



Review

Deep transcranial magnetic stimulation (DTMS) in the treatment of major depression: An exploratory systematic review and meta-analysis



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ABSTRACT

Background: Deep transcranial magnetic stimulation (DTMS) is a relatively new, non-invasive method of stimulating larger and, presumably, deeper brain regions. The current study investigated if DTMS delivered with H-coils has acute antidepressant effects in major depression using a systematic literature review and a quantitative meta-analysis.

Methods: Seventeen studies on 'DTMS or H-coil' and 'depression' were identified on Medline, PsycInfo, and Google Scholar (until November 2014). Data from nine open-label studies were meta-analysed using a random-effects model with inverse-variance weights. The outcome measures were the standardised paired mean difference (Cohen's *d*) in depression scores on Hamilton Depression Rating Scale (HDRS), response, remission, and dropout rates after acute DTMS treatment compared to baseline.

Results: There was a large antidepressant effect after 20 acute, high-frequency DTMS sessions compared to baseline according to HDRS change scores (overall mean weighted *d* = 2.04, 95% confidence interval: 1.53–2.55; nine studies; 150 patients). Overall weighted response, remission, and dropout rates were 60%, 29%, and 18% respectively. HDRS change scores and response rates tended to be higher in four studies with 68 patients on concurrent antidepressants compared to two studies with 26 patients who received DTMS as a monotherapy.

Limitations: These results are based on data from a low number of open-label studies.

Conclusion: High-frequency DTMS appears to have acute antidepressant effects after 20 sessions in mostly unipolar and treatment-resistant patients. Concurrent treatment with antidepressants might enhance the efficacy of DTMS.

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1. Introduction

According to the largest randomised-controlled trials (RCTs), high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) of the left dorsolateral prefrontal cortex (DLPFC) is an effective and well tolerated treatment for major depression, particularly in patients with resistant conditions (George et al., 2010; O'Reardon et al., 2007). The largest meta-analyses to date have shown that the antidepressant effects of acute HF-rTMS treatment were moderate to large in magnitude (Berlim et al., 2013b, 2014b; Kedzior et al., 2014; Kedzior and Reitz, 2014). Particularly, HF-rTMS was associated with a clinically-relevant remission rate of approximately 30% (George et al., 2013).

A novel alternative to the conventional figure-of-eight or circular rTMS coils is the so-called H-coil system (Roth et al., 2002) whose derived therapeutic application has been called the deep transcranial magnetic stimulation (DTMS) (Levkovitz et al., 2009). The H-coil was developed to enable a focused, non-invasive stimulation of deeper brain regions while reducing the activation of cortical areas (Roth et al., 2002). It can be speculated that if the H-coils are indeed able to stimulate deeper reward-mediating neural pathways then they might produce antidepressant effects of greater magnitudes compared to the conventional rTMS coils which directly activate mostly superficial cortical regions (Roth et al., 2002). However, no head-to-head study has yet compared the efficacy of HF-rTMS and DTMS.

Although the antidepressant properties of the H-coils have been assessed in patients with major depression since 2009, no quantitative meta-analysis regarding its effectiveness and acceptability has been published to date. The results of a recent large multisite RCT involving patients with treatment-resistant, unipolar depression suggest that active DTMS monotherapy was significantly more effective than sham DTMS in reducing depression scores and improving response and remission rates (Levkovitz et al., 2015). However, it remains unexplored how the results from this RCT (Levkovitz et al., 2015) compare to those of open-label DTMS studies in major depression which are usually more representative of the 'real world' clinical populations. Therefore, the main aim of the current study was to systematically review the existing literature on the clinical utility of DTMS in major depression and quantitatively synthesise the findings using a meta-analysis.

2. Material and methods

2.1. Systematic literature search and study selection

The systematic literature search was performed in the EBSCO PsycInfo and Medline databases from any date until November 18, 2014. The search terms included DTMS (or H-coil) and depression (Table 1). The electronic search identified $k=14$ studies published in peer-reviewed academic journals. Three additional studies (in

press at the time of search) were identified using Google Scholar.

The study selection procedure and exclusion criteria are summarised on the PRISMA flowchart (Moher et al., 2009), Fig. 1. Seven studies were excluded because one was a review (Minichino et al., 2012), three included data from the same patients as in other studies already integrated in the analysis (Levkovitz et al., 2011; McGirr et al., 2014; Rosenberg et al., 2011), one included patients with a primary diagnosis of alcohol use disorder (Girardi et al., 2014), and two were case studies with one patient each (Bersani et al., 2013a; Harvey et al., 2015).

A total of $k=9$ studies (Berlim et al., 2014a; Harel et al., 2014, 2011; Isserles et al., 2011; Levkovitz et al., 2009; Rapinesi et al., 2015a, 2015b; Rosenberg et al., 2010a, 2010b), all using an open-label design and published in 2009–2015, met the following inclusion criteria for the current meta-analysis:

1. included at least five patients with a primary diagnosis of a major depressive disorder or episode according to DSM-IV or ICD-10 criteria;
2. administered DTMS treatment with H coils;
3. assessed depression severity using any version of any standardised depression rating scale, such as the Hamilton Depression Rating Scale, HDRS (Hamilton, 1960);
4. reported adequate data to compute effect sizes (if such data were not reported then the authors of studies were contacted via email by the first author).

Since only one double-blind, parallel-design RCT with active DTMS and inactive sham groups was published to date (Levkovitz et al., 2015), the results of this study are treated descriptively and are not included in the quantitative meta-analysis.

Table 1
Systematic search strategy.

k Studies	Search terms	Databases (time frame)
14 (No duplicates)	TI OR SH [{"deep transcranial magnetic stimulation" OR "deep transcranial magnetic stimulation" OR "deep repetitive transcranial magnetic stimulation" OR "deep repetitive transcranial magnetic stimulation" OR "deep rTMS" OR "deep TMS" OR "H-coil" OR "H-coil"} AND (depress* OR dysthy* OR MDD OR bipolar OR cyclothymi* OR "mani-depress*")] NOT TX (tDCS OR "transcranial direct current stimulation" OR "deep brain stimulation")	PsycINFO (any date – November 18, 2014) Medline (any date – November 18, 2014)

Note. The search was performed in English (there were no language restrictions). Abbreviations: k, number of studies; SH, subject heading; TI, title; TX, text.

