High-Frequency Repetitive Transcranial Magnetic Stimulation Accelerates and Enhances the Clinical Response to Antidepressants in Major Depression: A Meta-Analysis of Randomized, Double-Blind, and Sham-Controlled Trials

Marcelo T. Berlim, MD, MSc; Frederique Van den Eynde, MD, PhD; and Z. Jeff Daskalakis, MD, PhD

ABSTRACT

Objective: High-frequency repetitive transcranial magnetic stimulation (HF-rTMS) is a safe and effective treatment for major depression. However, its utility as a strategy to accelerate and improve clinical response to antidepressants is still unclear.

Data Sources: We searched the literature from 1995 through May 2012 using EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, Scopus, and ProQuest Dissertations and Theses, and, from October 2008 until May 2012, by using MEDLINE. We included only studies written in the English language.

Study Selection: We selected all randomized, double-blind, and sham-controlled trials on HF-rTMS used as an accelerating (add-on) strategy to antidepressants for major depression.

Data Extraction: We performed a random effects meta-analysis using odds ratios (ORs) for response and remission rates following HF-rTMS and sham rTMS. Two time points were considered: the end of the add-on HF-rTMS stimulation period (T_1) and the end of the study (T_2).

Results: Data were obtained from 6 randomized controlled trials (RCTs), totaling 392 subjects with major depression. For T_1 (at mean ± SD 2.67 ± 0.82 weeks following start of combined rTMS + antidepressant treatment), 6 studies reported on response and 4 on remission rates. We found significantly higher response rates for active HF-rTMS (43.3%; 84/194) compared to sham rTMS (26.8%; 53/198) (OR = 2.5; 95% CI, 1.12–5.56; $P = .025$); however, remission rates did not differ between groups ($P = .33$). Heterogeneity between the included RCTs reporting data on response and remission rates at T_1 was significant (response: $Q_5 = 11.4$, $P = .044$, $I^2 = 56.12$; remission: $Q_3 = 12.24$, $P = .007$, $I^2 = 75.45$). For study end (T_2; at mean ± SD 6.80 ± 3.11 weeks following start of combined rTMS + antidepressant treatment), 5 studies reported on response and 4 on remission rates; overall, response rates at T_2 were significantly higher for subjects receiving HF-rTMS in comparison to those receiving sham rTMS (62% [104/168] and 46% [79/172], respectively; OR = 1.9; 95% CI, 1.003–3.56; $P = .049$). Also, 53.8% (57/106) and 38.64% (36/107) of subjects receiving active HF-rTMS and sham rTMS, respectively, were in remission at T_2 (OR = 2.42; 95% CI, 1.27–4.61; $P = .007$). Heterogeneity between the included RCTs reporting data on remission rates at T_2 was not significant, although RCTs reporting on response rates at T_2 were heterogeneous. The baseline depression scores for active and sham rTMS groups were similar. Finally, HF-rTMS was comparable to sham rTMS in terms of dropout rates.

Conclusions: HF-rTMS is a promising strategy for accelerating clinical response to antidepressants in major depression, providing clinically meaningful benefits that are comparable to those of other agents such as triiodothyronine and pindolol. Furthermore, HF-rTMS seems to be an acceptable treatment for depressed subjects.

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Corresponding author: *Marcelo T. Berlim, MD, MSc, Douglas Mental Health University Institute, 6875 LaSalle Blvd, FBC-3 Pavilion, Montréal, Québec, Canada, H4H 1R3 (nrc.douglas@me.com).*

Major depression is characterized by the presence of depressed mood, anhedonia, or both, as well as a number of somatic, vegetative, and psychological symptoms.[1] It is highly prevalent in the general population,[2] and is associated with substantial morbidity, mortality, and societal costs.[3,4] Consequently, depressive episodes are major health issues requiring rapid and effective treatment.[5,6]

Despite recent advances in the treatment of major depression, the delayed onset of therapeutic effects of antidepressants remains a major clinical concern.[7–10] Overall, standard antidepressants do not yield clinically meaningful benefits before the second or third week of treatment and, as demonstrated in the Sequenced Treatment Alternatives to Relieve Depression study,[11] less than a third of depressed patients achieve remission within 12 weeks of starting a first-line antidepressant. Thus, full therapeutic effects usually take several weeks to manifest and a considerable number of patients remain significantly ill despite relatively long-term treatment.[12] This therapeutic delay results not only in a more prolonged patient experience of suffering but also in a potentially increased suicide risk and in greater illness burden.[10,13]

Research focusing on the acceleration of antidepressant response is thus clearly warranted.[8,9,13,14] Novel strategies designed to accelerate treatment response are expected to promote an earlier restoration of functional well-being and productivity, a sustained and meaningful clinical improvement, and a lower risk of poor psychosocial outcomes in the long term.[13] Furthermore, they are expected to limit the harmful neurobiological effects associated with chronic major depression[15] and also improve patients' overall compliance with treatment.[16]

However, the development of novel treatment acceleration paradigms for major depression has not yet been sufficiently pursued.[7,13,17,18] For example, there is still no consensus as to which agents, interventions, or both can reliably accelerate the clinical response to antidepressants.[13,19] Despite encouraging preliminary findings with pharmacologic agents (eg, triiodothyronine,[20] pindolol,[21] lithium carbonate[22]), they are still far from conclusive.

In this context, neuromodulation techniques, such as repetitive transcranial magnetic stimulation

Clinical Points

- High-frequency repetitive transcranial magnetic stimulation (HF-rTMS) combined at the outset with an antidepressant medication is effective for accelerating and enhancing response and remission rates.
- HF-rTMS is well tolerated overall.
- HF-rTMS could be used as a second- or third-line add-on strategy to antidepressant medications.

(rTMS), are novel and promising nonpharmacologic therapeutic strategies for major depression.[23] Repetitive transcranial magnetic stimulation is a noninvasive and safe technique that allows for the focal depolarization of neurons in targeted cortical areas through the use of changing magnetic fields that penetrate the skull unimpeded.[24] The induction of local and transsynaptically mediated metabolic and biochemical changes in fronto-cingulate mood-regulating circuits is believed to underlie the antidepressant effects of rTMS.[23] High-frequency rTMS (HF-rTMS) applied over the left dorsolateral prefrontal cortex, in particular, has been shown in several meta-analyses to be effective for treating major depression either as a monotherapy or as an augmenting strategy (M.T.B., unpublished data, 2012; references 25 and 26). However, its use for accelerating antidepressant response has received relatively little attention. Thus, the goal of our systematic review and meta-analysis of randomized, double-blind and sham-controlled trials was to examine whether HF-rTMS can hasten the therapeutic effects of standard antidepressants in major depression. In order to produce more clinically meaningful results, we focused on the rates of response and remission. Furthermore, we assessed the acceptability of HF-rTMS based on the differential dropout rates between groups receiving active or sham neuromodulation.

DATA SOURCES

We identified articles for inclusion in this meta-analysis by screening the bibliographies of all meta-analyses on rTMS for major depression published to date[25–37] as well as of all included randomized controlled trials (RCTs); searching MEDLINE from October 1, 2008, until May 7, 2012 (as previous meta-analyses have screened this database up to late 2008[27]); searching EMBASE, PsycINFO, the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and ProQuest Dissertations and Theses from January 1, 1995, until May 12, 2012; and consulting the Web of Science Citation Index Expanded for all included RCTs in order to identify published articles that have prospectively cited them up to June 12, 2012.

The search procedures (including syntaxes, parameters, and results) are described in detail in section 2 of supplementary material.

STUDY SELECTION

Candidate studies had to fulfill the following criteria[38]: studies were randomly allocated, with double-blind (ie, patients and clinical raters blinded to treatment conditions), sham-controlled (ie, coil angled on the scalp or use of a specific sham coil), parallel, or crossover design (with only data from the initial randomization being used for the latter to avoid carryover effects) and ≥ 5 subjects with major depression randomized per study arm; subjects were aged 18–75 years, with a diagnosis of primary major depressive episode (unipolar or bipolar) according to the *Diagnostic and Statistical Manual of Mental Disorders* or the *International Classification of Diseases* criteria; HF-rTMS (≥ 5 Hz) over the left dorsolateral prefrontal cortex was given for ≥ 5 sessions and started concomitantly with a new antidepressant medication; and articles were written in the English language.

Studies were excluded if they enrolled subjects with "narrow" diagnoses (eg, postpartum depression) or secondary major depression (eg, vascular depression), offered HF-rTMS as an augmentation strategy (ie, subjects were on stable antidepressant regimens at the start of neuromodulation) or as a monotherapy for major depression, or did not report rates of response to treatment, remission, or both.

DATA EXTRACTION

The following data were recorded in a structured fashion: mean age, gender, presence of treatment-resistant major depression; stimulation frequency and intensity (including the total number of stimuli delivered), number of treatment sessions, and type of sham; antidepressant(s) used and target dose(s); number of responders to treatment based on the RCT's primary efficacy measure (defined as a ≥ 50% reduction in posttreatment scores on the Hamilton Depression Rating Scale [HDRS][39] or on the Montgomery-Asberg Depression Rating Scale [MADRS][40]) at the end of the rTMS add-on period (T_1) as well as at study end (T_2); number of remitters based on the RCT's primary efficacy measure (eg, 17-item or 21-item HDRS scores ≤ 7 or ≤ 8, respectively, or MADRS scores ≤ 6) at T_1 and T_2; and overall dropout rates between active and sham rTMS groups at T_2.

