Title: A systematic review of the clinical relevance of repetitive transcranial magnetic stimulation

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Word count:

Running title: Clinical relevance of repetitive transcranial magnetic stimulation for depression

Abstract

Objective: Repetitive transcranial magnetic stimulation (rTMS) is an approved treatment for depression. The clinical relevance of its efficacy is unclear. The clinical relevance of findings in the rTMS literature were assessed by translating Hamilton Depression Rating Scale (HAMD) data into Clinical Global Impression - Improvement scale (CGI-I) scores.

Method: Electronically searches of MEDLINE, Embase, PsycInfo, Pubmed, and Cochrane Central Register of Controlled Trials for RCTs and non-RCT trials on rTMS using Hamilton Depression Rating Scale (HAMD). Articles were included if published in English before January 2014. We translated HAMD scores into nominal CGI-I scores for rTMS for depression and for treatment resistant depression (TRD).

Results: 960 abstracts were retrieved. 63 studies were included yielding 130 study arms. For depression the mean percentage change for HAMD scores in all sham-controlled rTMS treatment arms was 35.63 (SD 16.35) and for sham-rTMS 23.33 (SD 16.51) For TRD, active rTMS in sham-controlled studies showed a mean HAMD percentage reduction of 45.21 (SD 10.94) versus 25.04 (SD 17.55) for sham-rTMS. When aggregated scores were translated into notional CGI-I scores, for the treatment of depression the notional CGI-I score difference between rTMS and sham-rTMS was 0.5 in favour of rTMS; for TRD it was 0.75 in favour of rTMS. Differences between rTMS and sham-rTMS were bigger when all study arms were combined.

Conclusion: Whilst rTMS appears to be efficacious for both non-refractory and treatment resistant depression, the clinical relevance of its efficacy is doubtful.

Key words:

Repetitive transcranial magnetic stimulation, depression, treatment resistant depression, clinical relevance, systematic review

Summations:

- rTMS does have a small demonstrable antidepressant effect.
- rTMS generates very small improvements when used in the treatment of non-refractory depression.
- The results in treatment resistant depression are somewhat better, but still reflect only minimal clinical improvement.

Considerations:

- The studies are heterogeneous.
- We could not consider cumulative doses.
- The method of translating HAMD to CGI scores is an indirect comparison.

  The minimal clinical improvement found on average does not preclude the possibility that rTMS can be associated with a reasonable Numbers Needed to Treat (NNT).

Introduction

Depressive disorders are common throughout the world. They are the most important cause of Years Lost due to Disability (YLD) for men and women in high, middle and low income countries (1, 2). Transcranial magnetic stimulation (TMS) was developed in the mid-1980s in Sheffield, UK, as a non-invasive brain stimulation tool (3). Improvements in electro-technology led to the development of repetitive TMS (rTMS). Several neuroimaging studies reported activation changes in medial and dorsolateral regions of the prefrontal cortex in unipolar depressed patients (4-7). These were proposed as patho-physiological correlates of depressed mental states, as the changes reversed after symptom recovery, irrespective of the therapeutic strategy used (8-10). From 1995, research groups used rTMS at frequencies between 1 and 25 Hz to stimulate the dorsolateral prefrontal cortex (DLPFC) of depressed patients (11, 12). By consensus, stimulation frequencies above 1 Hz are categorized as high-frequency rTMS, while stimulation frequencies $\leq$ 1 Hz are categorized as low-frequency rTMS (13). Extended exposure to high- or low-frequency rTMS was found to alter cortical excitability in different ways, influenced by basal cortical activity state (14).

Since the first experimental antidepressant TMS trial by Höflich and colleagues (15), more than 150 studies of rTMS have been published, using various research designs and stimulation parameters. They have reported varying results, but most suggest that rTMS has an active therapeutic effect in depression. The DLPFC has been the targeted region in almost all studies of rTMS treatment of depression. Nonetheless, heterogeneity in parameters and study designs are important limiting factors when assessing the antidepressant efficacy of rTMS. An influential review by Ridding and Rothwell (16) pointed out that the functional mechanisms of rTMS in depression were unknown and recommended further basic research in order to develop greater precision in rTMS treatment strategies. Another systematic review by Hermann & Ebmeier (2006) found no parameters that predicted a favourable treatment response for active rTMS in randomized controlled trials (RCTs) (17). Two years later the same authors published a meta-analysis of RCTs (18), limiting studies included to those with

more than 10 subjects in each group (active and sham rTMS). This showed a statistically significant result in favour of active rTMS. In October 2008, the US Federal Drug Administration approved rTMS for the treatment of treatment resistant depression, and later for major depressive disorder. A review by Schutter in 2009 concluded “there is a fairly consistent positive statistical effect […] but the clinical relevance remains unclear” (19). In 2010, Slotema and colleagues produced the largest meta-analysis published thus far, which included 34 RCTs (n = 1383 patients). The mean weighted effect size for all included studies comparing rTMS with sham treatment was 0·55 (p<·001). Furthermore, rTMS was marginally more efficacious as a mono-therapy than as a combined treatment with an antidepressant agent. However, they found Electro-Convulsive Treatment (ECT) to be more effective than rTMS when used as a comparator (20). In a 2014 review of high frequency rTMS, Berlim and colleagues found higher response and remission rates in rTMS compared to sham-TMS with associated Numbers Needed to Treat of 6 and 8, respectively (21).

