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ORIGINAL RESEARCH

More female patients and fewer stimuli per session are associated with the short-term antidepressant properties of repetitive transcranial magnetic stimulation (rTMS): a meta-analysis of 54 sham-controlled studies published between 1997–2013

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Background: Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) appears to have short-term antidepressant properties. The aim of the current study was to update our previous meta-analysis and to investigate factors associated with the antidepressant properties of rTMS.

Method: Following a systematic literature search conducted in Medline and PsycInfo, N=14 sham-controlled, parallel design studies (published after 2008 to August 2013) that had utilized rTMS of the DLPFC in major depression were included in the current meta-analysis. The sensitivity and moderator analyses also included data from N=40 studies (published in 1997–2008) from our previous meta-analysis. The effect size (Cohen's *d*) in each study was the standardized difference in mean depression scores (on Hamilton Depression Rating Scale, Beck Depression Inventory, Montgomery Åsberg Depression Rating Scale) from baseline to final (after last session) in rTMS compared to sham groups.

Results: According to a random-effects model with inverse-variance weights, depression scores were significantly reduced after rTMS compared to sham in studies published from 2008–2013 based on N=659 patients (overall mean weighted *d*=–0.42, 95% confidence interval: –0.66, –0.18, *P*=0.001). Combining studies from our past and current meta-analyses (published in 1997–2013; N=54) revealed that depression was significantly reduced after left-fast (>1 Hz), right-slow (≤1 Hz), and bilateral (or sequential) rTMS of DLPFC compared to sham. Significant antidepressant properties of rTMS were observed in studies with patients who were treatment resistant, unipolar (or bipolar), non-psychotic, medication-free (or started on antidepressants concurrently with rTMS). According to univariate meta-regressions, depression scores were significantly lower in studies with more female patients and fewer stimuli per session. There was little evidence that publication bias occurred in the analysis.

Conclusion: According to this study, the largest meta-analysis to date, short-term antidepressant properties of rTMS are independent of concurrent antidepressants and might depend on sex and the number of stimuli per session.

Keywords: repetitive transcranial magnetic stimulation (rTMS), depression, sham-controlled, DLPFC, meta-analysis, systematic review

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Background

A large volume of academic publications has been dedicated to the antidepressant properties of repetitive transcranial magnetic stimulation (rTMS) in the treatment of

major depression. Our search of the Medline and PsycInfo databases identified N=963 sources (duplicates excluded) with terms "rTMS" and "depression" in their titles or subject between (any date to September 2013). A vast majority of these sources are narrative literature reviews largely suggesting that approximately ten sessions of daily rTMS appear to be effective in acute cases of major depression (or major depressive episode) in the short-term (by comparing depression scores before the first versus after the last session of rTMS). However, the exact factors mediating the antidepressant properties of rTMS are still not well understood. According to randomized-controlled trials (RCTs) and open-label studies conducted on mostly unipolar patients, rTMS was more effective in patients who were younger,[1,2] less treatment-resistant (in the current episode or with less prior treatment failures),[1,3–5] with a shorter current episode,[3,5] and without a comorbid anxiety disorder.[5] Furthermore, extension trials in patients who failed to respond during the short-term, double-blind phases of studies showed that the antidepressant response to rTMS was superior in female patients,[5] was observed only after longer stimulation periods (such as 4 weeks or more),[5,6] and required an alteration in the stimulation site and frequency (from left-fast to right-slow rTMS of dorsolateral prefrontal cortex [DLPFC]).[6]

Surprisingly, the antidepressant predictors of rTMS from the primary studies listed above have not been systematically confirmed in the relevant 17 quantitative meta-analyses (published 2001–2013) of the high-quality primary studies (sham-controlled randomized trials).[7–23] According to the meta-analyses to date, the short-term antidepressant properties were most consistently observed in studies using the fast (>1 Hz) rTMS of the left DLPFC.[22,24] The slow (≤1 Hz) rTMS of the left or right DLPFC and bilateral or sequential designs were also effective at reducing depression severity in the short-term but were utilized in only very few primary studies.[14,18,19,21,23]

Similarly to the RCTs, the benefit of longer study designs (with ten or 15 rTMS sessions) in treating depression has already been noted in the earlier meta-analyses.[9,12,15] However, neither duration of study and other rTMS parameters (frequency of stimulation, motor threshold, stimuli/session, total stimuli) nor mean age of patients were associated with the effect sizes in meta-analyses.[8,14,17,19,20,23] Furthermore, rTMS was effective in studies with medicated or medication-free patients,[11,14,19,22,23] as well as in studies with medication-resistant patients.[14,16,17,20] However, a better outcome was expected with less resistance.[8,15] Finally, the antidepressant effect of rTMS was higher in studies with non-psychotic patients[19] but was similar in studies with unipolar versus bipolar patients.[20,23]

One reason for such inconsistent findings is that most past meta-analyses included too few studies to reliably detect any differences in effect sizes based on study characteristics (clinical and/or rTMS parameters). Furthermore, unlike in meta-analyses, predictors of rTMS response were often identified during different (open-label and/or follow-up) phases of primary studies. Finally, meta-analyses were computed based on group data compared to primary studies that had utilized individual patient data.