Data Synthesis and Analyses

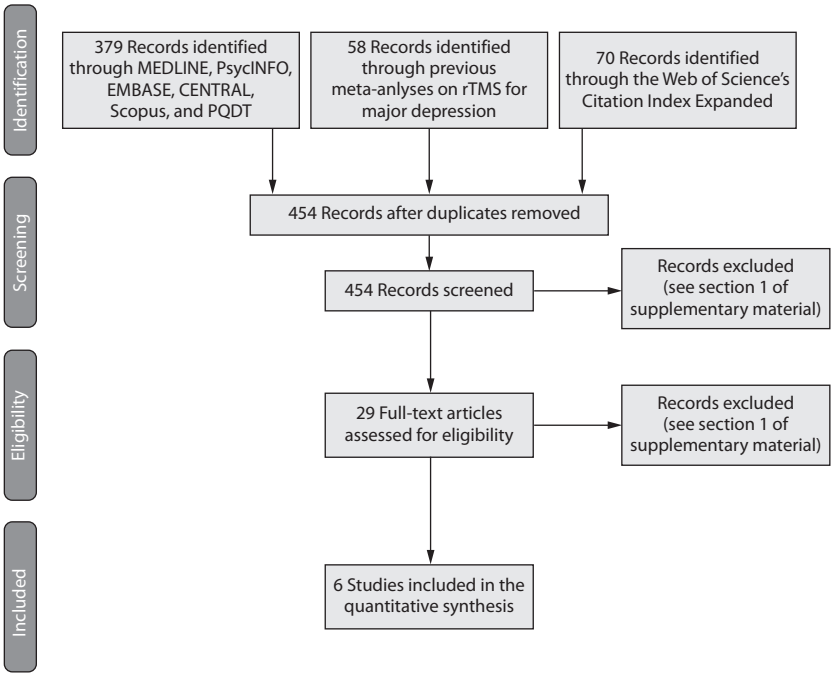
Analyses were performed by using Comprehensive Meta-Analyses Version 2.0 (Biostat, Englewood, New Jersey), and IBM SPSS Version 20 (IBM Corporation, Chicago, Illinois).

We used a random-effects model, as it assumes that each individual observed study result is estimating its own unknown underlying effect, which in turn can be used as a group to estimate a common population mean.[41] Thus, the random-effects model specifically allows for the existence of between-study heterogeneity as well as the within-study variability.[42] If provided, intention-to-treat data, for which we used a method such as last observation carried forward, were preferred over data from completers.[43] The efficacy of HF-rTMS as an accelerating strategy for antidepressants as well as its acceptability were investigated by calculating odds ratios (OR) and the number needed to treat (NNT)[44] for rates of response/remission and dropouts. We considered an NNT < 10 as clinically meaningful because such a treatment difference would be routinely encountered in

day-to-day clinical practice.[45] Also, to rule out the presence of baseline differences in depressive symptoms between active and sham rTMS groups, we computed the pooled standardized mean difference of subjects' baseline scores on the HDRS or the MADRS. We also conducted sensitivity analyses to determine the potential impact of primary diagnosis (ie, unipolar depression only samples vs mixed unipolar/bipolar depression samples) and of potential outliers on effect size estimates for response and remission.

Heterogeneity was assessed by using the Q statistics and I^2 (ie, which assesses the proportion of the observed variance that reflects real differences in effect size).[46] Values of $P < .1$ for the former and > 35% for the latter were deemed as indicative of study heterogeneity.[44] Finally, we used funnel plots, Rosenthal fail-safe N (ie, which estimates the number of missing studies needed to change the results of a meta-analysis to nonsignificant), and Egger regression intercept (ie, which assesses the degree of funnel plot asymmetry by the intercept from regression of standard normal deviates against precision) to test for the presence of publication bias.[44,46]

Figure 1. Study Selection Procedures: PRISMA Flowchart[53]



Abbreviations: PQDT = ProQuest Dissertations and Theses, rTMS = repetitive transcranial magnetic stimulation.

RESULTS

Literature Search

Five RCTs included in the previous meta-analyses on rTMS for major depression were selected for the present investigation.[47–51] Also, we retrieved 379 references (after discarding duplicates) from MEDLINE, PsycINFO, EMBASE, Cochrane Central Register of Controlled Trials, Scopus, and ProQuest Dissertations and Theses. Of these, 1 met our eligibility criteria.[52] Finally, our review of the Web of Science Citation Index Expanded for each of the included RCTs generated 70 references (after discarding duplicates), but none of these were included in this meta-analysis. A detailed description of the study selection procedures is shown in a PRISMA flowchart[53] in Figure 1 and in section 2 of supplementary material.

Included RCTs and Subject Characteristics

Overall, 6 RCTs were included in our meta-analysis, totaling 392 subjects with major depression, of whom 194 were randomized to HF-rTMS (mean ± SD age = 44.47 ± 7.55 years; 73.2% female subjects), and 198 were randomized to sham rTMS (mean age = 44.9 ± 9.06 years; 66.2% female subjects). The mean number of rTMS sessions and magnetic pulses delivered were 13.3 ± 4.08 and 17,200 ± 9,028, respectively. Also, rTMS was used in combination with either selective serotonin reuptake inhibitors (ie, citalopram, escitalopram, sertraline) or serotonin-norepinephrine reuptake inhibitors (ie, venlafaxine) in the majority of RCTs (5 of 6). The first (T_1) and final (T_2) clinical assessments were performed at a mean ± SD of 2.67 ± 0.82 and 6.80 ± 3.11 weeks following the start of combined rTMS + antidepressant treatment. The main characteristics of the included RCTs are described in Table 1.

Efficacy: Response and Remission Rates at T_1

Data relating to response and remission rates at T_1 were available from 6 and 4 RCTs, respectively. Overall, 84 of 194 subjects (43.3%) receiving active HF-rTMS and 53 of 198 (26.8%) receiving sham rTMS were classified as responders to treatment. The pooled OR was 2.50 (95% CI, 1.12–5.56; $Z = 2.245$; $P = .025$), indicating a significant difference in outcome favoring active HF-rTMS (Figure 2). The risk difference translated into a NNT of 7 (95% CI, 3.9–13.8), meaning that about 1 in every 7 patients will present with a response at stimulation period end following HF-rTMS started concomitantly with antidepressants. However, there were no significant differences between active HF-rTMS and sham rTMS at T_1 in terms of remission rates (23.2% vs 11.95%, respectively; OR = 2.09; 95% CI, 0.47–9.20; $Z = 0.97$; $P = .33$) (for the associated forest plot, see section 4 of supplementary material).

Heterogeneity between RCTs reporting on response and remission rates at T_1 exceeded that expected by chance (Table 2), implying that the variance among the effect sizes was greater than expected by sampling error. The associated

Table 1. Included Randomized, Double-Blind and Sham-Controlled Trials on High-Frequency rTMS (HF-rTMS) Acceleration of Antidepressants: Demographic/Clinical Characteristics and rTMS Parameters

	Active HF-rTMS			Sham rTMS			rTMS Parameters								
Study	n	Age, Mean ± SD, y	Female/Male, n/n	n	Age, Mean ± SD, y	Female/Male, n/n	Type	Frequency, Hz	Resting Motor Threshold, %[a]	No. of Sessions	Total Pulses	T_1,[b] wk	T_2,[c] wk	Primary Diagnosis	Antidepressant (target dose)	Treatment-Resistant Depression
Garcia-Toro et al[47]	11	43.2 ± 13.1	6/5	11	45 ± 18.3	6/5	90°	20	90	10	12,000	2	—	All with MDD	Sertraline (50 mg/d)	N/A
Rossini et al[48]	50	48.4 ± 13.7	39/11	49	47.4 ± 12.9	40/9	90°	15	100	10	9,000	2	5	All with MDD	Escitalopram (15 mg/d), sertraline (150 mg/d), or venlafaxine (225 mg/d)	No
Rumi et al[49]	22	39.3 ± 12.8	19/3	24	38.9 ± 8.8	20/4	Sham coil	5	120	20	25,000	4	7	All with MDD	Amitriptyline (150 mg/d)	Yes[d]
Herwig et al[50]	62	50 ± 15	44/18	65	49 ± 13	32/33	45°	10	110	15	30,000	3	6	6.3% with bipolar depression; 93.7% with MDD	Venlafaxine (75 mg/d) or mirtazapine (15 mg/d); doses could be increased after first week at the discretion of the treating physician	Yes[d]
Bretlau et al[51]	22	53.1 ± 10.1	15/7	23	57.8 ± 10	13/10	Sham coil	8	90	15	19,200	2	4	9% with bipolar depression; 91% with MDD	Escitalopram (20 mg/d)	Yes[e]
Huang et al[52]	28	32.8 ± 7.3	19/9	28	31.3 ± 7.4	20/8	90°	10	90	10	8,000	3	12	All with MDD	Citalopram (20–40 mg/d)	No

[a]Percentage of the resting motor threshold. [b]End of add-on rTMS treatment. [c]Study end. [d]Failure to respond to ≥ 2 antidepressants in the current major depressive episode. [e]Failure to respond to ≥ 1 antidepressant in the current major depressive episode.
Abbreviations: MDD = major depressive disorder, rTMS = repetitive transcranial magnetic stimulation.

funnel plots were reasonably symmetrical (see section 3 of supplementary material). The fail-safe N for response rates at T_1 was 13, and we found a low risk of publication bias (Table 2).

Efficacy: Response and Remission Rates at T_2

Data relating to response and remission rates at T_2 were available from 5 and 4 RCTs, respectively. There was a significant difference between active HF-rTMS over sham rTMS in terms of response rates (62% [n/n = 104/168] vs 46% [n/n = 79/172], respectively; OR = 1.9; 95% CI, 1.003–3.56; $Z = 1.97$; $P = .049$) (Figure 3). Furthermore, at T_2, significantly more patients receiving active HF-rTMS were classified as remitters as compared to those receiving sham rTMS (53.8% [n/n = 57/106] vs 33.64% [n/n = 36/107], respectively). The pooled OR was 2.42 (95% CI, 1.27–4.61; $Z = 2.7$; $P = .007$) (Figure 4). The risk difference translated into a NNT of 7 (95% CI, 3.80–18.10) and 5 (95% CI, 3.01–14.10) for response and remission rates at T_2, respectively.

Heterogeneity between RCTs reporting on response rates at T_2 slightly exceeded that expected by chance, whereas heterogeneity between RCTs reporting on remission rates at T_2 was not significant (Table 2). The associated funnel plot was reasonably symmetrical (see section 3 of supplementary material). The fail-safe N values for response and remission rates at T_2 were 8 and 6, respectively, and we found a low risk of publication bias for RCTs reporting remission rates at T_2 but a possibility of bias in those reporting response rates at T_2 (Table 2).