Leucht and colleagues have translated changes in HAMD scales into notional scores on the Clinical Global Impressions scales, severity and improvement (CGI-S and CGI-I) (22). The method used for the translation was equi-percentile linking of HAMD-17 and CGI ratings (23). The method produced a non-linear graph that allows the manual extraction of notional CGI-I scores for every point on the HAMD change score scale (see Table 1). The method has limitations, but it generates an acceptably robust translation. An independent analysis by Furukawa and colleagues using a different dataset and a different approach yielded similar results (24). A similar method has previously been used to assess the clinical relevance of antipsychotic trial findings (25). That study demonstrated that antipsychotic trial findings show improvements of limited clinical relevance despite statistically significant results in individual trials for most antipsychotics (25). It also showed significant differences in CGI improvement scores between antipsychotics. Some reached a CGI change of two points indicating that patients were on average “much improved”. A similar efficacy hierarchy between drugs emerged in a later network meta-analysis (26).

Table 1 about here

Aims of the study

Most systematic reviews and meta-analyses show that there is a statistically significant superiority of active rTMS over sham treatment in depression, but the clinical relevance of these findings remains unclear. We have performed a systematic review of rTMS in depression and in treatment resistant depression in order to assess the clinical relevance of its reported efficacy.

Method

Search strategy and selection criteria: We searched MEDLINE, Embase, PsycInfo, Pubmed, and Cochrane Central Register of Controlled Trials for RCTs and non-RCT trials of rTMS using the Hamilton Depression Rating Scale (HAMD). The search terms were “Transcranial Magnetic Stimulation“ OR “TMS“ OR “rTMS“ OR “Repetitive TMS“ OR “Repetitive Transcranial Magnetic Stimulation“ AND “Depression“ OR “Anxiety“ OR “Anxiety Disorders“ OR “Depressive Disorder. Abstracts and reports from meetings were not included. Only articles published in English up to 15th January 2014 were included.

Inclusion criteria:

- Participants: human subjects, formal diagnosis of depression irrespective of the subtype of depression or the diagnostic criteria used.
- Intervention: rTMS as mono-therapy or add-on therapy
- Comparator: any (sham-rTMS, different forms of rTMS or rTMS delivery, ECT)
- Outcome measures: percentage change in mean Hamilton depression rating scale (HAMD/HDRS) score (given directly or calculated from baseline and endpoint data)
- Design: randomised controlled trial (RCT) or non-RCT (such as open-label or naturalistic trials).
- Reporting:

- published in a peer reviewed journal
- sample size for each study arm reported
- available as electronic or paper full-text.

Exclusion criteria:

- Studies where depression was not the primary diagnosis (for example, panic disorder, schizophrenia, obsessive-compulsive disorder, Parkinson Disease, dementia, depression after stroke, mania, alcohol related syndrome, insomnia, organic depression)
- Reviews, meta-analyses, insufficient data (e.g. an exact HAMD percentage change was impossible to calculate)
- Studies of adolescents or children
- Non-standard rTMS (for example, deep TMS or stimulation outside the DLPFC)

Outcome measures were taken from the last reported follow-up point. In cross-over trials, only the first treatment episode was included. Where more than one version of HAMD was used we assumed that the HAMD-17 had been used, as the original translation used HAMD-17 (as we calculated a percentage change from baseline, this should not have had an impact on the analysis).

Full text versions of all identified papers were obtained. Data were extracted independently by two reviewers (RSS & SVNL). The two databases were compared manually, then examined again by a third reviewer (CS-L) and discrepancies corrected by reference to the original papers. We excluded duplicate publications (the same patients reported in an earlier publication).

CGI-I score analysis of the following comparisons was performed:

1. Study arms from sham-controlled RCTs (rTMS versus sham-rTMS)
2. Study arms from all rTMS trials, controlled and uncontrolled
3. RCTs comparing ECT versus rTMS
4. Separate analyses were conducted on 1 and 2 for non-refractory depression and TRD.
5. High (above 1 Hz) versus low versus mixed frequency (Hz) rTMS treatment. 'Mixed frequency' includes all studies with changing frequency application methods. This usually involved switching impulses between high and low frequency application.

The primary analysis was based on all RCTs that compared rTMS with sham-rTMS and provided sufficient data for analysis (HAMD baseline and endpoint scores or percentage changes and standard deviations). In a second step we included all available rTMS studies in an attempt to analyse whether the results become better for rTMS when naturalistic studies are included, as sham-controlled trials often find less favourable results for active interventions. Percentage change between baseline and follow-up was calculated for each study. A weighted overall change was calculated for each study arm. Weighting was based on sample size (n). These values were used to calculate a mean percentage change score for each of the study arms being analysed. Percentage change gave a standardised measure of change, which allowed results from studies that used HAMD-17, 21, and 24 to be combined in the analysis. The percentage HAMD change was plotted with CGI-I scores on a graph. In Leucht et al (22) a HAMD reduction of 75%-85% (depending on the week) equals a CGI-I score of 1 (very much improved), a reduction of 50%-60% equals a CGI-I score of 2 (much improved), and of 25%-35% equals a CGI-I score of 3 (minimally improved). As the exact figures varied somewhat depending on the week of follow-up used in Leucht et al. (22), we used week 4 results for our analysis which was most similar to the average duration of the studies included (Tables 1 and 2). Translation was conducted manually for each point, as the conversion graphs are not linear (22). This allows indirect comparisons between the groups to examine the clinical relevance of the findings. Formal hypothesis tests were undertaken using the independent sample t-test. As the data were aggregated, the test statistics were calculated by hand and compared with

the tabulated values at the required significance level and number of degrees of freedom. A 5% significance level was applied, consequently p-values are quoted as being either <0.05 (statistically significant) or >0.05 (statistically non-significant)

Results

The search generated 464 abstracts after excluding duplicates (see figure 1, CONSORT chart). After examining the abstracts, full-text versions of 187 papers were obtained. Nine papers could not be procured. Three studies were added after hand-searching previous systematic reviews and meta-analyses for references. A total of 63 studies were included in the study (27-89). Reasons for exclusion are shown in Figure 1. The number of stimulation sessions varied between 5 and 30. The length of follow-up was between 5 days and 24 weeks. The total stimuli received varied between 3,600 and 90,000 impulses; study sample size varied between 5 and 155.