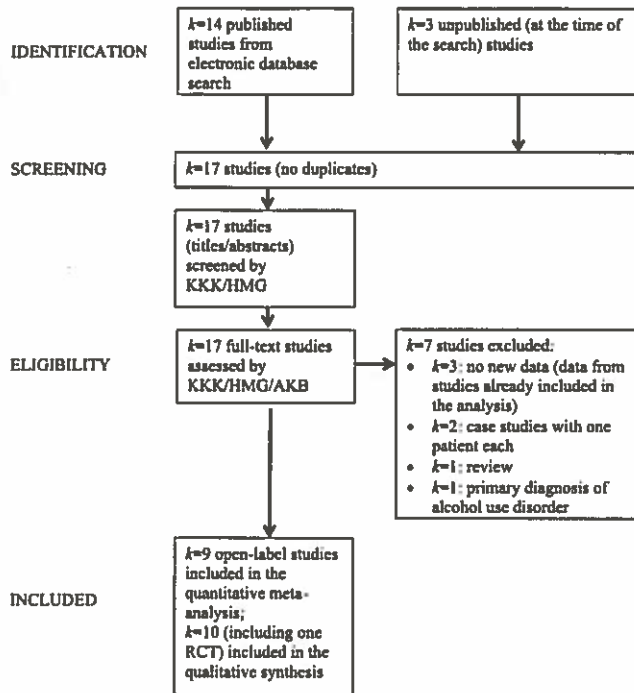


Fig. 1. Study assessment and exclusion criteria. Note. Abbreviations: DTMS, deep transcranial magnetic stimulation; k, number of studies; RCT, randomised-controlled trial with active DTMS and inactive sham DTMS groups.

2.2. Data extraction

Data were extracted from all k=9 studies independently by three authors (KKK, HMG, AKB) and any inconsistencies were resolved using a consensual approach. If available, depression scores using the intention-to-treat analysis or the last-observation-carried-forward procedure were preferred over completers-only data. The DTMS parameters, clinical and demographic patient characteristics, and effect size data are shown in Tables 2–4.

2.3. Data analysis

The current study focused on four clinically-relevant outcomes as follows:

- standardised HDRS change scores (pre-treatment baseline-post-acute DTMS treatment),
- response rates (≥ 50% reduction in HDRS scores after acute DTMS treatment),
- remission rates (according to definitions used in individual studies – final HDRS scores of < 10, ≤ 10 or ≤ 7 after acute DTMS treatment),
- acceptability (dropout rates after acute DTMS treatment compared to baseline).

The effect size used to measure the change in HDRS scores was a standardised paired difference in means, Cohen's d (for data at two points in time collected from the same patients). The interpretation criteria for the absolute size of Cohen's d are: d = .20–.49 (small), d = .50–.79 (moderate), and d ≥ .80 (large) (Cohen, 1988). A positive value of d and its 95% confidence interval (95%CI) indicate that depression severity (HDRS scores) is reduced after acute DTMS treatment compared to baseline. Since Cohen's d tends to be overestimated in studies with small samples, we have also computed Hedges' g, which is a sample-size-adjusted version of Cohen's d (Borenstein et al., 2009).

Table 2
Stimulation parameters in k=10 DTMS studies.

Study by year and first author, country	Stimulation location	Location definition (cm)	Frequency (Hz)	Intensity (% MT)	Coil type	Total stimuli	Stimuli/ session	Trains/ session	Inter-train interval (s)	No. of sessions
Levkovitz et al. (2009), Israel ^a	L	5.5	20	120	H1	33,600	1680	42	20	20
Rosenberg et al. (2010a), Israel	L	5.5	20	120	H1	33,600	1680	42	20	20
Rosenberg et al. (2010b), Israel	L	5.5	20	120	H1	33,600	1680	42	20	20
Harel et al. (2011), Israel	L	5.5	20	120	H1	33,600	1680	42	20	20
Isserles et al. (2011), Israel ^b	L	5.5	20	120	H1	33,600	1680	42	20	20
Berlim et al. (2014a), Canada	L	6	20	120	H1	60,000	3000	75	20	20
Harel et al. (2014), Israel	L	6	20	120	H	33,600	1680	42	20	20
Rapinesi et al. (2015a), Italy	L	5.5	18	120	H1	39,600	1980	55	20	20
Rapinesi et al. (2015b), Italy ^c	L	5.5	18	120	H1	39,600	1980	55	20	20
Levkovitz et al. (2015), multicentre RCT ^d	L	6	18	120	H1	39,600	1980	55	20	20

Notes. Magstim Super Rapid stimulator andBrainsway H-coil were used in all studies. For the definition of location, '5.5 cm' refers to 5.5 cm away from the motor 'hot-spot'. Abbreviations: DTMS, deep transcranial magnetic stimulation; H1, H1 coil; L, left prefrontal cortex; MT, resting motor threshold; RCT, randomised-controlled trial with an inactive sham group.

^a Data from H1 coil group only.

^b Data from 'No cognitive' group only.

^c Data from patients without alcohol use disorders.

^d Parameters of the active DTMS (sham stimulation was performed using H1-sham coil).

Table 3
Demographic and clinical characteristics of patients in $k=10$ DTMS studies.