HF-rTMS Versus Sham rTMS: Baseline Depression Severity

No differences on mean baseline depression scores for active versus sham rTMS groups were observed (standardized mean difference = 0.123; $Z = 1.22$, $P = .22$), thus ruling out illness severity at baseline as a confounding factor. For the associated forest plot, see section 4 of supplementary material.

Acceptability of HF-rTMS Treatment

Data relating to dropout rates were available in 5 RCTs. Overall, no difference was observed at T_2 between HF-rTMS (9.9% [n/n = 17/173]) and sham rTMS groups (14.03% [n/n = 24/171]) (OR = 0.7; $Z = -0.991$, $P = .32$) (Figure 5).

Sensitivity Analyses: Subtypes of Major Depression and Outliers

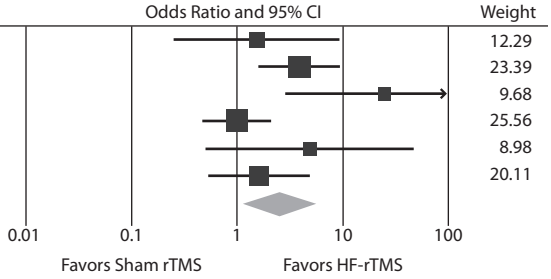
Overall, we found no differences in terms of response and remission rates between the RCTs including subjects with unipolar major depression only and those including mixed samples of subjects with unipolar and bipolar major depression. Furthermore, excluding the RCT by Rumi and colleagues[49] from the analyses (as its overall efficacy results could be seen as outliers) did not impact the original estimates of response and remission rates (for the associated forest plots, see section 4 of supplementary material).

DISCUSSION

To our knowledge, this is the first meta-analysis to assess whether HF-rTMS applied over the left dorsolateral prefrontal cortex is an effective and acceptable strategy for accelerating the

Figure 2. Meta-Analysis of High-Frequency rTMS (HF-rTMS) Versus Sham rTMS as Add-On to Antidepressants in Major Depression: Response Rates at the End of the rTMS Add-on Period

Study	Odds Ratio	95% CI Lower Limit	95% CI Upper Limit	*Z* Value	*P* Value	Active TMS	Sham rTMS	Relative Weight
Garcia-Toro et al[47]	1.524	0.250	9.295	0.457	.648	4/11	3/11	12.29
Rossini et al[48]	3.854	1.574	9.436	2.953	.003	25/49	10/47	23.39
Rumi et al[49]	24.818	2.860	215.377	2.913	.004	21/22	11/24	9.68
Herwig et al[50]	0.994	0.468	2.114	−0.015	.988	19/62	20/65	25.56
Bretlau et al[51]	4.889	0.501	47.708	1.365	.172	4/22	1/23	8.98
Huang et al[52]	1.618	0.529	4.942	0.844	.399	11/28	8/28	20.11
	2.499	1.123	5.559	2.245	.025	84/194	53/198	



Abbreviation: rTMS = repetitive transcranial magnetic stimulation.

Table 2. Randomized Controlled Trials on High-Frequency rTMS for Accelerating Antidepressants in Major Depression: Heterogeneity and Publication Bias

Variable	End of rTMS Add-On Period: Response	End of rTMS Add-On Period: Remission	End of Study: Response	End of Study: Remission
Heterogeneity				
Q	11.4	12.24	6.45	3.23
df	5	3	4	3
P value	.044	.007	.17	.36
I^2	56.12	75.45	37.96	7.16
Publication bias				
Egger regression				
Intercept	2.07	−0.56	2.76	2.13
df	4	2	3	2
t	1.46	2	3.25	1.57
P value[a]	.22	.9	.047	.26

[a]Two-tailed.
Abbreviation: rTMS = repetitive transcranial stimulation.

response to antidepressants in major depression. Our results show that this neuromodulation technique is most likely effective in terms of response rates at stimulation add-on period end and clearly superior to sham rTMS in terms of remission rates at study end (with pooled ORs of 2.50 and 2.42, and NNTs of 7 and 5, respectively). Furthermore, we did not find significant differences in dropout rates as well as on baseline depressive symptomatology between active and sham rTMS. Thus, HF-rTMS seems to be an acceptable accelerating strategy for major depression that is associated with clinically meaningful improvements.

This notion is further strengthened when HF-rTMS is compared to the most commonly used accelerating agents. For example, pindolol was shown, in a recent meta-analysis, to accelerate early clinical response to selective serotonin reuptake inhibitors, with a relative risk of 1.68 (95% CI, 1.18–2.39)[54]; our estimate for HF-rTMS converted to relative risk is 1.65 (95% CI, 1.17–2.32). Moreover, meta-analytic data for lithium carbonate indicate that it has no accelerating effect on antidepressants (OR = 1.37; 95% CI, 0.53–3.52).[22] Finally, triiodothyronine, when used to accelerate antidepressant action, is associated with a medium effect size (Cohen *d*, 0.58; 95% CI, 0.21–0.94) for reducing depression severity scores only (unfortunately, response and remission rates were not assessed).[55]

Our findings are relevant to daily clinical practice. In particular, achieving an early response to antidepressants and later remission with HF-rTMS during the first weeks of treatment might be associated with long-lasting psychosocial benefits (eg, improvements in quality of life and social adjustment[13]) as well as with a reduction in the deleterious neurobiological effects of recurrent and/or unremitting major depression (eg, hippocampal volume loss[56]). However, considering the labor-intensive and time-consuming nature of rTMS,[57] as well as its inherent costs and relatively low availability, we suggest its clinical use as a second- or third-line add-on strategy to antidepressant medications (eg, if pharmacologic approaches such as pindolol, triiodothyronine, or both are ineffective or poorly tolerated).

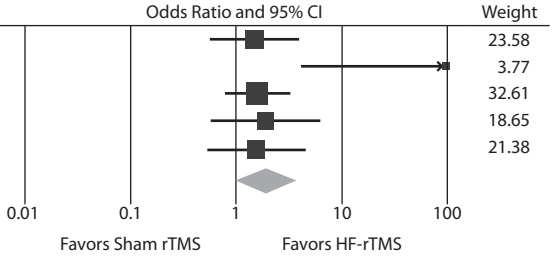
As the therapeutic use of rTMS involves several variables, it is possible that the optimum acceleration protocol is yet to be determined. Accordingly, future studies should investigate new ways of improving the acceleration effects of HF-rTMS, such as the identification of more clinically relevant stimulation parameters (eg, use of priming[58] and different frequencies, intensities, brain targets[59]) as well as the use of baseline electrophysiological and/or neuroimaging evaluations to better predict which patients might benefit from rTMS.[60]

Limitations

The first limitation of this study is that the included RCTs enrolled a relatively small number of depressed subjects. Second, the quality of the available sham rTMS conditions is still unresolved,[59] and the use of coil tilting, first-generation sham coils, or both is clearly not optimal.[24,61] Third, the most commonly used strategy for locating the dorsolateral prefrontal cortex (ie, the "5-cm method") has been recently criticized for its inaccuracy,[59] and future studies might benefit from neuronavigation approaches.[62] Fourth, we examined only the efficacy of HF-rTMS immediately after the add-on period as well as at study end and thus cannot estimate the stability of its medium- to long-term accelerating/antidepressant effects, its cost-effectiveness, or both. Fifth, owing to the relatively small sample size, we could not assess the efficacy of HF-rTMS when combined to specific antidepressants or whether it has differential effects on either

Figure 3. Meta-Analysis of High-Frequency rTMS (HF-rTMS) Versus Sham rTMS as Add-On to Antidepressants in Major Depression: Response Rates at the End of Study

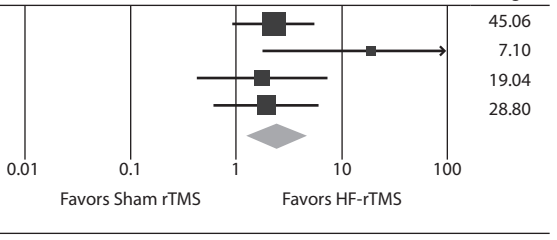
Study	Odds Ratio	95% CI Lower Limit	95% CI Upper Limit	*Z* Value	*P* Value	Active HF-rTMS, n/n	Sham rTMS, n/n	Relative Weight
Rossini et al[48]	1.500	0.559	4.024	0.805	.421	36/45	32/44	23.58
Rumi et al[49]	96.600	4.142	2253.153	2.844	.004	11/11	2/12	3.77
Herwig et al[50]	1.602	0.789	3.252	1.303	.193	30/62	24/65	32.61
Bretlau et al[51]	1.909	0.579	6.296	1.062	.288	14/22	11/23	18.65
Huang et al[52]	1.560	0.534	4.557	0.813	.416	13/28	10/28	21.38
	1.891	1.003	3.565	1.971	.049	104/168	79/172	



Abbreviation: rTMS = repetitive transcranial magnetic stimulation.

Figure 4. Meta-Analysis of High-Frequency rTMS (HF-rTMS) Versus Sham rTMS as Add-On to Antidepressants in Major Depression: Remission Rates at the End of Study

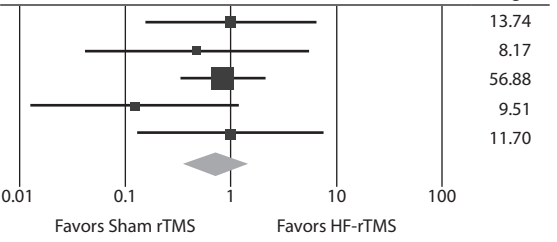
Study	Odds Ratio	95% CI Lower Limit	95% CI Upper Limit	*Z* Value	*P* Value	Remitters/Total, n/n Active HF-rTMS	Remitters/Total, n/n Sham rTMS	Relative Weight
Rossini et al[48]	2.292	0.943	5.570	1.830	.067	33/45	24/44	45.06
Rumi et al[49]	19.250	1.768	209.546	2.428	.015	7/11	1/12	7.10
Bretlau et al[51]	1.781	0.427	7.438	0.792	.429	6/22	4/23	19.04
Huang et al[52]	1.941	0.619	6.089	1.137	.255	11/28	7/28	28.80
	2.422	1.273	4.608	2.695	.007	57/106	36/107	



Abbreviation: rTMS = repetitive transcranial magnetic stimulation.