Figure 1 about here

The 63 studies included (27-89) (see Table 2 for study characteristics) had between two and four study arms and yielded 83 separate study arms relating to treatment with rTMS. Thirty-two studies were sham-controlled RCTs with sufficient data to be included in the primary analysis. By adding comparator sham-rTMS (36 study arms) and ECT (5 study arms), a total of 130 study arms were included in the analysis. As some studies have more than 2 study arms there were more study arms than the number of studies. The studies comprised a total of 3236 participants (2330 for rTMS, 806 for sham-rTMS and 100 for ECT). All studies reported baseline HAMD scores that indicated that the participants on average reached the threshold for major depression (most studies used HAMD 17 or 21; baseline scores were between 22 and 28 depending on the version used). Tables 3 and 4 shows the results of the analysis of HAMD scores including mean change in HAMD scores in absolute numbers and as percentages, with the translation into notional CGI–I scores. It shows the results for non-refractory depression and treatment resistant depression (TRD) separately, comparing sham-rTMS and rTMS.

Looking at sham-controlled RCTs alone first, we found that rTMS was better in both diagnostic categories. The finding was statistically significant for non-refractory depression (T=-13.85) and for TRD (T=-10.10). The difference in CGI-I scores between sham and real TMS was 0.5 for depression and 0.75 for TRD.

When we take all included studies into account (i.e. sham controlled RCTs and all other trials) the results remain significant at $p<0.05$ for depression (T=-19.59) and TRD (T=-27.74). For depression, rTMS had a CGI-I advantage of 0.6 over sham-TMS, whilst in TRD rTMS had a CGI-I advantage of 1.0 over sham-rTMS. By way of comparison, in the ECT group the combined mean difference in HAMD scores was 12.58 (SD 6.98) with a CGI-I of 2.45 (percentage HAMD reduction: 46.36 (SD 27.47)). In those rTMS studies that used ECT as a comparator, ECT was more effective than rTMS, which only reached a HAMD percentage reduction of 33.7%.

Tables 3 and 4 about here

Analysis of different rTMS frequencies has to be interpreted with caution. It is presented here to exclude potential bias from the inclusion of all frequencies in the rTMS versus sham-rTMS analysis above. We found some statistically significant differences between frequencies, but the magnitude of the effect was minimal. In terms of HAMD percentage change, low frequency was statistically significantly better than high frequency (T=-7.21) and mixed frequency (T=-4.17). Furthermore, mixed was better than high (T=-5.37). High frequency trials showed a HAMD percentage reduction of 40.94% (SD17.57) (47 studies, 52 study arms, 1295 participants, 10.58 absolute HAMD score reduction). For low frequency trials the percentage reduction was 46.57% (SD 10.77) (15 studies, 20 study arms, 593 participants, 10.70 absolute HAMD score reduction). For mixed frequency trials the percentage reduction was 43.56% (SD 10.44) (7 studies, 13 study arms, 997 participants, 9.97 absolute HAMD score reduction).

Discussion

As can be seen from Table 3, rTMS has a measurable effect on symptoms in depression, reflected by a 35% and 45% reduction of the HAMD score in our primary analysis. However, as is the case in antidepressant trials, there is a strong placebo effect, as shown by a 22-25% HAMD reduction using sham-rTMS. Whilst rTMS does have a demonstrable specific antidepressant effect, this translates into a CGI-I reduction of only 0.5 points, which is of highly questionable clinical relevance in the routine treatment of depression. The difference between rTMS and sham-rTMS is somewhat larger in treatment resistant depression, but even in the most favourable analysis, where uncontrolled studies are combined with sham-controlled RCTs, the difference only just reaches the threshold of "minimally improved" on the CGI-I. These findings create serious doubt over the clinical relevance of the therapeutic effects of rTMS.

We have followed the method of our previous review of antipsychotics (25) in using a translation of a symptom-rating instrument (HAMD) into a measure of clinical relevance (CGI-I scores) to compare rTMS with sham-rTMS and ECT. Our systematic review is the largest performed so far. It is the first to report notional CGI-I scores for rTMS. When only sham-controlled RCTs are included in the analysis, our results confirm a statistically significant superiority of rTMS over sham-TMS in the treatment of both depression and TRD. When non-sham-controlled RCTs and non-RCT trials are included, the very small advantage of TMS over sham-rTMS in depression and the modest advantage of rTMS in TRD remain robust.

How do our findings compare with the rest of literature? In the first meta-analysis combining RCTs of DLPFC stimulation in depression, which included five studies, the authors found a beneficial effect of active rTMS compared to sham-rTMS, but the extent and the duration of the antidepressant effects of rTMS could not be defined (90). Burt and colleagues (2002) included 16 trials in their meta-analysis (n = 377 patients) and found that the effect of active rTMS was fairly robust from a statistical viewpoint (effect sizes: $d_{pooled} = 0.67$), but they were doubtful about the effect's clinical significance (91). Indeed, a conventional meta-analysis of the RCTs included in our review yielded similar results (non-refractory depression: 22 RCTs, n=1488, SMD =

0.63 [0.5,0.74], treatment resistant depression: 10 RCTs, n=376, SMD = 0.74 [0.52,0.95]. Details can be obtained from the authors upon request). Couturier and colleagues (2005) used strict methodological inclusion criteria for rTMS studies (only six RCTs were included) and came to the conclusion that active rTMS was no different to sham-rTMS (92). Lam and colleagues reviewed the efficacy of rTMS for TRD and found that active rTMS was significantly superior to sham conditions in producing clinical response, with a modest risk difference of 17% (93). Fitzgerald and colleagues (2002), however, were less cautious and asserted that rTMS "appears to have considerable potential as a therapeutic tool in depression, and perhaps a role in several other disorders" (94).