Study by year and first author	Mean age (all patients baseline)	% Female (all patients baseline)	Diagnosis (all patients baseline)	% Bipolar (all patients baseline)	% Psychotic (all patients baseline)	Treatment-resistance	Antidepressants (all patients baseline)	Mean age of onset (years) ^f	Mean total duration of illness (years) ^f	Episodes total illness (no.) ^f	Mean duration current episode (months)
Levkovitz et al. (2009) ^d	46	48%	MDD	0%	0%	Failed 2 antidepressants current episode	–	29	17	13	32
Rosenberg et al. (2010a)	47	14%	MDD	0%	0%	Failed 2 antidepressant trials current episode	–	33	14	–	9
Rosenberg et al. (2010b)	41	67%	MDD	0%	0%	Failed ≥ 2 antidepressant courses	0%	17	24	–	19
Harel et al. (2011)	45	4/6	BDI/II	100%	0%	–	50%	27	18	–	11
Isleres et al. (2011) ^e	45	58%	MDD	0%	0%	Failed ≥ 2 antidepressants	+	29	16	4	25
Berlim et al. (2014a)	47	45%	MDD	0%	0%	Failed ≥ 2 antidepressant courses	100%	44	3	1	36
Harel et al. (2014)	41	76%	MDD	0%	0%	Failed ≥ 1 pharmacological trial or intolerant to 2 antidepressants	+	24	17	4	26
Rapinesi et al. (2015a)	56	48%	MDD	62%	0%	Failure to respond to ≥ 3 adequate doses of ≥ 2 classes antidepressants	38%	41	15	–	–
Rapinesi et al. (2015b) ^f	51	46%	BDI/II	0%	0%	Unsatisfactory response to ≥ 1 adequate course of antidepressant treatment current episode	+	34	17	–	–
Levkovitz et al. (2015) ^g	46	10/23	MDD	0%	0%	Failed 1–4 antidepressant trials or intolerant to ≥ 2 antidepressants current episode	–	26	20	–	21

Abbreviations: BDI/II, bipolar disorder (I or II); DTMS, deep transcranial magnetic stimulation; MDD, major depressive disorder; RCT, randomised-controlled trial with an inactive sham group.

^a If not reported, mean age of onset (all patients; in years) was computed as the difference between mean current age (all patients) and mean duration of total illness (all patients).

^b If not reported, mean duration of total illness (all patients; in years) was computed as the difference between mean current age (all patients) and mean age of onset (all patients).

^c Episodes (total illness) include past episodes + one (current) episode

^d Data from H1 coil group only.

^e Data from 'No cognitive' group only.

^f Data from patients without alcohol use disorders.

^g RCT data from all patients, including the sham group.

Table 4
Outcome measures (effect size data) in $k=10$ DTMS studies.

Study by year, first author	Response rate	Remission definition	Remission rate	Dropout rate	Scale	Baseline acute phase mean \pm SD (N)	Final acute phase mean \pm SD (N)
Levkovitz et al. (2009) ^{ab}	47% 9/19	HDRS \leq 10	42% 8/19	17% 4/23	HDRS24	31 \pm 4 (19)	16 \pm 13 (19) completers
Rosenberg et al. (2010a)	43% 3/7	HDRS < 10	14% 1/7	29% 2/7	HDRS24	27 \pm 4 (7)	17 \pm 7 (7) LOCF
Rosenberg et al. (2010b)	67% 4/6	HDRS < 10	17% 1/6	67% 4/6	HDRS24	31 \pm 4 (6)	16 \pm 10 (6) LOCF
Harel et al. (2011) ^b	63% 12/19	HDRS < 10	53% 10/19	11% 2/19	HDRS24	32 \pm 9 (19)	16 \pm 8 (17)
Isserles et al. (2011) ^{ac}	60% 12/20	HDRS \leq 10	30% 6/20	40% 10/25	HDRS24		16 \pm 2 (20) completers of \geq 2 treatment weeks
Berlim et al. (2014a)	71% 12/17	HDRS < 10	41% 7/17	12% 2/17	HDRS21	22 \pm 6 (17)	11 \pm 5 (17)
Harel et al. (2014) ^d	46% 12/26	HDRS \leq 10	–	10% 3/29	HDRS21		9 \pm 1 (26) completers
Rapinesi et al. (2015a)	96% 23/24	HDRS \leq 7	8% 2/24	0%	HDRS21	24 \pm 3 (24)	10 \pm 2 (24)
Rapinesi et al. (2015b) ^e	58% 7/12	HDRS \leq 7	0%	0%	HDRS17	27 \pm 6 (12)	13 \pm 4 (12)
Levkovitz et al. (2015) ^f Active DTMS Sham	38% 21%	HDRS < 10	33% 15%	8% 16%	HDRS21		

Note. Response rate was defined as at least 50% reduction in HDRS scores after the final acute DTMS treatment in all studies. Dropout rate was computed based on the number of patients who did not complete the entire acute protocol of 20 sessions compared to the sample size at baseline. All values ending with exactly 0.5 were rounded as follows to reduce the rounding error in the current analysis: zero and uneven numbers were rounded upwards (1.5=2), even numbers were rounded downwards (2.5=2). Abbreviations: DTMS, deep transcranial magnetic stimulation; HDRS, Hamilton Depression Rating Scale; LOCF, last observation carried forward; N, number of patients; RCT, randomised-controlled trial with an inactive sham group; SD, standard deviation; SEM, standard error of the mean.

^a Data from H1 coil group only were provided by the authors (SEM values of 1 at baseline and 3 after final acute DTMS were converted into SD values using the formula: $SD = SEM \times \sqrt{N}$, where $N=19$ patients).

^b Remission, response, and dropout rates are reported one week after the last DTMS session.

^c Data from 'No cognitive' group only.

^d Change from baseline (baseline – final) \pm SEM.

^e Data from patients without alcohol use disorders.

^f RCT data – per protocol sample (sample at baseline DTMS).

The effect size used to measure response, remission, and dropout rates was the event rate (i.e., the number of responders, remitters, or dropouts out of the total sample per study). The mathematical approach to computation of effect sizes used in the current analysis is explained in detail in [Supplementary materials](#).