Figure 5. Meta-Analysis of High-Frequency rTMS (HF-rTMS) Versus Sham rTMS as Add-On to Antidepressants in Major Depression: Dropout Rates at the End of Study

Study	Odds Ratio	95% CI Lower Limit	95% CI Upper Limit	*Z* Value	*P* Value	Dropouts/Total, n/n Active HF-rTMS	Dropouts/Total, n/n Sham rTMS	Relative Weight
Garcia-Toro et al[47]	1.000	0.153	6.531	0.000	1.000	3/11	3/11	13.74
Rossini et al[48]	0.480	0.042	5.467	−0.592	.554	1/50	2/49	8.17
Herwig et al[50]	0.849	0.338	2.136	−0.347	.729	10/62	12/65	56.88
Bretlau et al[51]	0.124	0.013	1.181	−1.815	.070	1/22	5/18	9.51
Huang et al[52]	1.000	0.131	7.644	0.000	1.000	2/28	2/28	11.70
	0.704	0.351	1.411	−0.991	.322	17/173	24/171	



Abbreviation: rTMS = repetitive transcranial magnetic stimulation.

unipolar or bipolar depression. Sixth, we decided not to conduct meta-regression analyses to identify potential sources of heterogeneity because of the relatively small number of trials included. Finally, meta-analyses have often been criticized for combining heterogeneous studies, for the potential of publication bias, and for the inclusion of unrepresentative poor-quality trials.[44] In the present study, however, these concerns were addressed by the comprehensive systematic review of the literature as well as the use of stringent inclusion criteria and by the examination of both publication bias and study heterogeneity.

CONCLUSION

The current meta-analysis, which included 392 depressed subjects, shows that HF-rTMS over the left dorsolateral prefrontal cortex is a promising strategy for hastening the clinical response to antidepressants in major depression. Moreover, HF-rTMS seems to be at least as effective and well tolerated as other available accelerating strategies, such as pindolol and triiodothyronine.

Overall, HF-rTMS is a welcome addition to the therapeutic armamentarium of major depression owing to its favorable side effects profile and lack of drug interactions and especially because of its capacity to reduce the delay in onset of antidepressant effects (thus reducing the duration of patients' functional impairment). Nevertheless, major tasks for future research include the investigation of whether patients with distinct subtypes of major depression preferentially respond to add-on HF-rTMS and whether its beneficial effects are maintained over time. Also, the search for optimal

stimulation parameters and a clarification of which specific antidepressants work best in combination with rTMS should be the focus of further RCTs.

Drug names: citalopram (Celexa and others), escitalopram (Lexapro and others), lithium (Lithobid and others), mirtazapine (Remeron and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Author affiliations: Neuromodulation Research Clinic (Drs Berlim and Van den Eynde) and Depressive Disorders Program (Dr Berlim), Douglas Mental Health University Institute and McGill University, Montréal, Québec; and Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health and University of Toronto, Ontario (Dr Daskalakis), Canada.

Potential conflicts of interest: **Dr Daskalakis** received external funding from Neuronetics, Brainsway, and Aspect Medical; has received travel allowance from Pfizer and Merck; has received speaker funding from Sepracor; and has served on the advisory board for Hoffmann-La Roche. **Drs Berlim** and **Van den Eynde** report no conflicts of interest.

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Supplementary material follows this article.

THE JOURNAL OF CLINICAL PSYCHIATRY

Supplementary Material

Article Title: High-Frequency Repetitive Transcranial Magnetic Stimulation Accelerates and Enhances the Clinical Response to Antidepressants in Major Depression: A Meta-Analysis of Randomized, Double-Blind and Sham-Controlled Trials

Author(s): Marcelo T. Berlim, MD, MSc; Frederique Van den Eynde, MD, PhD; and Z. Jeff Daskalakis, MD, PhD

DOI Number: 10.4088/JCP.12r07996

List of Supplementary Material for the article

1. eSection 1 Previous Meta-Analyses on RTMS for Major Depression
2. eSection 2 Databases Search (1995-2012)
3. eSection 3 Funnel Plots
4. eSection 4 Forrest Plots

Disclaimer

Supplementary eSection 1. ***PREVIOUS META-ANALYSES ON rTMS FOR MAJOR DEPRESSION***

1.1 ***Excluded Randomized Controlled Trials and Main Reasons for Exclusion (Supplementary eTable 1)***

Supplementary eTable 1. Previous meta-analyses on rTMS for major depression: excluded randomized controlled trials and main reasons for exclusion.

Reference	Reason for Exclusion (example)
2008	
Fitzgerald et al[1]	n=60, but active rTMS primed by twenty 5-second, 6-Hz trains of stimulation
Jorge et al[2]	Only subjects with vascular depression
Mogg et al[3]	n=59, but rTMS used as an augmenting strategy for major depression
2007	
Anderson et al[4]	n=25, but rTMS used as an augmenting strategy for major depression
Bortolomasi et al[5]	n=19, but rTMS used as an augmenting strategy for major depression
Loo et al[6]	n=34, but rTMS used as either an augmenting strategy or a monotherapy for major depression
O'Reardon et al[7]	n=301, but rTMS used as a monotherapy for major depression
Stern et al[8]	n=25, but rTMS used as a monotherapy for major depression
2006	
Avery et al[9]	n=68, but rTMS used as a monotherapy for major depression
Fitzgerald et al[10]	n= 50, but only bilateral rTMS used as an augmenting strategy for major depression
Garcia-Toro et al[11]	n=30, but only bilateral rTMS used as an augmenting strategy for major depression
Januel et al[12]	n=27, but rTMS used as a monotherapy for major depression
McDonald et al[13]	n=62, but only bilateral rTMS used as an augmenting strategy for major depression
Moller et al[14]	n=10, but rTMS used as an augmenting strategy for major depression
2005	
Miniussi et al[15]	n=71, but rTMS used as an augmenting strategy for major depression
Rossini et al[16]	n=54, but rTMS used as an augmenting strategy for major depression
Su et al[17]	n=30, but rTMS used as an augmenting strategy for major depression
2004	
Hansen et al[18]	n=15, but rTMS used as an augmenting strategy for major depression
Hausmann et al[19]	n=41, unilateral and bilateral rTMS used as accelerating strategies, but no reported outcomes for

	unilateral rTMS
Hausmann et al[20]	n=41, but data overlap with Hausmann et al, 2004[19]
Holtzheimer et al[21]	n=14, but rTMS used as a monotherapy for major depression
Jorge et al[22]	Only subjects with post-stroke depression
Kauffmann et al[23]	n=12, but rTMS used as an augmenting strategy for major depression
Koerselman et al[24]	n=55 but rTMS used as an augmenting strategy for major depression
Mosimann et al[25]	n=24, but rTMS used as an augmenting strategy for major depression
Poulet et al[26]	n=19, but insufficient data for this meta-analysis (e.g., age, gender, baseline depression scores)
2003	
Fitzgerald et al[27]	n=60, but rTMS used as an augmenting strategy for major depression
Herwig et al[28]	n=25, but 19 subjects received rTMS as an augmenting strategy for major depression
Hoppner at al[29]	n=21, but rTMS used as an augmenting strategy for major depression
Loo et al[30]	n=19, but bilateral rTMS used as either an augmenting strategy or a monotherapy for major depression
Nahas et al[31]	n=23, but rTMS used as an augmenting strategy for major depression
2002	
Boutros et al[32]	n=21, but rTMS used as an augmenting strategy for major depression
Padberg et al[33]	n=30, but rTMS used as an augmenting strategy for major depression
2001	
Garcia-Toro et al[34]	n=35, but rTMS used as an augmenting strategy for major depression
Lisanby et al[35]	n=24, but unreported outcomes[36] (i.e., response and/or remission rates); main author contacted by email but did no reply
Manes et al[37]	n=20, but rTMS used as a monotherapy for major depression
Szuba et al[38]	n=16, but rTMS used as a monotherapy for major depression
2000	
Berman et al[39]	n=20, but rTMS used as a monotherapy for major depression
Eschweiler et al[40]	n=12, but used as an augmenting strategy for major depression
George et al[41]	n=30, but rTMS used as a monotherapy for major depression
Grunhaus et al[42]	n=40, but open-label
Pridmore[43]	n=22, but single-blind
1999	
Avery et al[44]	n=6, and rTMS used as an augmenting strategy for major depression
Kimbrell et al[45]	n=13, but rTMS used as either an augmenting strategy or a monotherapy for major depression
Klein et al[46]	n=70, rTMS used as an augmenting strategy for major depression
Loo et al[47]	n=18, but rTMS used as either an augmenting strategy or a monotherapy for major depression
Padberg et al[48]	n=18, but rTMS used as either an augmenting strategy or a monotherapy for major depression

Stikhina et al[49]	Written in Russian
1997	
George et al[50]	n=12, but rTMS used as a monotherapy for major depression
Haag et al[51]	n=18, but rTMS used as an augmenting strategy for major depression
1996	
Conca et al[52]	n=24, but not sham-controlled
Pascual-Leone et al[53]	n=17, but rTMS used as either an augmenting strategy or a monotherapy for major depression
1995	
Kolbinger et al[54]	n=10, but rTMS used as either an augmenting strategy or a monotherapy for major depression

Supplementary eSection 2. ***DATABASES SEARCH (1995-2012)***

2.1 ***Electronic Databases – Selection***

- MEDLINE: October 2008 - May 7, 2012
- EMBASE: January 1st, 1996 - May 12, 2012
- PsycINFO: January 1st, 1995 - May 12, 2012
- Cochrane Central Register of Controlled Trials (CENTRAL): January 1st, 1995 - May 12, 2012
- SCOPUS: January 1st, 1995 – May 12, 2012
- ProQuest Dissertations & Theses (PQDT): January 1st, 1995 – May 12, 2012
- Web of Science's Citations Index Expanded: Up to May 27, 2012

2.2 ***Electronic Databases – Syntaxes***

2.2.1 MEDLINE (PubMed)
An advanced search was conducted on 2012/05/07 using the following search syntax (derived from Corrao et al[55]):

("randomized controlled trial"[PT] OR ((randomized[TIAB] OR randomised[TIAB]) AND controlled[TIAB] AND trial[TIAB]))
AND ("magnetic stimulation"[TIAB] OR rTMS[TIAB]) AND depress*[TI]

This search retrieved 44 references (Figure 1).