Applying these standards to our results for non-refractory depression, the result is statistically significant, and favourable to rTMS. The advantage of rTMS against sham-rTMS in sham-controlled RCTs is a HAMD percentage change of 12.30% and a CGI-I difference of 0.5 points, which would be barely noticeable in clinical practice. This advantage remains robust when all trials are included, with 15.04% HAMD reduction (CGI: 0.6). However, it is well recognised that naturalistic studies exaggerate effects.

Applying the same standards to TRD, the results are somewhat more favourable. The additional percentage HAMD reduction of TMS against sham-rTMS in TRD is 20.17% when only sham-controlled RCTs are included in the analysis. We found a CGI-I advantage of 0.75. When all trials are included the advantage of rTMS increases to 24.74%, which equates to a clinically noticeable, but still small effect.

Sham-rTMS achieves HAMD reductions around 22-25% in both non-refractory and treatment-resistant depression, indicating a substantial placebo effect which must be subtracted to assess the effect of rTMS. Our results suggest that, in terms of clinically meaningful change, rTMS leads to minimal improvements when used in the treatment of depression.

To put our findings into context, we have looked at the cognitive-behavioural psychotherapy (CBT) and antidepressant literatures using similar methods. Cuijpers and colleagues found a considerable difference between psychotherapy and any

control in their main analysis (95). However, when the meta-analysis was restricted to placebo-pill controlled trials, the advantage of psychotherapy for depression over placebo-pill was only 2.66 HAMD absolute points (96).

Our group has found 45.21% difference in HAMD percentage change between cognitive behavioural therapy arms and waiting list control arms for non-refractory depression (CGI-I difference: 1.85). Against treatment-as-usual, the advantage reduced to 29.93% or a CGI-I difference of 1.15; against placebo-pill the difference is 21.64% or a CGI-I difference of 0.85 (97). In a re-analysis of the controversial Kirsch paper, the weighted mean improvement was 2.68 absolute HAMD points in drug response over placebo (1.8 in the original paper by Kirsch et al) (98). This compares to a 3.38 HAMD point reduction for rTMS in depression in our analysis. Most antidepressant reviews compare the percentage of responders (normally defined as a HAMD reduction above 50%). Mean percentage reductions are rarely reported. Placebo and drug responses show large variability between studies but, on average, treatment groups show a 16% higher response rate than placebo. Treatment arm response rates can be as high as 70% (99). A meta-analysis on ECT showed average absolute HAMD score changes of 9.7 in favour of ECT (100). In summary, our findings for rTMS are at the lower end of the range for treatments of depression, a number of which do not appear to be highly effective by these standards.

We found few important differences between frequencies used, and we would not wish to exaggerate the strength of our method in this regard. Slotema did not find a difference between frequency regimes (20). More studies are needed to clarify this.

Our study has some limitations. A major limitation is that our method is indirect. We planned to include an analysis of reported CGI results, but we were unable to do so as CGI is rarely used in rTMS studies. Translation is only validated for HAMD-17, but different versions were used in the studies, and correlations between CGI and HAMD were moderate in the original publication (22) suggesting high variability.

As is commonly the case in systematic reviews, a large number of studies were excluded for a variety of reasons. There is no reason to suppose that the exclusion of

studies has created a bias to minimise the clinical effects of rTMS. Furthermore, most studies were small, and small studies tend to overestimate effects. We included non-randomised studies in secondary analyses, because we wished to perform a review with broad inclusion criteria rather than reviewing a small number of RCTs with very specific inclusion criteria. This procedure was favourable for rTMS, because it is well recognised that uncontrolled trials tend to produce larger effects. Whilst this increases heterogeneity, in exchange it produces a large sample size. This is a particular strength of our review compared to many smaller reviews previously published. We did not, however, examine heterogeneity in this study.

Leucht and colleagues have pointed out that their method of converting HAMD (or PANSS/BPRS) continuous scores into CGI categorical scores involves the translation of psychometrically validated instruments into impressionistic scales using conversion graphs that are not perfectly linear (22, 23, 101). The fact that equi-percentile linking does not require linearity is an advantage of the method but means that exact translations are difficult to calculate. As the method produces global impression scores, it measures something different to meta-analyses that focus on effect sizes. It is possible for a treatment to achieve statistically significant results and reasonable numbers-needed-to-treat in meta-analyses whilst at the same time achieving low CGI-I scores (102), therefore having little or no clinical relevance for many patients.

The studies we included did not use a consistent definition of TRD. It cannot be assumed that TRD in the context of this literature implies severe or long-term depression. Furthermore, previous apparent treatment resistance might have been due to poor treatment adherence.

We have not examined duration of treatment or cumulative dose as factors affecting outcome, but this would be worthwhile in future research. Many studies measure short-term outcomes. This is a general weakness of the existing literature. We minimised this problem by taking the last available follow-up data in each study. We do not believe that the limitations of our study invalidate the principle findings.

Table 2 about here

Acknowledgments

We would like to thank staff at the John Spalding library in Wrexham for their help with the search and Rebecca Hoofe for her secretarial support.

Declaration of interest:

Peter Lepping received speaker fees from ElyLilly. Stefan Leucht received speaker/consultancy/advisory board honoraria from SanofiAventis, BMS, EliLilly, AstraZeneca, Essex Pharma, GlaxoSmithKline Janssen/Johnson and Johnson, Lundbeck, Medavante and Pfizer. All other authors have no conflicts of interest to declare.