The effect sizes were meta-analysed using Comprehensive Meta-Analysis 2.0 (CMA; Biostat, USA). The analysis was performed according to the random-effects model with inverse-variance weights (the inverse of the sum of within- and between-study variance) (Borenstein et al., 2009). This weighing method assumes that studies with low variability of scores (and thus, higher precision) have a higher weight (more influence) on the overall mean weighted effect sizes in contrast to studies with highly variable data. The random-effects model was chosen based on the following assumptions (Borenstein et al., 2009):

1. a random sample of all studies available on this topic was included in the current analysis (meaning that the observed effect sizes in the primary studies in the analysis were sampled from a distribution of the true effects in all published and unpublished studies on this topic conducted to date),
2. the effect sizes of studies included in the analysis would differ due to heterogenous methods used in the primary studies (stimulation parameters and patient characteristics),
3. the results of the current analysis could be generalised beyond the studies included in the analysis.

Heterogeneity among the effect sizes was assessed using the Q statistic and the I^2 index (Borenstein et al., 2009), where $I^2 \leq 25\%$ indicates little heterogeneity, 50% moderate heterogeneity, and $\geq 75\%$ high heterogeneity due to real differences among studies (Higgins et al., 2003).

2.4. Publication bias analysis

Publication bias refers to selecting studies with high effect sizes for a meta-analysis (Borenstein et al., 2009). Publication bias was assessed using a funnel plot of study effect sizes and their estimated precision (1/standard error of the mean, SEM) (Sterne and Egger, 2001). It was assumed that if studies are symmetrically distributed around the overall mean weighted effect size then there is little evidence for publication bias. This is because high-precision studies (that contribute most weight to the overall mean weighted effect sizes) have either low or high effect sizes instead of high effect sizes only. The same rule applies to the low precision studies which also have either low or high effect sizes. Although studies with low precision contribute little weight to the overall mean weighted effect sizes, they are often prone to publication bias. This is because such studies often include small sample sizes and are more likely to be published only if they show high (and statistically significant) effect sizes.

Presence of asymmetry in the funnel plot could indicate that publication bias might have occurred in the analysis. In this case it is important to assess the influence of such a putative publication bias on the results of meta-analysis using the trim-and-fill analysis (Duval and Tweedie, 2000). This analysis is used to mathematically correct the asymmetry in the funnel plot. The advantage of this analysis is that it graphically shows the position (precision and effect size) of the theoretically missing studies necessary to make the plot mathematically symmetrical. Furthermore, the analysis recomputes the overall mean weighted effect size by including the effect sizes from such theoretically missing studies in the calculation. If following this adjustment the magnitude of the overall mean weighted effect sizes is reduced or even reversed then publication bias might have seriously confounded the results of

the analysis. If the interpretation of results remains the same or the magnitude of the overall mean weighted effect sizes increases with the theoretically missing studies then there is little evidence for publication bias or, even if present, the effects of publication bias might be negligible in the analysis.

2.5. Sensitivity analyses

The stability of the overall mean weighted effect sizes over time was investigated using a cumulative analysis (i.e., one study at a time added to all previous studies). The influence of individual studies on the overall mean weighted effect sizes was investigated using a one-study removed analysis (i.e., one study at a time removed from the overall analysis).

3. Results

3.1. Study characteristics

The nine open-label studies included 162 patients (at baseline) and were conducted in Israel ($k=6$), Italy ($k=2$), and Canada ($k=1$; Tables 2 and 5). The RCT (Levkovitz et al., 2015) included 181 patients (at baseline) and was a multicentre study conducted at 20 medical centres in the USA, Israel, Germany, and Canada (Tables 2 and 5).

3.1.1. Stimulation parameters

In contrast to the highly variable stimulation parameters used in the studies with the conventional (figure-of-eight or circular) rTMS coils (Kedzior et al., 2014; Kedzior and Reitz, 2014), those used in the nine DTMS studies were reasonably consistent (Tables 2 and 5). The majority of studies utilised the H1-coil which induces greater stimulation over the left DLPFC (Levkovitz et al., 2009), a high frequency of stimulation (18–20 Hz), intensity of 120% of the resting motor threshold, 1680–3000 stimuli per session applied in 42–75 trains, and 20 stimulation sessions (Tables 2 and 5).

3.1.2. Patient characteristics

Most of the 162 patients in the open-label studies were treatment-resistant, unipolar, and on concurrent antidepressants (only two studies utilised DTMS as a monotherapy; Tables 3 and 5). The patients in most studies were middle-aged (with about 50% or more females) with depression onset in mid 20s, 14–24 years of illness, and 9–36 month duration of the current episode.

The RCT (Levkovitz et al., 2015) was the largest study to date with treatment-resistant, unipolar, and medication-free patients (89 received active DTMS and 92 received sham DTMS at baseline; Tables 3 and 5). Similarly to the open-label studies, the patients were middle-aged (with 48% females) with depression onset in mid 20s, 20 years of illness, and 21 month duration of the current episode.

3.2. Outcome measures

The data necessary to compute the effect sizes (HDRS change scores, response, remission, and dropout rates) are shown in Table 4. Although there were 162 patients at baseline in nine open-label studies, the HDRS change scores and response rates are computed based on 150 patients because some studies reported data for completers only. Remission rates are computed for 124 patients in eight out of nine studies that reported remission data.

3.3. HDRS change scores

Our results show that a large antidepressant effect of DTMS

Table 5
Stimulation parameters and patient characteristics in DTMS studies.

	Open-label studies ($k=9$)	RCT ($k=1$)
Stimulation parameters		
Frequency (Hz)	18–20	18
Intensity (% motor threshold)	120	120
Stimuli/session	1680–3000	1980
Trains/session	42–75	55
Intertrain interval (s)	20	20
Sessions	20	20
Patient characteristics		
Total patients at baseline	162	181
Mean age (years)	41–56	46
Proportion of females (%)	14–76	48
Mean onset age (years)	17–44	26
Mean duration of illness (years)	3–24	20
Unipolar	56% ($k=5$) studies	All patients
Treatment-resistant	89% ($k=8$) studies	All patients
DTMS as monotherapy	22% ($k=2$) studies	All patients

Note. Abbreviations: DTMS, deep transcranial magnetic stimulation; k , number of studies; RCT, randomised-controlled trial with an inactive sham group.

occurred in nine open-label studies with 150 patients. Specifically, HDRS scores were significantly reduced after acute DTMS compared to baseline (overall mean weighted $d=2.04$, 95% CI: 1.53–2.55, $k=9$; Table 6, Fig. 2A). Since most primary studies included in our analysis had relatively small sample sizes at baseline (6–29 patients; Table 4) we also computed the sample-size corrected effect size, Hedges' g (overall mean weighted Hedges' $g=1.91$, 95% CI: 1.43–2.39, $k=9$; Fig. S1). Since the interpretation of results was the same using both effect sizes, Cohen's d is reported in the subsequent analyses while the results with Hedges' g are shown in Supplementary materials.