***Supplementary eFigure* 1**. MEDLINE: search strategy.

History

Clear history

Search	Add to builder	Query	Items found	Time
#1	Add	Search **("randomized controlled trial"[PT] OR ((randomized[TIAB] OR randomised[TIAB]) AND controlled[TIAB] AND trial[TIAB])) AND ("magnetic stimulation"[TIAB] OR rTMS[TIAB]) AND depress* [TI]** Limits: **English, Publication Date from 2008/10/01 to 2012/05/07**	44	19:10:56

2.2.2 EMBASE (OVID interface)

An advanced search was conducted on 2012/05/12 using the following search syntax (derived from Wong et al[56]):

(random$.tw. or placebo$.mp. or double-blind$.tw.) and (magnetic stimulation.ti. or rtms.ti. or transcranial magnetic.ti.) and depress$.ti. and (English language and yr="1996-Current")

This search retrieved 180 references (Figure 2).

***Supplementary eFigure* 2**. EMBASE: search strategy.

# ▲	Searches	Results
1	(random$.tw. or placebo$.mp. or double-blind$.tw.) and (magnetic stimulation or rtms or transcranial magnetic).ti. and depress$.ti.	199
2	**limit 1 to (english language and yr="1996 -Current")**	**180**

2.2.3 PsycINFO (OVID interface)

An advanced search was conducted on 2012/05/12 using the following syntax (derived from Wong et al[56]):

(random$.tw. or placebo$.mp. or double-blind$.tw.) and (magnetic stimulation.ti. or rtms.ti. or transcranial magnetic.ti.) and depress$.ti. and (English language and yr="1995-Current")

This search retrieved 137 references (Figure 3).

***Supplementary eFigure* 3**. PsycINFO: search strategy.

	# ▲	Searches	Results
☐	1	(random$.tw. or placebo$.mp. or double-blind$.tw.) and ("magnetic stimulation" or rtms or "transcranial magnetic").ti. and depress$.ti.	147
☐	2	limit 1 to (english language and yr="1995 -Current")	137

2.2.4 CENTRAL

An advanced search was conducted on 2012/05/12 using the following syntax:

depress*:ti AND (magnetic stimulation:ti OR rTMS:ti OR transcranial magnetic:ti), from 1995 to 2012 in Trials

This search retrieved 207 references (Figure 4).

Supplementary eFigure 4. CENTRAL: search strategy.

Current Search History

ID	Search	Hits
#1	depress*:ti AND (magnetic stimulation:ti OR rTMS:ti OR transcranial magnetic:ti), from 1995 to 2012 in Trials	207

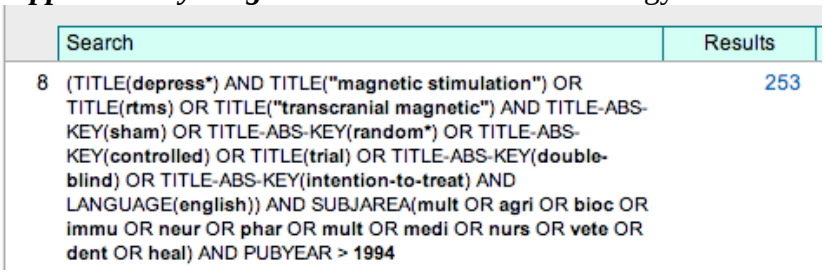
2.2.5 SCOPUS

An advanced search was conducted on 2012/05/12 using the following syntax:

(TITLE(**depress***) AND TITLE("**magnetic stimulation**") OR TITLE(**rtms**) OR TITLE("**transcranial magnetic**") AND TITLE-ABS-KEY(**sham**) OR TITLE-ABS-KEY(**random***) OR TITLE-ABS-KEY(**controlled**) OR TITLE(**trial**) OR TITLE-ABS-KEY(**double-blind**) OR TITLE-ABS-KEY(**intention-to-treat**) AND LANGUAGE(**english**)) AND SUBJAREA(**mult** OR **agri** OR **bioc** OR **immu** OR **neur** OR **phar** OR **mult** OR **medi** OR **nurs** OR **vete** OR **dent** OR **heal**) AND PUBYEAR > **1994**

This search retrieved 253 references (Figure 5).

Supplementary eFigure 5. SCOPUS: search strategy.



	Search	Results
8	(TITLE(**depress***) AND TITLE(**"magnetic stimulation"**) OR TITLE(**rtms**) OR TITLE(**"transcranial magnetic"**) AND TITLE-ABS-KEY(**sham**) OR TITLE-ABS-KEY(**random***) OR TITLE-ABS-KEY(**controlled**) OR TITLE(**trial**) OR TITLE-ABS-KEY(**double-blind**) OR TITLE-ABS-KEY(**intention-to-treat**) AND LANGUAGE(**english**)) AND SUBJAREA(**mult** OR **agri** OR **bioc** OR **immu** OR **neur** OR **phar** OR **mult** OR **medi** OR **nurs** OR **vete** OR **dent** OR **heal**) AND PUBYEAR > **1994**	253

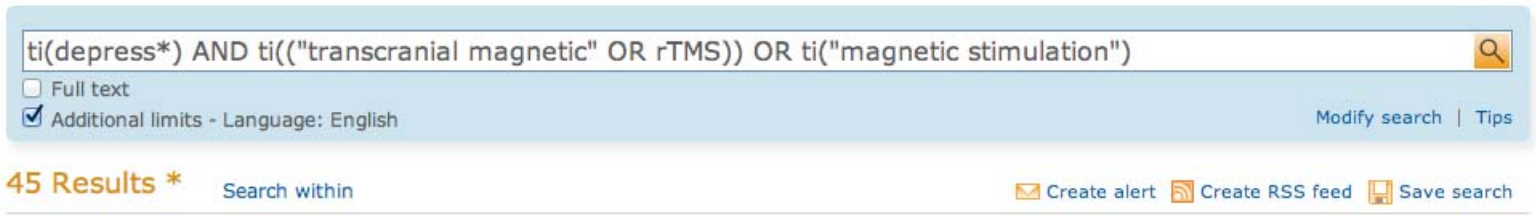
2.2.5 PQDT

An advanced search was conducted on 2012/05/12 using the following syntax:

ti(depress*) AND ti((“transcranial magnetic” OR rTMS)) OR ti(“magnetic stimulation”)

This search retrieved 45 references (Figure 6).

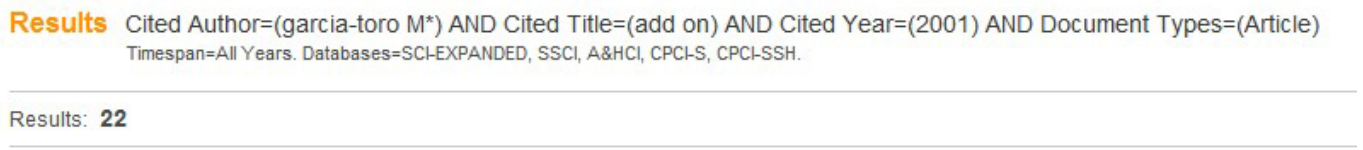
Supplementary eFigure 6. PQDT: search strategy.



2.2.6 Web of Science Citations Index

An advanced search was conducted on 2012/06/12.

Supplementary eFigure 6. *Garcia-Toro et al, 2001*

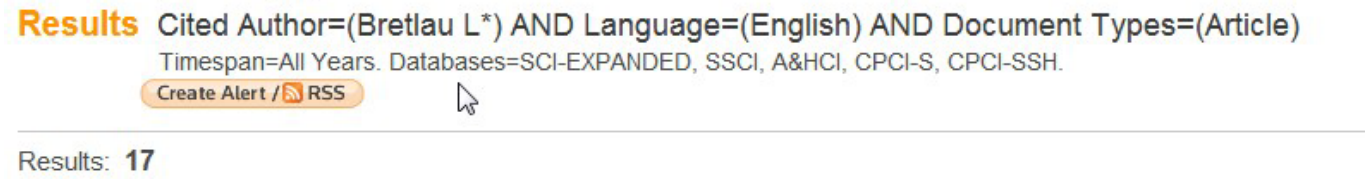


Supplementary eFigure 7. *Rossini et al, 2005*

Supplementary eFigure 8. *Rumi et al, 2005*

Supplementary eFigure 9. *Herwig et al, 2007*

Supplementary eFigure 10. *Bretlau et al, 2008*



Supplementary eFigure 11. *Huang et al, 2012*

No register.

2.3 ***Excluded Studies and Reasons for Exclusion***

2.3.1 MEDLINE, PsycINFO, EMBASE, CENTRAL, SCOPUS and PQDT

Searches on MEDLINE, PsycINFO, EMBASE, CENTRAL, SCOPUS and PQDT yielded 379 references (after discarding duplicates). Of these, only 1 was included in this meta-analysis[57] (please refer to Supplementary eTables 2 and 3 for information on excluded studies).

Supplementary eTable 2. MEDLINE, PsycINFO, EMBASE, CENTRAL, SCOPUS and PQDT: reasons exclusion - non-randomized controlled trials.

REASON FOR EXCLUSION	n
No Primary Data	
Review	50
Book or book chapter	2
Erratum	1
Post-hoc and/or secondary analysis	18
Comment	10
Clinical trial registration	17
Non-Primary MDD Samples	
Bipolar depression	10
No separate results for subjects with MDD	1
Postpartum MDD	1
Secondary MDD (e.g., Parkinson's, obsessive-compulsive disorder)	20
Clinical Studies, but Non-RCT Design	
Randomized trial but no sham rTMS	20
Case report or series	11
Retrospective design	1
Open label trial	49
Other	
Non-treatment rTMS study in subjects with MDD (e.g., neuroimaging, neurochemistry, neurophysiology, coil positioning)	66
Other neuromodulation techniques (e.g., transcranial direct current stimulation, vagus nerve stimulation)	11
Theta burst stimulation	2
Stimulation of a region other than the DLPFC	2
Study in subjects with psychotic disorders	3
Study in subjects with anxiety disorders	1
Study in subjects with addiction disorders	1
Study in subjects with autistic disorders	1
Study in subjects with neurological illnesses	2
Study in animals	12
Study in healthy subjects or using computer/mathematical modeling	27
Study in subjects with > 75 years	2
Study on children and/or adolescents	3

TOTAL	356

Supplementary eTable 3. MEDLINE, PsycINFO, EMBASE, CENTRAL, SCOPUS and PQDT: reasons for exclusion - randomized controlled trials.