In an attempt to improve the statistical power of the past analyses, we have conducted a meta-analysis on N=40 sham-controlled studies selected from the past 13 meta-analyses[4,7–14,16–19] published between 2001 and 2010. A short-term antidepressant effect of the left-fast rTMS of DLPFC was univariately observed in studies with higher proportions of female patients not controlling for any other study characteristics (clinical and/or properties of rTMS). The antidepressant effect of the left-fast rTMS was also present in studies with patients who were medication-free, unipolar (or bipolar), treatment-resistant and without psychotic features.

The current study had three main aims. Since our previous meta-analysis included primary studies published up to 2008, the first aim of the current study was to update our results by conducting a new meta-analysis of the short-term effects of rTMS in depression in studies published after 2008 until August 2013. These "new" studies were located using a novel systematic literature search in contrast to the N=40 "old" studies in our previous meta-analysis that were selected from the past 13 meta-analyses published in 2001–2010. Thus, the second aim of the current study was to compare the overall mean weighted effect sizes of the "old" studies with the "new" studies due to the different methods of searching for primary studies utilized in the two meta-analyses. Furthermore, our previous meta-analysis focused on the characteristics of studies that had utilized only the left-fast rTMS of DLPFC. Thus, the third aim of the current analysis was to find out if any patient characteristics or rTMS parameters would be associated with the short-term antidepressant properties of rTMS in all "new" and "old" sham-controlled studies published between September 1997 and August 2013. The reason for combining all studies was to improve the statistical power of all statistical (moderator and subgroup) analyses.

Based on our and other past meta-analyses, it was hypothesized that depression would be reduced following the active rTMS compared to sham in the "new" studies (those after

2008). It was expected that such an antidepressant effect would be higher in the "new" compared to the "old" studies if the quality of the more recent studies has improved due to more advanced stimulators and better established parameters of rTMS. Based on our past meta-analysis of the left-fast rTMS studies, it was expected that, when combining all studies regardless of rTMS parameters, depression scores would be significantly reduced in studies with higher proportions of female patients. We also expected that, based on results from primary studies, the antidepressant properties of rTMS could be related to other patient characteristics and/or rTMS parameters if the statistical power of such comparisons were improved by adding the "new" studies to the "old" ones.

Methods

Systematic literature search and study selection

The details of the systematic literature search are shown in Table 1. A "control search" was first conducted in the PsycInfo and Medline databases for N=40 studies published between 1995 and 2008 that were included in our previous meta-analysis. These N=40 studies were obtained from the past 13 meta-analyses (published 2001–2010) rather than from a systematic literature search (Table S1). Since all N=40 studies were located during the control search, we concluded that these two databases were adequate for performing the current literature search for studies published in (any month of) 2008 until August 2013.

The results of the systematic literature search and the study selection procedure are summarized in the PRISMA flowchart (Figure 1).[25] Following the exclusion of irrelevant studies (based on titles and abstracts), N=50 primary studies were assessed in full-length (Figure 1 and Table S2). A total of N=18 out of 50 "new" studies (published 2010–2013) located during our systematic search met the inclusion criteria for the current analysis (none of the studies published in 2009 met the inclusion criteria). Most studies were excluded because they were not sham-controlled or contained data published in other studies already included in the current analysis (other exclusion criteria are listed in Figure 1). The inclusion criteria for the current meta-analysis were:

1. sham-controlled parallel design;
2. major depressive disorder or episode diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) or International Statistical Classification of Diseases and Related Health Problems (ICD-10) criteria;
3. depression severity assessed using any version of a standardized scale (Hamilton Depression Rating Scale (HAMD),[26] Beck Depression Inventory (BDI),[27] and Montgomery Åsberg Depression Rating Scale (MADRS[28]));
4. and active rTMS and sham administered at the same location of DLPFC (left, right, or bilateral).