Antidepressant effects based on HDRS change scores tended to increase over time (from 1.30 to 2.04) as studies were cumulatively added to the analysis (Fig. S2). However, the one-study removed analysis (Fig. S3) revealed that the overall effect of DTMS was marginally inflated due to one study (Rapinesi et al., 2015a). Following the exclusion of this study from the analysis, the antidepressant effect of DTMS remained large in magnitude (overall mean weighted $d=1.75$, 95% CI: 1.47–2.03, $k=8$; Fig. S3). Thus, this study was kept in the current analysis because its addition did not change the interpretation of the results.

The individual study effect sizes based on HDRS change scores varied from 1.30 to 5.29 (Fig. 2A) in nine studies in our analysis. This moderate variability ($I^2=67%$; Table 6) was attributable to one study (Rapinesi et al., 2015a) and was reduced to 0% once the latter was removed from the analysis (the effect sizes in remaining eight studies varied from 1.30 to 2.65; Fig. 2A).

Three systematic differences among studies emerged after data were coded. Therefore, the overall effect sizes were inspected in subgroups of studies grouped according to these differences: concurrent antidepressant use (all patients on antidepressants vs. all patients medication-free), depression diagnosis (all patients unipolar vs. all patients bipolar), and a number of stimuli per session (1680 vs. 1980 vs. 3000). The antidepressant effect of DTMS tended to be consistently higher in four studies with 68 patients on concurrent antidepressants ($d=1.96$, 95% CI: 1.55–2.55) compared to two studies with 26 patients who received DTMS as a monotherapy for major depression ($d=1.38$, 95% CI: .84–1.92; Fig. S4). The antidepressant effects tended to be similar in the other subgroups of studies (unipolar vs. bipolar depression; lower vs. higher number of stimuli per session; Fig. S4).

There was little evidence for publication bias in this analysis (Fig. S5).

Table 6
Outcome measures (effect sizes).

Outcome measures	Open-label studies ^a	RCT (N= 181 patients)
HDRS change scores (baseline-post DTMS) Overall mean weighted <i>d</i> (95% CI) Heterogeneity statistics	2.04 (1.53–2.55), <i>k</i> = 9, <i>N</i> = 150 patients ^a <i>Q</i> (<i>df</i> 8) = 24.10; <i>p</i> _{two-tailed} = .002; <i>I</i> ² = 67%	
Response: ≥ 50% HDRS reduction post DTMS Overall mean weighted response (95% CI) Heterogeneity statistics	60% (49–70%), <i>k</i> = 9, <i>N</i> = 150 patients ^a <i>Q</i> (<i>df</i> 8) = 12.06; <i>p</i> _{two-tailed} = .149; <i>I</i> ² = 34%	38% DTMS, 21% sham
Remission ^b Overall mean weighted remission (95% CI) Heterogeneity statistics	29% (17–44%), <i>k</i> = 8, <i>N</i> = 124 patients ^a <i>Q</i> (<i>df</i> 7) = 14.36; <i>p</i> _{two-tailed} = .045; <i>I</i> ² = 51%	33% DTMS, 15% sham
Dropouts (post DTMS compared to baseline) Overall mean weighted dropout rate (95% CI) Heterogeneity statistics	18% (10–33%), <i>k</i> = 9, <i>N</i> = 162 patients ^a <i>Q</i> (<i>df</i> 8) = 19.73; <i>p</i> _{two-tailed} = .011; <i>I</i> ² = 59%	8% DTMS, 16% sham

Abbreviations: CI, confidence interval; DTMS, deep transcranial magnetic stimulation; HDRS, Hamilton Depression Rating Scale; *k*, number of studies; *N*, number of patients; RCT, randomised-controlled trial with an inactive sham group.

^a Nine open-label studies included 162 patients at baseline. However, HDRS change scores and response rates are computed based on data from 150 patients because some studies reported data for completers only. Remission rates are computed based on data from 124 patients because one study did not report remission (Harel et al., 2014).

^b Remission was defined according to definitions used in the individual studies (final HDRS score of ≤ 7, < 10, ≤ 10).

3.4. Response rates

Ninety-four out of 150 patients in nine open-label studies responded to the acute DTMS treatment (overall mean weighted response rate of 60%, 95% CI: 49–70%; Table 6, Fig. 2B). Response rates tended to increase over time (from 47% to 60%) as studies were cumulatively added to the analysis (Fig. S6). The overall mean weighted response rate decreased to 56% when one study (Rapinesi et al., 2015a) was removed from the current analysis (Fig. S7).

Response rates varied from 43% to 96% in nine studies in our analysis (Fig. 2B). This variability (*I*² = 34%; Table 6) was attributable to one study (Rapinesi et al., 2015a) and was reduced to 0%

when the latter was removed from the analysis (response rates in remaining eight studies varied from 43% to 71%; Fig. 2B).

Response rates tended to be higher in four studies with 68 patients on concurrent antidepressants (63%, 95% CI: 51–74%) compared to two studies with 26 patients who received DTMS as a monotherapy for major depression (46%, 95% CI: 28–65%; Fig. S8). Response rates tended to be similar in the other subgroups of studies (unipolar vs. bipolar depression; lower vs. higher number of stimuli per session; Fig. S8).

There was little evidence for publication bias in this analysis (Fig. S9).