Reference	Reason for Exclusion (example)
2012	
Fitzgerald et al[58]	n=67, but rTMS used as an augmenting strategy for major depression
Hernandez-Ribas et al[59]	n=21, but rTMS used as an augmenting strategy for major depression
Peng et al[60]	n=30, but rTMS used as an augmentation strategy for major depression
2011	
Aguirre et al[61]	n=34, but rTMS used as an augmenting strategy for major depression
He et al[62]	n=164, but only rTMS used as a monotherapy for major depression
Karamustafalioglu et al[63]	n=44, but unreported outcomes[36] (i.e., response and/or remission rates); main author contacted by email but did not respond; nevertheless, their main findings were that "*…in terms of response, study group was significantly superior to the control group. This significant superiority continued to the endpoint. By the second week, study group was superior to the control group in terms of remission…*"
Lingeswaran et al[64]	n=23, but rTMS used as an augmenting strategy for major depression
Ray et al[65]	n=40, but single-blind, and rTMS used as a monotherapy for major depression
Zhang et al[66]	n=28, but rTMS used as an augmenting strategy for major depression
2010	
George et al[67]	n=190, but rTMS used as a monotherapy for major depression
Karamustafalioglu et al[68]	n=35, but rTMS used as an augmenting strategy for major depression
Lee et al[69]	n=14, but rTMS used as an augmenting strategy for major depression
Paillere-Martinot et al[70]	n=48, but rTMS used as an augmenting strategy for major depression
Pallanti et al[71]	n=60, but rTMS used as an augmenting strategy for major depression
Triggs et al[72]	n=25, but rTMS used as an augmenting strategy for major depression
Zheng et al[73]	n=34, but rTMS used as an augmenting strategy for major depression
2009	
Bares et al[74]	n=60, but no sham rTMS group
Carretero et al[75]	n=28, but single-blind rTMS
Speer et al[76]	n=22, but rTMS used as a monotherapy for major depression
2008	
Fitzgerald et al[77]	n=50, but bilateral rTMS used as augmenting strategy for major depression
Jakob et al[78]	n=36, but rTMS used as either an augmenting strategy or a monotherapy for major depression

2005	
Chistyakov et al[79]	n=59, but no active rTMS + antidepressant group

2.3.2 Web of Science Citations Index

Searches on the Web of Science's Citation Index Expanded yielded 70 references (after discarding duplicates), but none of these were included in this meta-analysis (please refer to Supplementary eTables 4 and 5 for additional information).

Supplementary eTable 4. Web of Science's Citations Index Expanded: reasons for exclusion - non-randomized controlled trials.

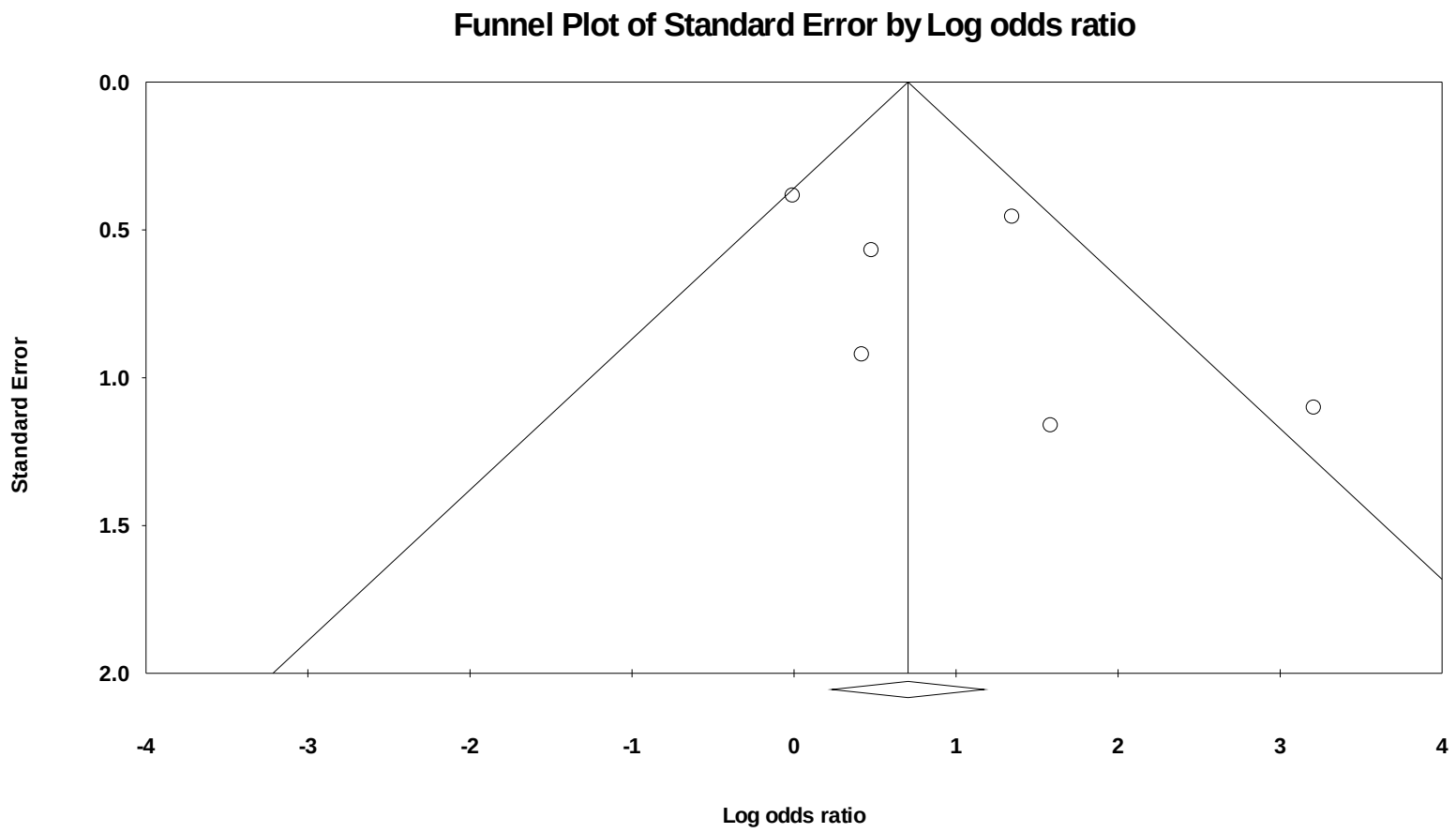
REASON FOR EXCLUSION	n
No Primary Data	
Review	26
Post-hoc and/or secondary analysis	4
Clinical Studies, but Non-RCT Design	
Randomized trial but no sham rTMS	5
Case report or series	4
Retrospective design	2
Open label trial	9
Other	
Other neuromodulation techniques (e.g., transcranial direct current stimulation, vagus nerve stimulation)	3
Theta burst stimulation	2
Study in subjects with mania	1
Study in subjects with psychotic disorders	1
Study in subjects with anxiety disorders	1
Study in subjects with neurological illnesses	5
Study in animals	1
Study in healthy subjects, using computer/mathematical modeling or describing new equipment	5
TOTAL	**69**

Supplementary eTable 5. Web of Science's Citations Index Expanded: reasons for exclusion - randomized controlled trials.

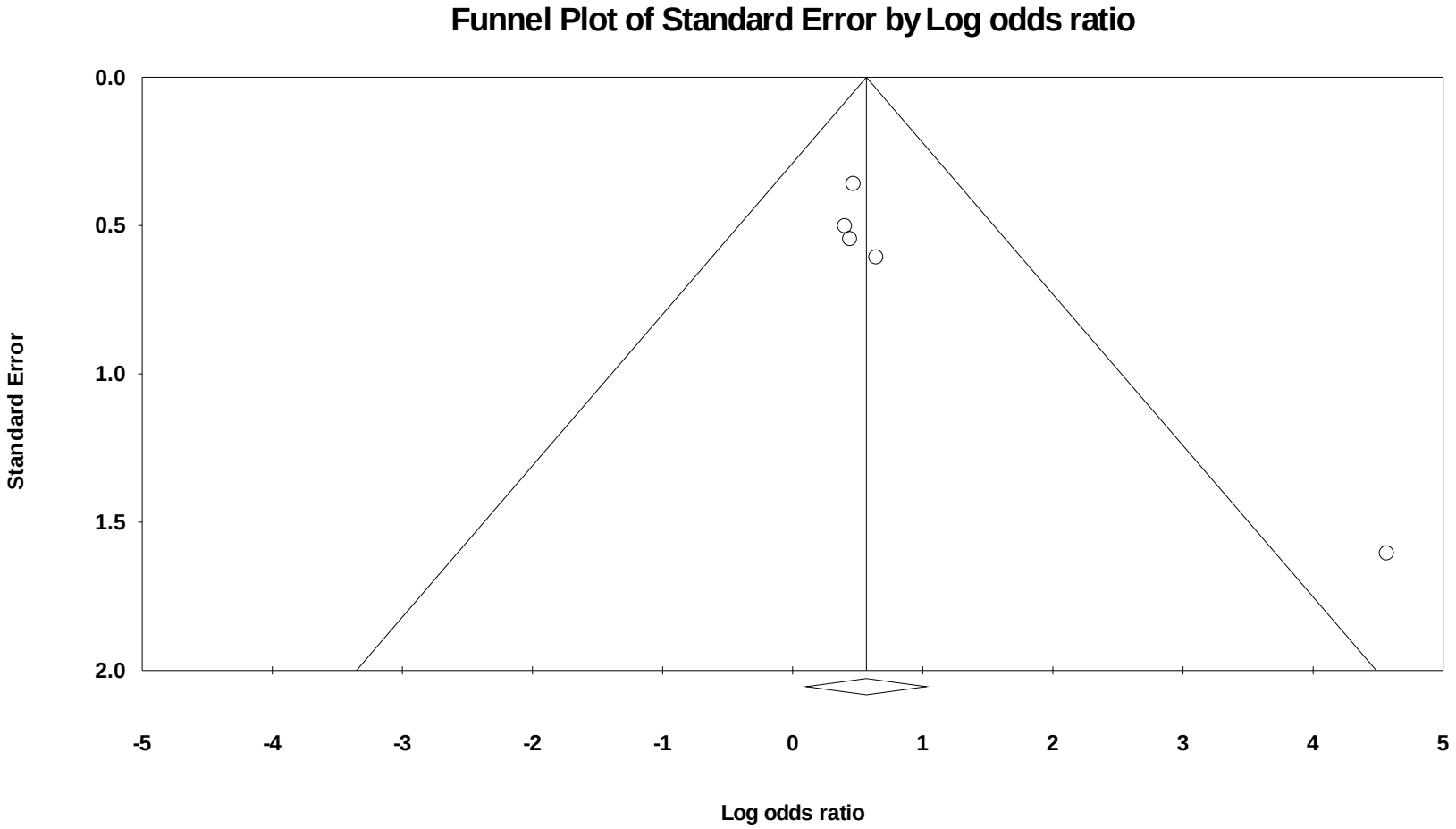
Reference	Reason for Exclusion (example)
2010	
Hoeppner et al[80]	n=30, but data overlap with Herwig et al, 2007[81]