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TABLES AND FIGURES

Table 1: HAMD to CGI translation (adapted from Leucht et al (22), based on changes at 4 week follow-up)

CGI-I	HAMD % change	Interpretation
1	-84%	Very much improved
2	-59%	Much improved
3	-33%	Minimally improved
4	-9%	No change
5	+8%	Minimally worse
6	+27.5%	Much worse
7	+60%	very much worse

Table 2: included studies

Author	Design	Arms	Type of rTMS	Location	Frequency	Diagnosis	Tool	Sample size	Length of study	HAMD version	Comments
Abraham – 2007 (27)	Non RCT trial	1	High frequency	Left DLPFC	10Hz	TRD	DSM-IV	20	6 weeks	HD 21	Subjects were 60 yrs or older
Avery 2006 (28)	RCT	2	High Frequency	Left DLPFC	10 Hz	TRD	DSM-IV	35	5 wks	HD 17	
			Sham					33	5 wks		
Avery 2008 (29)	Non RCT extension trial	2 Extended rTMS	High frequency rTMS	Left DLPFC	10 Hz	TRD	DSM-IV	73	9 wks	HD 24 HD17	Non RCT extension of non-responders in an RCT
		Sham followed by rTMS	High frequency rTMS	Left DLPFC	10 Hz			85	9 wks		
Bajbouj 2005 (30)	Non RCT trial	1	High frequency	Left DLPFC	20 Hz	Depression	DSM-IV	30	2 wks	HD 24	Study compared motor cortex excitability in responders versus non responders to rTMS
Bakim 2012 (31)	RCT	3	80% MT	Left DLPFC	20 Hz	TRD	DSM-IV	12	6 wks	HD 17	
			110% MT	Left DLPFC	20 Hz			11	6 wks		
			Sham rTMS					12	6 wks		
Benadhira 2005 (32)	Non RCT trial	1	High Frequency	Left DLPFC	10 Hz	TRD	NA	11	4 wks	NA	
Berlim 2011 (33)	Non RCT	1	High Frequency	Left DLPFC	10 Hz	TRD	DSM-IV	15	4 wks	HD 24	rTMS was augmentation to antidepressant Rx
Bretlau 2008 (34)	RCT	2	rTMS	Left DLPFC	8 Hz	TRD	DSM-IV	25	12 wks	HD 17	
			Sham rTMS					24	12 wks		
Chen 2013 (35)	RCT	2	High frequency	Left DLPFC	20 Hz	Depression	DSM-IV	10	4 wks	HD 17	
			Sham rTMS					10	4 wks		
Conca 2002 (36)	RCT	3	High + Low frequency	Left + Rt DLPFC	Left 10 Hz Right 1 Hz	TRD	ICD 10	12	5 days	HD 21	

			High + Low frequency	Left DLPFC	10 Hz alternate with 1 Hz			12	5 days		
			High Frequency	Left DLPFC	10 Hz			12	5 days		
Crevits 2005 (37)	Non RCT	1	High Frequency	Left DLPFC	10 Hz	Depression	DSM-IV	11	3 wks	HD 21	
Dannon 2002 (38)	RCT	2	rTMS	Left DLPFC	10 Hz	Depression	DSM-IV	21	24 wks	HD 17	
			ECT					20	24 wks		
Dolberg 2002 (39)	RCT	2	rTMS	NA	NA	Bipolar Depression	NA	10	4 wks		Subjects had bipolar depression
			Sham TMS					10	6 wks		
Fitzgerald 2006 (40)	RCT	4	Low frequency rTMS	Right DLPFC	1 Hz	TRD	MINI	67	4 wks	HD 17	High frequency rTMS was provided to the non responders to the Right sided rTMS as an extension trial for another 4 weeks
			Low frequency rTMS	Right DLPFC	2 Hz		MINI	63	4 wks	HD 17	
			High frequency	Left DLPFC	5 Hz		MINI	16	4 wks	HD 17	
			High Frequency	Left DLPFC	10 Hz		MINI	14	4 wks	HD 17	
Fitzgerald 2009 (41)	RCT	2	High frequency rTMS	Left DLPFC	NA	TRD	DSM-IV	15	4wks	NA	Stimulation parameters were calculated at varying duration of stimulus and intervals
			Low frequency rTMS	Right DLPFC	NA			11	4 wks		
Fitzgerald 2013 (42)	RCT	2	Sequential Bilateral rTMS	Right DLPFC followed by Left DLPFC	Right 1 Hz Left 10 Hz	TRD	MINI	76	4 wks	HD 17	
			Priming stimulation rTMS	Right DLPFC	Right 6 Hz followed by 1 Hz			85	4 wks	HD 17	
Fitzgerald 2011 (43)	RCT	3	Low frequency	Right DLPFC	1 Hz	TRD	MINI	71	4 wks	HD 17	
			Sequential bilateral mixed	Right followed by Left DLPFC	Right 1 Hz followed by left 10 Hz		MINI	71	4 wks	HD 17	
			Sequential bilateral low frequency	Right followed by Left DLPFC	Right 1 Hz followed by left 1 Hz			76			
Fujita 2005 (44)	Non RCT	1	Single pulse TMS	Bilateral Frontal	NA	Depression	DSM-IV	23	5 days	NA	Single pulse TMS was administered at 20 stimuli per session
Galletly 2012 (45)	RCT	2	Spaced rTMS	Left DLPFC followed by right	Left 10 Hz Right 1 Hz	Depression	DSM-IV	42	6 wks	HD 21	
			Daily rTMS	Left DLPFC	Left 10 Hz Right 1 Hz		DSM-IV	35	6 wks	HD 21	