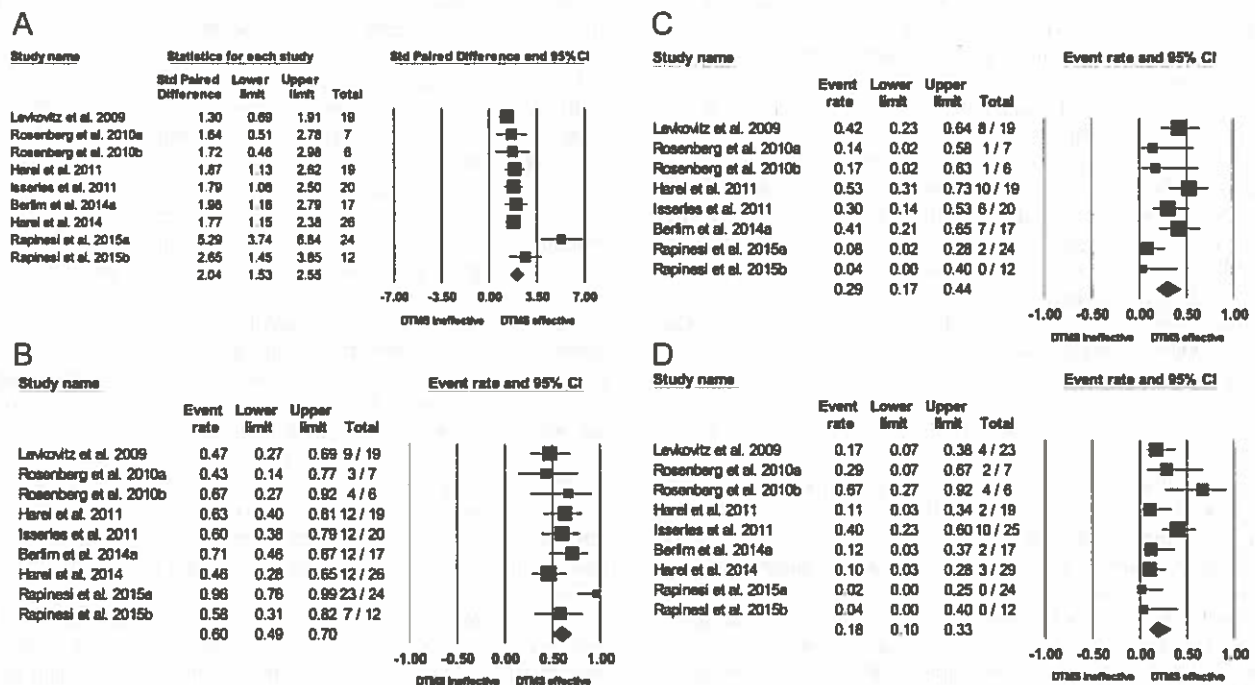


Fig. 2. Forest plots of random-effects meta-analyses of open-label studies. Note. Abbreviations: CI, confidence interval; DTMS, deep transcranial magnetic stimulation; HDRS, Hamilton Depression Rating Scale; Std Paired Difference, standardised paired difference in means (Cohen's *d*; effect size). A. Standardised HDRS change scores (baseline - after acute DTMS); B. Response rates after acute DTMS; C. Remission rates after acute DTMS; D. Dropout rates after acute DTMS.

3.5. Remission rates

Remission rates are computed based on data from 124 patients because one study (Harel et al., 2014) did not report remission. Thirty-five out of 124 patients in eight open-label studies remitted after the acute DTMS treatment (overall mean weighted remission rate of 29%, 95% CI: 17–44%; Table 6, Fig. 2C). Remission rates tended to decrease over time (from 42% to 29%) as studies were cumulatively added to the analysis (Fig. S10). However, this apparent decrease might have been due to low remission rates resulting from a more conservative cut-off for remission (final HDRS score of ≤ 7) used in the two most recent studies (Rapinesi et al., 2015a, 2015b) compared to the earlier studies in the analysis (Table 4). Indeed, the overall mean weighted remission rate increased to 39% when the two recent studies (Rapinesi et al., 2015a, 2015b) were removed from the current analysis or when each of the two studies was removed from the analysis one at a time (Figure S11).

Remission rates varied from 0% to 53% in eight studies in our analysis (Fig. 2C). This moderate variability ($I^2=51\%$; Table 6) was attributable to two studies (Rapinesi et al., 2015a, 2015b) and was reduced to 0% when both studies were removed from the analysis (remission rates in the remaining six studies varied from 14% to 53%; Fig. 2C).

Remission rates tended to be similar in all subgroups of studies (on antidepressants vs. medication-free; unipolar vs. bipolar depression; lower vs. higher number of stimuli per session; Fig. S12).

There was little evidence for publication bias in this analysis (Fig. S13).

3.6. Dropout rates

Twenty seven out of 162 patients dropped out from nine open-label studies between baseline and the last acute DTMS session (overall mean weighted dropout rate of 18%, 95% CI: 10–33%; Table 6, Fig. 2D). Dropout rates increased over time from 17% to 33% in the earlier studies (from 2009–2010) and then decreased to 18% as further studies (from 2011–2015) were cumulatively added to the analysis (Fig. S14). The overall mean weighted dropout rate remained stable around 16% to 21% as each study was removed from the current analysis one at a time (Fig. S15).

Dropout rates varied from 0% to 67% in nine studies in our analysis (Fig. 2D). This moderate variability in dropout rates ($I^2=59\%$; Table 6) was not dependant on any one study alone.

Dropout rates tended to be similar in all subgroups of studies (on antidepressants vs. medication-free; unipolar vs. bipolar depression; lower vs. higher number of stimuli per session; Fig. S16).

Publication bias could not be ruled out in this analysis (Fig. S17). Specifically, the overall mean weighted dropout rate would have increased from 18% to 23% if two theoretically missing studies with higher than average dropout rates were included in the current analysis (Fig. S17).

3.7. Qualitative comparison between open-label studies and RCT

The stimulation parameters and patient characteristics in the RCT (Levkovitz et al., 2015) were similar to those reported in nine open-label studies included in our analyses (Tables 2–5). One important exception was that DTMS was administered as a monotherapy for major depression in the RCT (Levkovitz et al., 2015) and in only two out of nine open-label studies. Furthermore, the RCT (Levkovitz et al., 2015) was conducted on unipolar patients while two out of nine open-label studies included mostly or only bipolar patients.