Supplementary eSection 3. Funnel Plots

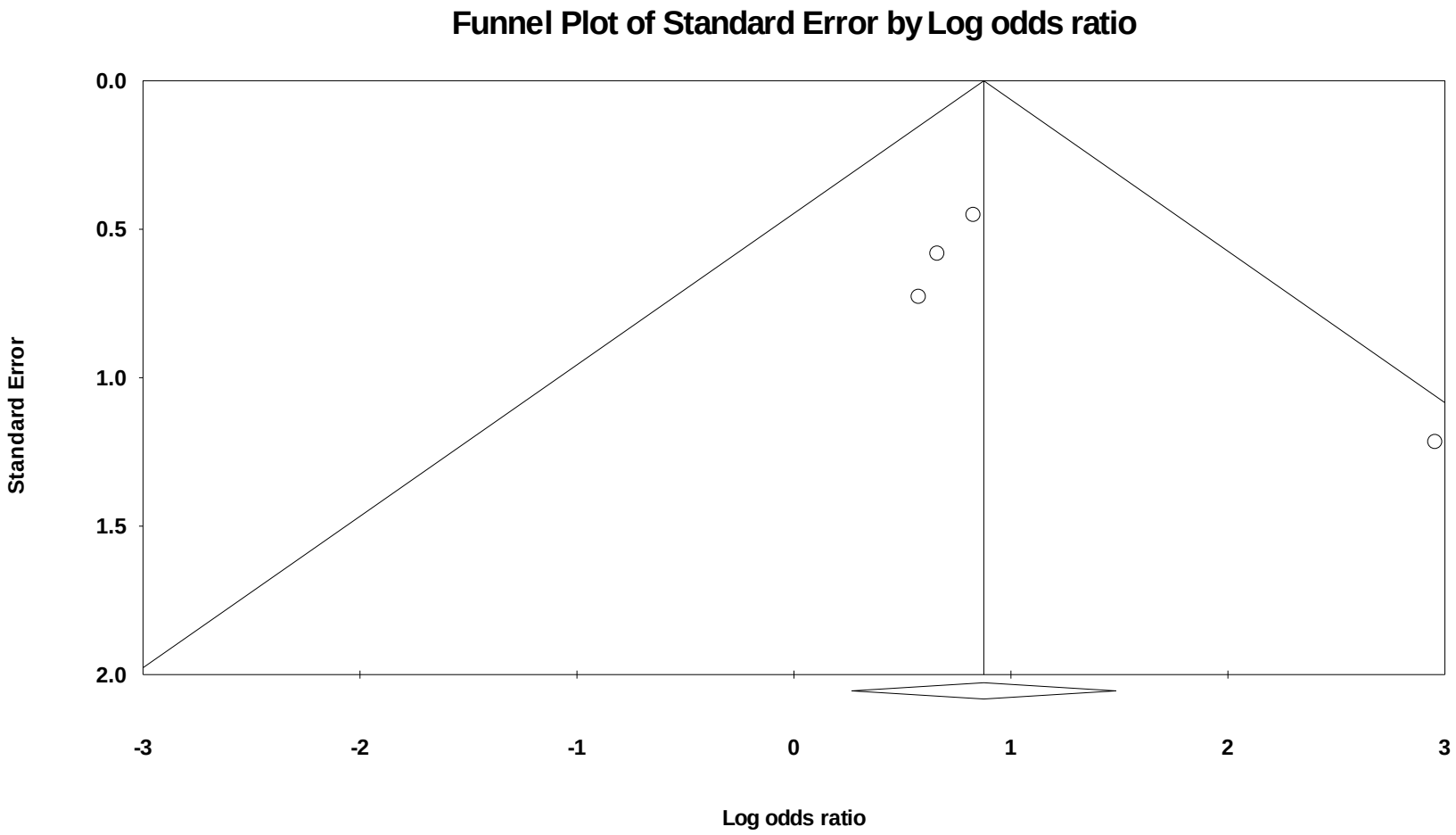
3.1 *Supplementary eFigure 12.* *Response rates at T_1*



3.2 *Supplementary eFigure 13.* *Response rates at T_2*



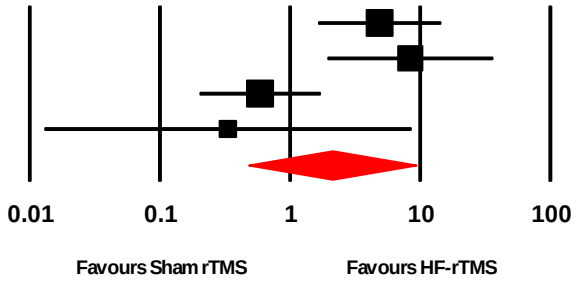
3.3 *Supplementary eFigure 14.* *Remission at T_2*



Supplementary eSection 4. Forest Plots

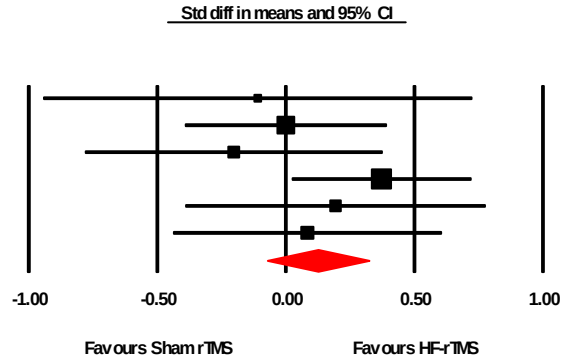
4.1 *Supplementary eFigure 15.* *Remission Rates at T_1*

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Remitters / Total: Active rTMS	Remitters / Total: Sham rTMS	Relative weight
Rossini et al, 2005	4.877	1.633	14.567	2.839	0.005	18 / 49	5 / 47	30.08
Rumi et al, 2005	8.400	1.927	36.618	2.833	0.005	12 / 22	3 / 24	26.55
Herwig et al, 2007	0.589	0.200	1.732	-0.961	0.336	6 / 62	10 / 65	30.22
Bretlau et al, 2008	0.333	0.013	8.627	-0.662	0.508	0 / 22	1 / 23	13.16
	2.090	0.475	9.197	0.975	0.329	36 / 155	19 / 159	



4.2 *Supplementary eFigure 16.* *Baseline Depression Scores*

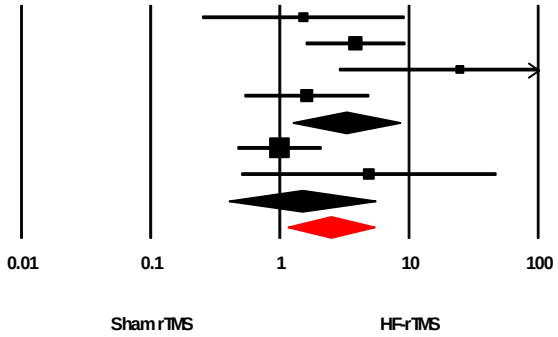
Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Sample size: Active rTMS	Sample size: Sham rTMS	Relative weight
Garcia-Toro et al, 2001	-0.109	0.427	0.182	-0.946	0.727	-0.256	0.798	11	11	5.60
Rossini et al, 2005	0.000	0.201	0.040	-0.394	0.394	0.000	1.000	50	49	25.24
Rumi et al, 2005	-0.203	0.296	0.088	-0.783	0.377	-0.685	0.494	22	24	11.65
Herwig et al, 2007	0.372	0.179	0.032	0.021	0.723	2.080	0.038	62	65	31.82
Bretlau et al, 2008	0.193	0.299	0.089	-0.393	0.779	0.647	0.518	22	23	11.42
Huang et al,2012	0.084	0.267	0.071	-0.440	0.608	0.314	0.753	28	28	14.27
	0.123	0.101	0.010	-0.075	0.321	1.216	0.224	195	200	



4.4 *SENSITIVITY ANALYSES*

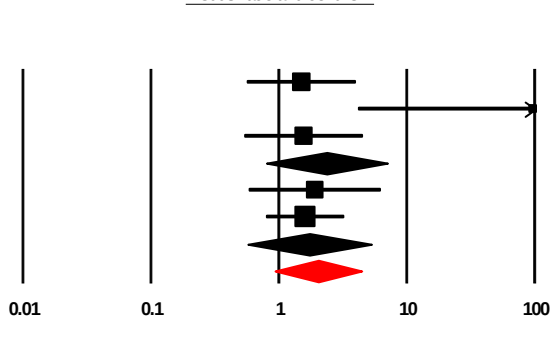
4.4.1 ***Supplementary eFigure 17.*** *Unipolar vs. Mixed (Unipolar/Bipolar) Samples: Response Rates at T_1*

