficacious than placebo immediately after treatment but not at a 2-week follow-up. Thus, the results of this meta-analysis should be treated with caution, as they do not necessarily imply any long-term clinical effects of rTMS.

Risks and Safety

Since its introduction, rTMS has induced a small number of seizures in normal controls, particularly before the safety guidelines for its use were established.[21,40] However, it appears that rTMS treatment according to the guidelines conveys a very small risk of seizure induction. Furthermore, a recent study on rTMS stimulation of nonhuman primates produced very encouraging results.[41] Even though stimulation parameters (i.e., the number of interventions and their frequency) in this study were at the upper limit of normal clinical practice, Dwork et al.[41] failed to identify any neuropathologic lesions caused by the rTMS procedure. However, common side effects of rTMS treatment include muscle tension headaches, especially when frontal areas are stimulated, where many superficial nerves and muscles overlie the skull.[40] This mild pain can easily be alleviated by common pain analgesics.[21,40]

With respect to transient cognitive effects of rTMS, accumulating evidence is similarly encouraging, with a number of studies indicating that rTMS treatment is not associated with any negative cognitive effects.[25,30,42,43] In fact, some studies have found rTMS treatment to have slight beneficial effects on some areas of cognition, such as verbal memory[44] and psychomotor speed and concentration,[1,44] regardless of its antidepressant efficacy. However, it should be acknowledged that the effects of long-term rTMS treatment are less well researched and future studies should, therefore, continue to investigate the effects of rTMS on cognition using longer follow-up periods.[40]

CONCLUSIONS

This meta-analysis indicates that studies that have examined rTMS efficacy in the treatment of depression are heterogeneous in terms of outcome, sample characteristics, and treatment parameters. Moreover, most of them have recruited a relatively small number of participants. Strict double-blinding often cannot be guaranteed because of sham conditions that may be detected by patients. All of these factors have the potential to lead to variability in the results of individual studies[6] and will have affected the results of the present meta-analysis. Unfortunately, the variables predicting successful treatment outcome could not be identified, presumably either because of their small effect or an overall absence of specific treatment effects.

It has been argued that systematic delineation of the optimal stimulation parameters will ultimately result in an increase in rTMS efficacy. Unfortunately, there is as yet no compelling evidence regarding the most effective combination of rTMS parameters.[5] Similarly, the present study failed to identify any treatment parameters that systematically predict rTMS efficacy. Until the optimal treatment parameters are found, rTMS remains an experimental approach for the treatment of depression.[45] More knowledge regarding the characteristics of patients who benefit from this treatment and the size and persistence of clinical effects is much needed. Although meta-analyses can distil preliminary evidence from smaller studies, large, rigorously controlled studies are needed to arrive at definitive judgments about predictors of treatment outcome.

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