Since the effect size of .76 in the RCT (Levkovitz et al., 2015) was computed by comparing regression slopes in two groups (active

DTMS and sham), it is not directly comparable to the standardised difference in mean HDRS scores (Cohen's *d*) at baseline and after acute DTMS in one group only (active DTMS) used in the current meta-analysis. However, compared to the active DTMS group in the RCT (Levkovitz et al., 2015), all other outcome measures (response, remission, and dropout rates) were more prominent in the open-label studies (Table 6). Interestingly, the response rate of 46% and the remission rate of 32% in two open-label studies with DTMS as a monotherapy (Figs. S8 and S12) tended to be similar to those reported in the active DTMS group in the RCT (38% and 33% respectively) (Levkovitz et al., 2015) while the dropout rate was higher in two open-studies (20%, Fig. S16) compared to the RCT (8%) (Levkovitz et al., 2015).

4. Discussion

Based on the results of the current exploratory meta-analysis of nine open-label studies and the outcome of the only RCT published to date (Levkovitz et al., 2015), it appears that high-frequency DTMS is efficacious and acceptable as an acute treatment for major depression. The large magnitude of the overall effect size based on the pre-post differences in HDRS scores in the current analysis was likely inflated by the open-label nature of the included studies (i.e. the possible placebo and expectancy effects). While the standard practise is to deduct the effect of placebo from the active treatment in a meta-analysis, the placebo effect is actually added to the effect of a real treatment in clinical practise (Aleman et al., 2014). Thus, the significant antidepressant effects of DTMS observed in the current meta-analysis might be comparable to those observed in naturalistic settings involving more 'real world' patients (Berlim et al., 2014a).

The current results cannot be entirely explained by the placebo effect because there is compelling RCT-based evidence that DTMS is significantly more clinically effective than sham DTMS in unipolar, treatment-resistant, and medication-free patients with major depression (Levkovitz et al., 2015). However, it remains unclear which brain stimulation methods produce the best clinical effects in the treatment of major depression. Therefore, future research should focus on comparing the antidepressant effects of DTMS and conventional rTMS using head-to-head randomised, controlled designs. In general, it appears that the conventional rTMS, pharmacotherapy, and psychotherapy produce similar (moderate) effect sizes in the treatment of major depression (Cuijpers et al., 2013; Lepping et al., 2014). Thus, direct comparisons are necessary to establish whether any of the currently available brain stimulation methods (including DTMS) is clinically superior for acutely treating major depression in terms of higher efficacy and/or acceptability/safety.

The high effect sizes observed in the current meta-analysis might have resulted from the larger volume of cortical stimulation produced by the H1 coil (Berlim et al., 2014a) and/or the possible deeper penetration of stimulation (Zangen et al., 2005). Such stimulation of more widespread brain structures could increase the activity of brain regions linked to cognitive functioning, such as working memory (Harvey et al., 2015). Therefore, the clinical improvement after DTMS could be concurrent or even secondary to improvements in cognitive functioning (Bersani et al., 2013b). Although still limited, the evidence so far suggests that DTMS might in fact improve various cognitive domains, such as sustained attention, visuospatial memory, cognitive planning, and working memory (Levkovitz et al., 2009; Minichino et al., 2012). DTMS was also found to improve four out of five quality of life domain scores (global, psychological, environmental, and social) in treatment-resistant depression patients (with associated moderate to large effect sizes) (Berlim et al., 2014a). Finally, personality

characteristics of patients might moderate the response to therapy, including DTMS. For example, depression patients who scored higher on agreeableness and conscientiousness at baseline achieved higher remission rates following DTMS treatment (McGirr et al., 2014). Therefore, it appears that the response to DTMS might depend on optimised stimulation parameters combined with specific personality characteristics. DTMS might improve the cognitive abilities and the clinical symptoms in depression patients through different neural systems. Neuroimaging studies are required to better understand the neural bases of DTMS particularly since it is unclear which symptoms improve first (clinical or cognitive) and if there is a cause–effect relationship between the improvements in these two domains.

All primary studies included in the current meta-analysis used well-optimised stimulation parameters, including high-frequency of stimulation (18–20 Hz), high intensity, and adequate stimulation period (daily for one month) during the acute phases. Such parameters have been often associated with more prominent antidepressant effects in the conventional rTMS literature (George et al., 2010). Although particularly high-frequency rTMS shows clinically-relevant antidepressant effects (Berlim et al., 2014b; Kedzior et al., 2014), low-frequency and bilateral rTMS also appear to reduce depression severity in treatment-resistant depression (Berlim et al., 2013a, 2013c; Kedzior et al., 2014). Therefore, future studies should also assess the efficacy of low-frequency DTMS in the treatment of major depression. It is also important to investigate if DTMS paradigms with a higher number of stimuli per session would produce better clinical outcomes.

The current results suggest that antidepressant effects occur after 20 sessions of DTMS compared to baseline. However, a systematic review comparing the antidepressant effects of DTMS, electroconvulsive therapy (ECT), and conventional rTMS showed that a clinically-relevant effects of DTMS might be observed already after 10 sessions (two weeks) of DTMS in medication-free patients with unipolar depression (Minichino et al., 2012). The weighted effect sizes from seven out of nine open-label studies included in the current meta-analysis (Kedzior and Gellersen, 2015) and the (unweighted) effects from the RCT (Levkovitz et al., 2015) do not support this claim. Specifically, it appears that all antidepressant effects (HDRS change score, response, and remission) improved after 20 sessions (four weeks) compared to 10 sessions (two weeks) of high-frequency DTMS in mostly treatment-resistant patients with unipolar or bipolar depression who were either medication-free or receiving concurrent antidepressants (Kedzior and Gellersen, 2015; Levkovitz et al., 2015). It is unlikely that these improvements in effects resulted from antidepressants alone because the RCT data (Levkovitz et al., 2015) were collected from medication-free patients. However, further primary studies are needed to investigate if concurrent antidepressants enhance the acute effects of DTMS using randomised, controlled designs.