				followed by right							
Garcia-Toro 2001 (46)	RCT	2	rTMS	Left DLPFC	20 HZ	Depression	DSM-IV	17	4 wks	HD 21	
			Sham rTMS					18	4 wks		
Garcia-Toro 2006 (47)	RCT	3	Bilateral rTMS	Left DLPFC followed by right	Left 20 Hz Right 1 Hz	TRD	DSM-IV	10	4 wks	HD 21	
			Sham TMS					10			
			SPECT guided rTMS	Different locations	20 Hz to lowactivity area 1 Hz to High activity area			10			
George 1997 (48)	RCT	2	High frequency	Left DLPFC	20 Hz	depression	DSM-IV	7	2 wks	HD 21	
			Sham					7	2 wks		
George 2000 (49)	RCT	3	High Frequency	Left DLPFC	20 Hz	Depression	DSM-IV	10	2 wks	HD 21	
			Low frequency	Left DLPFC	5 Hz			10	2 wks		
			Sham					10	2 wks		
George 2010 (50)	RCT	2	High frequency rTMS	Left DLPFC	10 Hz	Depression	DSM-IV	92	3 wks	HD 24	
			Sham rTMS					98	3 wks		
Grunhaus 2003 (51)	RCT	2	rTMS	Left DLPFC	10 Hz	TRD	DSM-IV	20	4 wks	HD 17	
			ECT					20	4 wks		
Hansen 2004 (52)	RCT	2	High frequency rTMS	Left DLPFC	10 Hz	Depression	DSM-IV	6	7 wks	HD 17	
			Sham TMS				DSM-IV	7	7 wks		
Hausmann 2004 (53)	RCT	2	Simultaneous bilateral rTMS	Left and right DLPFC	Left 20 Hz Right 1 Hz	Depression	DSM-IV	25	4 wks	HD 21	Treatment group consisted of two groups of simultaneous bilateral (13) and Left DLPFC rTMS (12).
			Sham rTMS					13	4 wks		
Hernandez-Ribas 2013 (54)	RCT	2	High Frequency rTMS	Left DLPFC	15 Hz	Depression	DSM-IV	10	3 wks	HD 21	Aim of the study is to identify brain imaging correlates of clinical response to rTMS
			Sham rTMS					11	3 wks		
Herwig 2003 (55)	RCT	2	High frequency rTMS	Left DLPFC	15 Hz	Depression	DSM-IV	13	2wks	HD 21	
			Sham rTMS					12	2 wks		
Herwig 2007 (56)	RCT	2	High frequency rTMS	Left DLPFC	10 Hz	Depression	DSM-IV	62	3 wks	HD 21	
			Sham rTMS					65	3 wks		
Holtzheimer III 2004 (57)	RCT	2	High frequency rTMS	Left DLPFC	10 Hz	Depression	DSM-IV	25	6 wks	HD 17	

			Sham rTMS					25	6 wks		
Janicak 2002 (58)	RCT	2	High frequency rTMS	Left DLPFC	10 Hz	Depression	DSM-IV	13	4 wks	HD 24	
			ECT					9	4 wks		
Janicak 2010 (59)	Non RCT trial	1	High frequency rTMS	Left DLPFC	10 Hz	TRD	DSM-IV	99	24 wks	HD 24	This is a non RCT extension study measuring durability of clinical benefit with rTMS. TMS in this study was for relapse
Januel 2006 (60)	RCT	2	Low frequency rTMS	Right DLPFC	1 Hz	Depression	DSM-IV	11	4 wks	HD 17	
			Sham rTMS					16	4 wks	HD 17	
Jhanwar 2011 (61)	Non RCT trial	1	High frequency rTMS	Left DLPFC	10 Hz	TRD	DSM-IV	21	4 wks	HD 17	
Kauffmann2004 (62)	RCT	2	Low frequency rTMS	Right DLPFC	1 Hz	TRD	DSM-IV	7	10 days	HD 21	
			Sham rTMS					5	10 days		
Keshtkar 2011 (63)	RCT	2	rTMS	Left DLPFC	NA	TRD	DSM-IV	40	10 days	HD 21	
			ECT	Bilateral				33	3 wks		
Kito 2008 (64)	Non RCT trial	1	Low frequency rTMS	Right DLPFC	1 Hz	TRD	DSM-IV	14	5 wks	NA	
Kito 2011 (65)	Non RCT	1	Low frequency rTMS	Right DLPFC	1 Hz	Depression	DSM-IV	26	5 wks	HD 21	
Klein 1999 (66)	RCT	2	Low frequency rTMS	Right DLPFC	1 Hz	Depression	DSM-IV	36	2 wks	HD 17	
			Sham rTMS					34	2 wks		
Koerselamn 2004 (67)	RCT	2	High frequency rTMS	Left DLPFC	20 Hz	Depression	DSM-IV	26	14 wks	HD 17	
			Sham rTMS					26	14 wks		
Loo 2006 (68)	RCT	2	High frequency rTMS	Left DLPFC	10 Hz	Depression	DSM-IV	19	6 wks	HD 17	
			Sham rTMS					19	6 wks		
Maihofner 2005 (69)	Non RCT	1	High frequency rTMS	Left DLPFC	10 Hz	Depression	DSM-IV	8	10 days	HD 21	
Manes 2001 (70)	RCT	2	High frequency rTMS	Left DLPFC	20 Hz	TRD	DSM-IV	10	12 days	NA	
			Sham rTMS					10	12 wks		
Martinot 2009 (71)	RCT	3	High frequency rTMS	Left DLPFC	10 Hz	TRD	DSM-IVR	18	10 day	HD 21	Aim of the study is to explore the influence of prefrontal target region on the efficacy of rTMS
			PET- guided rTMS	Variable	Variable			16	10 day	HD 21	
			Sham rTMS					14	10 day		
Ming-li 2009 (72)	RCT	3	SEM-rTMS	NA	NA	Depression	DSM-III	57	10 days	HD 24	SEM: Sleep electroencephalogram