Group by Diagnosis	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Active rTMS	Sham rTMS	Relative weight
MDD	Garcia-Toro et al, 2001	1.524	0.250	9.295	0.457	0.648	4 / 11	3 / 11	18.30
MDD	Rossini et al, 2005	3.854	1.574	9.436	2.953	0.003	25 / 49	10 / 47	36.49
MDD	Rumi et al, 2005	24.818	2.860	215.377	2.913	0.004	21 / 22	11 / 24	14.27
MDD	Huang et al, 2012	1.618	0.529	4.942	0.844	0.399	11 / 28	8 / 28	30.94
MDD		3.243	1.252	8.402	2.422	0.015	61 / 110	32 / 110	
MDD/BD	Herwig et al, 2007	0.994	0.468	2.114	-0.015	0.988	19 / 62	20 / 65	75.33
MDD/BD	Bretlau et al, 2008	4.889	0.501	47.708	1.365	0.172	4 / 22	1 / 23	24.67
MDD/BD		1.473	0.401	5.416	0.583	0.560	23 / 84	21 / 88	
Overall		2.463	1.142	5.312	2.299	0.021	84 / 194	53 / 198	



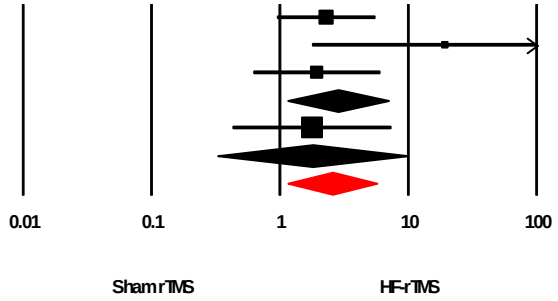
4.4.2 ***Supplementary eFigure 18.*** *Unipolar vs. Mixed (Unipolar/Bipolar) Samples: Response Rates at T_2*

Group by Diagnosis	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Active rTMS	Sham rTMS	Relative weight
MDD	Rossini et al, 2005	1.500	0.559	4.024	0.805	0.421	36 / 45	32 / 44	46.31
MDD	Rumi et al, 2005	96.600	4.142	2253.153	2.844	0.004	11 / 11	2 / 12	10.33
MDD	Huang et al, 2012	1.560	0.534	4.557	0.813	0.416	13 / 28	10 / 28	43.35
MDD		2.346	0.788	6.983	1.532	0.125	60 / 84	44 / 84	
MDD/BD	Bretlau et al, 2008	1.909	0.579	6.296	1.062	0.288	14 / 22	11 / 23	40.99
MDD/BD	Herwig et al, 2007	1.602	0.789	3.252	1.303	0.193	30 / 62	24 / 65	59.01
MDD/BD		1.721	0.566	5.235	0.957	0.339	44 / 84	35 / 88	
Overall		2.016	0.925	4.392	1.764	0.078	104 / 168	79 / 172	



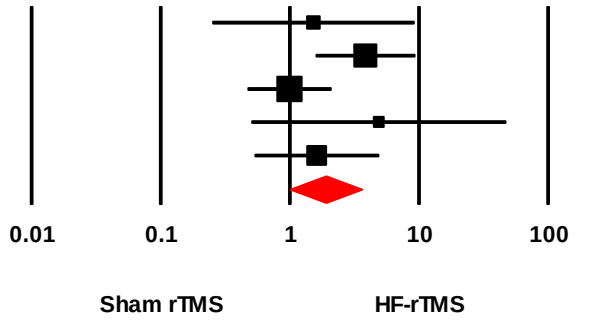
4.4.3 ***Supplementary eFigure 19.*** *Unipolar vs. Mixed (Unipolar/Bipolar) Samples: Remission Rates at T_2*

Group by Diagnosis	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Remitters / Total: Active rTMS	Remitters / Total: Sham rTMS	Relative weight
MDD	Rossini et al, 2005	2.292	0.943	5.570	1.830	0.067	33 / 45	24 / 44	49.72
MDD	Rumi et al, 2005	19.250	1.768	209.546	2.428	0.015	7 / 11	1 / 12	12.47
MDD	Huang et al, 2012	1.941	0.619	6.089	1.137	0.255	11 / 28	7 / 28	37.81
MDD		2.807	1.136	6.932	2.237	0.025	51 / 84	32 / 84	
MDD/BD	Bretlau et al, 2008	1.781	0.427	7.438	0.792	0.429	6 / 22	4 / 23	100.00
MDD/BD		1.781	0.325	9.775	0.665	0.506	6 / 22	4 / 23	
Overall		2.539	1.143	5.643	2.287	0.022	57 / 106	36 / 107	



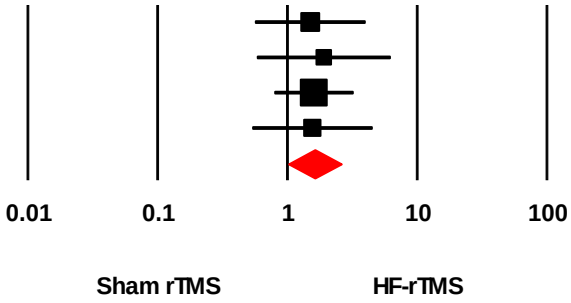
4.4.4 ***Supplementary eFigure 20.*** *Response Rates at T_1 Excluding Rumi and colleagues*[82]

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Active rTMS	Sham rTMS	Relative weight
Garcia-Toro et al, 2001	1.524	0.250	9.295	0.457	0.648	4 / 11	3 / 11	10.34
Rossini et al, 2005	3.854	1.574	9.436	2.953	0.003	25 / 49	10 / 47	27.98
Herwig et al, 2007	0.994	0.468	2.114	-0.015	0.988	19 / 62	20 / 65	33.35
Bretlau et al, 2008	4.889	0.501	47.708	1.365	0.172	4 / 22	1 / 23	6.94
Huang et al, 2012	1.618	0.529	4.942	0.844	0.399	11 / 28	8 / 28	21.39
	1.882	0.996	3.554	1.948	0.051	63 / 172	42 / 174	



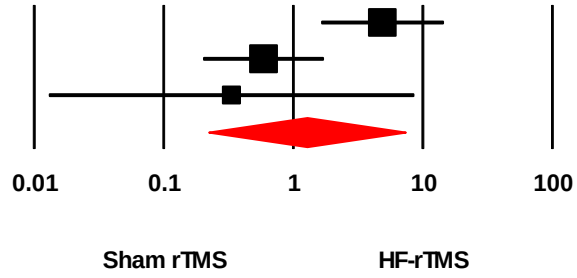
4.4.5 *Supplementary eFigure 21.* *Response Rates at T_2 Excluding Rumi and colleagues*[82]

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Active rTMS	Sham rTMS	Relative weight
Rossini et al, 2005	1.500	0.559	4.024	0.805	0.421	36 / 45	32 / 44	22.36
Bretlau et al, 2008	1.909	0.579	6.296	1.062	0.288	14 / 22	11 / 23	15.29
Herwig et al, 2007	1.602	0.789	3.252	1.303	0.193	30 / 62	24 / 65	43.39
Huang et al, 2012	1.560	0.534	4.557	0.813	0.416	13 / 28	10 / 28	18.95
	1.613	1.012	2.572	2.008	0.045	93 / 157	77 / 160	

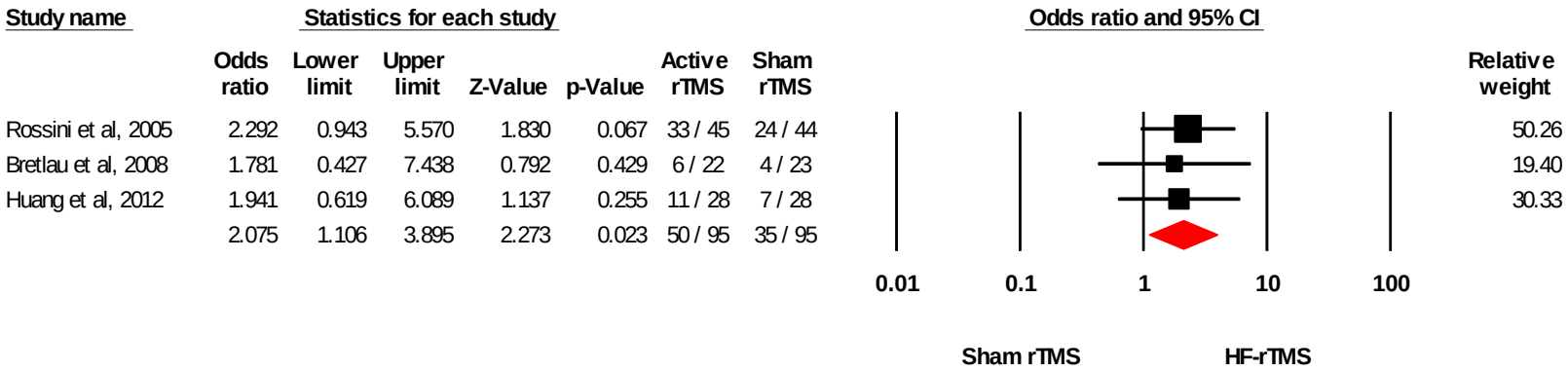


4.4.6 Supplementary eFigure 22. *Remission Rates at T_1 Excluding Rumi and colleagues*[82]

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Remitters / Total: Active rTMS	Remitters / Total: Sham rTMS	Relative weight
Rossini et al, 2005	4.877	1.633	14.567	2.839	0.005	18 / 49	5 / 47	40.85
Herwig et al, 2007	0.589	0.200	1.732	-0.961	0.336	6 / 62	10 / 65	41.04
Bretlau et al, 2008	0.333	0.013	8.627	-0.662	0.508	0 / 22	1 / 23	18.11
	1.260	0.220	7.234	0.259	0.795	24 / 133	16 / 135	



4.4.7 *Supplementary eFigure 23.* *Remission Rates at T_2 Excluding Rumi and colleagues*[82]



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