As explained in the Results section, four of the 18 "new" studies were identified as outliers and removed from all analyses. Thus, the current meta-analysis was performed on N=14 "new" studies. To improve the power of comparisons, the sensitivity analyses also included data from N=40 "old" studies (published in 1997–2008) from our previous meta-analysis (Table S1).

Table 1 Details of the systematic search strategy (all searches were performed in English with no language restrictions)

Search	Search terms	Databases (time frame)
Search 1 N=821	[TI or SU ("transcranial magnetic stimulation" or "trans- cranial magnetic stimulation" or "repetitive transcranial magnetic stimulation" or "repetitive trans- cranial magnetic stimulation" or TMS or rTMS)] AND [TI or SU (depress* or dysthy* or MDD or cyclothym* or bipolar or "mani*- depress*")]	PsycInfo and Medline (any date – 2008)
Search 2 N=584[a]	[TI or SU ("transcranial magnetic stimulation" or "trans- cranial magnetic stimulation" or "repetitive transcranial magnetic stimulation" or "repetitive trans- cranial magnetic stimulation" or TMS or rTMS)] AND [TI or SU (depress* or dysthy* or MDD or cyclothym* or bipolar or "mani*- depress*")]	EBSCO PsycInfo and Medline (2008 – August 2013)
Search 3 N=128[a]	[Title, Abstract, Keywords ("transcranial magnetic stimulation" or "trans-cranial magnetic stimulation" or "repetitive transcranial magnetic stimulation" or "repetitive trans- cranial magnetic stimulation" or TMS or rTMS)] AND [Title, Abstract, Keywords (depress* or dysthy* or MDD or cyclothym* or bipolar or "mani*- depress*")]	Cochrane Library (Category searched: Trials) (2008 – August 2013)

Notes: Search 1 was a "control search" to find out if the N=40 studies included in the past 13 meta-analyses (published in 2001–2010) could be located using two databases only. Since the search detected all these resources, Search 2 was conducted on PsycInfo and Medline that appeared to have an adequate coverage of studies in this area. Search 3 of the Cochrane library did not identify any additional studies than Search 2. [a]Duplicates excluded within search.
Abbreviations: MDD, major depressive disorder; N, number of sources; rTMS, repetitive transcranial magnetic stimulation; SU, subject; TI, title.