The current meta-analysis focused on the acute effects of DTMS. Meanwhile, there is evidence for durability of the antidepressant effects of conventional rTMS beyond the acute stimulation phase without maintenance treatment (Kedzior et al., 2015). Similarly, data from three of nine open-label studies included in the current meta-analysis suggest that the antidepressant effects of DTMS are durable for up to 12 months after the acute stimulation without maintenance treatment (Gellersen and Kedzior, 2015). However, maintenance treatment might improve and prolong the acute effects of DTMS (Gellersen and Kedzior, 2015). Specifically, response and remission rates observed after active daily DTMS remained stable following biweekly active maintenance stimulation for 12 weeks in the RCT (Levkovitz et al., 2015). Similarly, response and remission rates were higher in patients who received 12 weeks of maintenance treatment compared

to no maintenance treatment in one open label study included in our analysis (Rapinesi et al., 2015a). On the other hand, a second course of DTMS produced lower response rates in patients who initially responded well to DTMS but who relapsed within one year (Rosenberg et al., 2011). Thus, it is yet unclear whether tolerance (or even resistance) to DTMS could develop following the reintroduction of this treatment (Rosenberg et al., 2011). Therefore, the durability of antidepressant effects of DTMS beyond the acute stimulation (with or without maintenance treatment) should be investigated in future studies.

There were a number of limitations in the current study. First, since the DTMS method is still relatively new, our analysis is based on results of open-label studies without sham control groups. Thus, it is difficult to distinguish between the placebo and the real effects of DTMS in these studies. There is, however, indirect evidence to suggest that placebo response rates are lower in patients with more resistant depressive episodes (Fournier et al., 2010). Thus, placebo effects might have also been low in the mostly treatment-resistant patients who participated in the primary studies included in this analysis. Second, due to the low number of studies in the analysis we were unable to investigate the predictors of response to DTMS. Interestingly, the current results show that consistent stimulation parameters produce consistent magnitudes of effect sizes in relatively heterogeneous groups of patients (mostly treatment-resistant with unipolar or bipolar depression, on concurrent antidepressants or medication-free and with varying proportions of female patients, and with varying ranges of age, age of onset, total duration of illness, number of episodes, and length of the current episode). Overall, the current preliminary evidence suggests that DTMS might be effective for treating patients with both unipolar and bipolar depression who are resistant to pharmacotherapy and ill for prolonged periods of time. However, the effects of DTMS in bipolar depression need to be tested in larger samples because there were very few patients with bipolar depression in two open-label studies in the current analysis. Third, although the overall remission rate was similar in the active DTMS group in the RCT (Levkovitz et al., 2015) and in the open-label studies, different cut-off scores were used to define remission in the primary studies included in this analysis (Table 4). Future studies should use consistent cut-off scores depending on a specific version of HDRS (with 17, 21, or 24 items) to standardise the definition of remission in depression research. This is particularly important because the goal of any treatment, including DTMS, is to achieve an asymptomatic state with complete functional recovery which needs to be systematically and consistently defined in primary research before it can be synthesised in a meta-analysis (Lecrubier, 2002). Indeed, our results show that remission rate was particularly similar when the same definition for remission (final HDRS score of ≤ 10) was used in two open-label studies with DTMS as a monotherapy for major depression (Levkovitz et al., 2009; Rosenberg et al., 2010a) and the active DTMS group in the RCT (Levkovitz et al., 2015). Fourth, although the effect sizes (HDRS change scores and response rates) tended to be consistently lower in studies with DTMS as a monotherapy compared to studies with patients on concurrent antidepressants, it cannot be ruled out that this apparent trend is due to other factors than antidepressants alone. Specifically, both studies with medication-free patients (Levkovitz et al., 2009; Rosenberg et al., 2010a) were the first studies which utilised DTMS in the treatment of major depression. Therefore, patients included in these two studies might have been more severely treatment-resistant towards any therapy (including DTMS) compared to patients in the subsequent studies. Furthermore, one of the studies (Rosenberg et al., 2010a) included mostly male patients (86%). High proportions of male patients were associated with lower antidepressant effects in studies utilising conventional rTMS in the treatment of major depression

(Kedzior et al., 2014). Future studies are required to investigate if concurrent antidepressants could enhance the antidepressant effects of DTMS. Fifth, we have not explicitly assessed the quality of data in this meta-analysis. While the assessment criteria proposed by The Cochrane Collaboration focus mostly on the quality of randomisation and blinding within studies (Moja et al., 2005), these criteria were not applicable to this new field of research with mostly open-label study designs. Instead, we assessed the quality of studies with criteria commonly used in 965 other systematic reviews (Moja et al., 2005), including (a) application of a systematic study selection procedure according to the PRISMA guidelines (Moher et al., 2009), (b) exploration of the heterogeneity among effect sizes by inspecting plots, testing the impact of individual studies on the overall results, and conducting subgroup analyses, (c) conducting a publication bias analysis, and (d) utilisation of a weighting method which assigns higher weights to studies with higher precision of data. Finally, we have not included any grey (unpublished) data in the current analysis. There was little evidence for publication bias in the current analysis or, even if present, little influence of a putative publication bias on the current results. However, it cannot be ruled out, that additional studies with smaller (non-significant) effect sizes exist but are not published to date.

5. Conclusions

The current study suggests that the high-frequency DTMS is efficacious and acceptable in the treatment of particularly unipolar and resistant depression. Future studies should investigate if concurrent treatment with antidepressants could further enhance the efficacy of DTMS and if the effects of DTMS would persist beyond the acute stimulation phase without maintenance treatment. Furthermore, the effectiveness of DTMS needs to be tested in larger samples with bipolar depression. It is also of interest to compare the acute and long-term clinical effectiveness of DTMS with other brain stimulation methods applied in the treatment of major depression utilising RCTs with inactive sham groups.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jad.2015.08.033>.

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