			C-rTMS	NA	NA			55	10 days		modulated; c:conventional
			Sham rTMS	NA	NA			52	10 days		
Moller 2006 (73)	RCT	2	High frequency rTMS	Left DLPFC	10 Hz	Depression	ICD 10	7	5 days	HD 17	
			Sham rTMS					3	5 days		
Mossiman 2004 (74)	RCT	2	High frequency rTMS	Left DLPFC	20 Hz	Depression	DSM-IV	15	10 days	HD 21	
			Sham rTMS					9	10 days		
Myczkowski 2012 (75)	RCT	2	rTMS	Left DLPFC	5 Hz	Depression	DSM-IV	8	6 wks	HD 17	
			Sham rTMS					6	6 wks		
Nahas 2001 (76)	RCT	3	High frequency rTMS	Left DLPFC	20 Hz	Depression	DSM-IV	9	2 wks	NA	Study explored the role of stimulation frequency and coil-cortex distance
			Low frequency rTMS	Left DLPFC	5 Hz			5	2 wks		
			Sham rTMS					9	2 wks		
O'Reardon 2007 (77)	RCT	2	High frequency rTMS	Left DLPFC	10 Hz	Depression	DSM-IV	155	6 wks	HD 24 HD 17	
			Sham rTMS					146	6 wks		
Padberg 1999 (78)	RCT	3	High frequency rTMS	Left DLPFC	10 Hz	TRD	DSM-IV	6	5 days	HD 21	
			Low frequency rTMS	Left DLPFC	0.3 Hz			6	5 days		
			Sham rTMS					6	5 days		
Padberg 2002 (79)	Non RCT	1	High frequency rTMS	Left DLPFC	10 Hz	Depression	DSM-IV	33	2 wks	HD 21	partial sleep deprivation at least 5 days prior to rTMS; drug-free patients
Price 2010 (80)	RCT	3	Combined			Depression	DSM-IV	44	4 wks	HD 21	Interactive rTMS applied individual stimuli in response to real time EEG
			Standard rTMS	Left DLPFC	10 Hz			23	4 wks		
			Interactive rTMS	Varied	Varied			21	4 wks		
Rossini 2005 (81)	RCT	2	High frequency rTMS	Left DLPFC	15 Hz	Depression	DSM-IV	50	5 wks	HD 21	Study explored the adjunct response of rTMS to antidepressant Rx
			Sham rTMS					49	5 wks		
Rossini 2010 (82)	RCT	2	High frequency rTMS	Left DLPFC	15 Hz	Depression	DSM-IV	32	2 wks	HD 21	
			Low frequency rTMS	Right DLPFC	1 Hz			42	2 wks		

Stern 2007 (83)	RCT	4	High frequency rTMS	Left DLPFC	10 Hz	Depression	DSM-IV	10	4 wks	HD 21	Study compared the antidepressant effects of high and low frequency rTMS to DLPFC
			Low frequency rTMS	Left DLPFC	1 Hz			10	4 wks		
			Low frequency rTMS	Right DLPFC	1 Hz			10	4 wks		
			Sham rTMS					15	4 wks		
Su 2005 (84)	RCT	3	High frequency rTMS	Left DLPFC	20 Hz	TRD	DSM-IV	10	2 wks	HD 21	
			Low frequency rTMS	Left DLPFC	5 Hz			10	2 wks		
			Sham rTMS					10	2 wks		
Triggs 1999 (85)	Non RCT	1	rTMS	Left DLPFC	NA	Depression	DSM-IV	10	2 wks	NA	
Triggs 2010 (86)	RCT	4	Low frequency rTMS	Right DLPFC	5 Hz	TRD	DSM-IV	16	12 wks	HD 24	Study compared right and left DLPF rTMS treatment in TRD
			Low frequency rTMS	Left DLPFC	5 Hz			18	12 wks		
			Sham rTMS	Right DLPFC				7	12 wks		
			Sham rTMS	Left DLPFC				7	12 wks		
Turnier-Shea 2006 (87)	RCT	2	Daily rTMS	Left DLPFC	20 Hz	Depression	DSM-IV	8	12 wks	HD 17	Spaced rTMS group received 5 treatments on spaced business days, half of other group
			Spaced rTMS	Left DLPFC	20 Hz			8	12 wks		
Wang 2004 (88)	RCT	2	High Frequency rTMS	Left DLPFC	20 Hz	Depression	*	18	3 wks	HD 17	*Chinese Psychological Disease Classification and Diagnosis Standard - Second Revision
			ECT	Bilateral				18	3 wks	HD 17	
Zheng 2010 (89)	RCT	2	High frequency rTMS	Left DLPFC	15 Hz	TRD	DSM-IV	19	4 wks	HD 17	Study explored increase in pre frontal myoinositol with high frequency rTMS
			Sham rTMS					15	4 wks		

Table 3: Results for sham-rTMS and rTMS in depression: (first sham-controlled RCTs alone, then all trials combined)

Number of included studies (treatment arms)	Total sample size	Combined mean difference (SD) *	Percentage change mean (SD)	CGI-I
Sham-rTMS Depression (RCT alone)				
22 (22)	634	5.42 (4.18)	23.33 (16.51)	3·4
rTMS Depression (RCT alone)				
22 (27)	743	8.8 (4.31)	35.63 (16.35)	2.9
Sham-rTMS Depression (all trials)				
24 (24)	653	5·38 (4.15)	22.14 (16.55)	3.4
rTMS Depression (all trials)				
38 (48)	1192	9.26 (3.99)	37.18 (15.13)	2·8

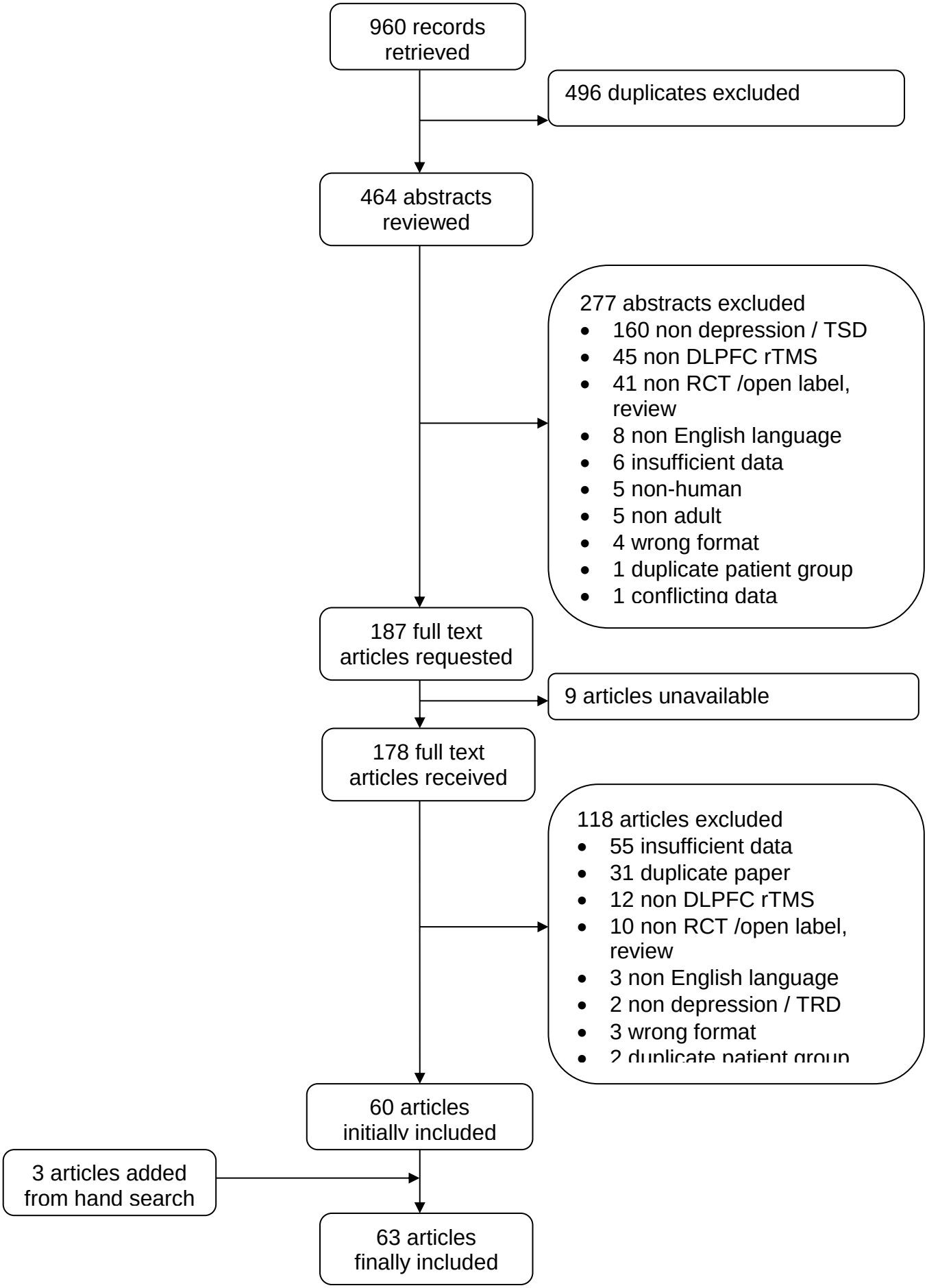
* The HAMD combined mean differences are approximate because of the use of 3 different HAMD scales in the included studies

Table 4: Results for sham-rTMS and rTMS in TRD: (first sham-controlled RCTs alone, then all trials combined)

Number of included Studies (treatment arms)	Total sample size	Combined mean difference (SD) *	Percentage change mean (SD)	CGI-I
Sham-rTMS Treatment Resistant Depression (RCT alone)				
10 (11)	120	6.18 (4.48)	25.04 (17.55)	3.3
rTMS Treatment Resistant Depression (RCT alone)				
10 (15)	103	11.11 (2.60)	45.21 (10.94)	2.55
Sham-rTMS Treatment Resistant Depression (all trials)				
11 (12)	153	5.65 (4.09)	23.03 (16.00)	3.4
rTMS Treatment Resistant Depression (all trials)				
25 (41)	1138	11.43 (3.98)	47.77 (12.80)	2.4

* The HAMD combined mean differences are approximate because of the use of 3 different HAMD scales in the included studies

Figure 1 CONSORT flow chart


960 records retrieved
496 duplicates excluded
464 abstracts reviewed
277 abstracts excluded
160 non depression / TSD
45 non DLPFC rTMS
41 non RCT /open label, review
8 non English language
6 insufficient data
5 non-human
5 non adult
4 wrong format
1 duplicate patient group
1 conflicting data
187 full text articles requested
9 articles unavailable
178 full text articles received
118 articles excluded
55 insufficient data
31 duplicate paper
12 non DLPFC rTMS
10 non RCT /open label, review
3 non English language
2 non depression / TRD
3 wrong format
2 duplicate patient group
60 articles initially included
3 articles added from hand search
63 articles finally included