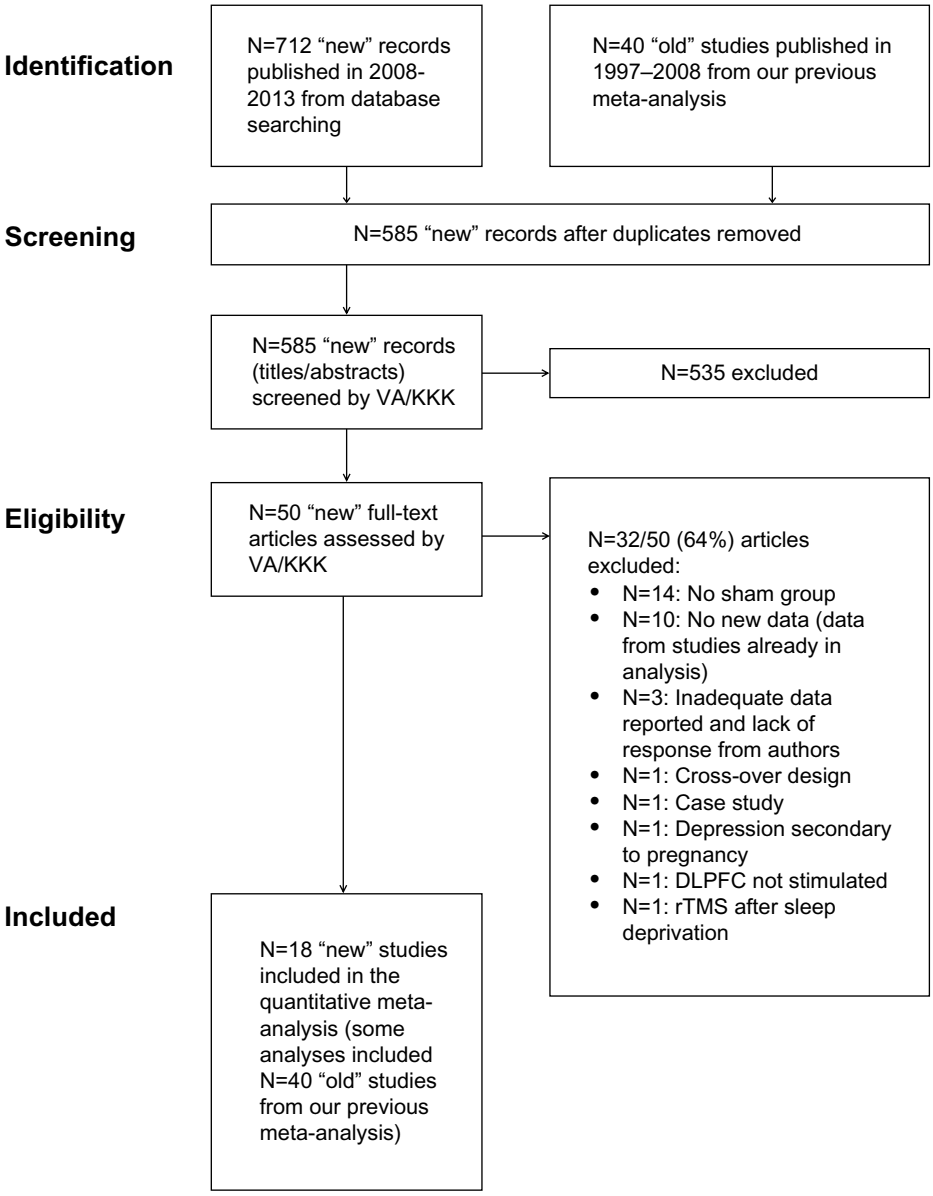

Figure 1 Study assessment and exclusionary criteria.
Abbreviations: DLPFC, dorsolateral prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation.

Data extraction

Data were extracted from all N=18 studies by two authors (VA and KKK) independently and any inconsistencies were resolved (there were no major inconsistencies requiring additional experts' opinion). The rTMS parameters are shown in Table 2, and the clinical and demographic characteristics of patients are shown in Table 3.

Meta-analysis

The mathematical approach used in the current meta-analysis is based on the method of Hedges et al.[29] The mean depression scores at baseline as well as after the last session (final) in the sham and the active rTMS groups in each study are listed in Table 3. The mean (M) and standard deviations (SD) of depression scores in the sham and the active rTMS groups were computed for each group separately in SPSS version 21 (IBM Corporation, Armonk, NY, USA) using the difference score (depression score at baseline – final). These difference scores and their SD are shown in the last two columns of Table 3. Multiple independent subgroups of patients were combined into one active rTMS and one sham group per scale and per study to comply with the assumption of meta-analysis that each study should contribute only one effect size to the overall

Table 2 rTMS parameters in the N=18 studies included in the current meta-analysis

Year	Study country	DLPFC location	Definition of location	Frequency (Hz)	Motor threshold (%)	Coil type	Coil diameter (mm)	Coil angle sham (°)	Stimuli/ session	Trains/ session	Inter-train interval (s)	Number of sessions	Stimulator (company)
2010	George et al[46]; USA	L	5 cm/MRI	10	120	F8	–	TS	3,000	75	26	15	Neuronetics
	Paillere Martinot et al[50]; France[a]	L	5 cm	10	90	F8	–	TS	1,600	20	60	10	MagStim
	Pallanti et al[51]; Italy[b]	B R L	5 cm	6*	105*	F8	70	TS	1,420	23	28*	15	MagStim
	Triggs et al[52]; USA	L R	5 cm	5	100	F8	70	TS	2,000	50	22	10	MagStim
	Zheng et al[41]; People's Republic of China	L	5 cm	15	110	F8	–	90	3,000	50	–	20	MagPro
2011	Aguirre et al[53]; Spain	R	5 cm	1	110	F8	85	90	1,200	20	45	20	MagPro
	He et al[54]; People's Republic of China[c]	B	–	9*	–	–	–	TI	–	–	–	10	Self-made
	Lingeswaran[55]; India	L	5 cm	10	100	F8	–	90	–	10	60	12	MagStim
	Ray et al[39]; India	L	5 cm	10	90	F8	–	45	1,200	20	24	10	MagStim
2012	Bakim et al[56]; Turkey[d]	L	5 cm	20	110	F8	–	45	800	20	28	30	MagStim
	Blumberger et al[57]; Canada[e]	L	5 cm	10	110*	F8	70	90	1,450	39*	30	15	MedTronic
	Fitzgerald et al[58]; Australia[f]	B R L	MRI	6*	120	F8	70	45	–	31	–	15	MagPro
	Huang et al[59]; People's Republic of China	L	5.5 cm	10	90	F8	–	90	800	20	56	10	MagStim
	Peng et al[38]; People's Republic of China	L	5 cm	15	110	F8	–	90	3,000	50	30	20	MagPro
2013	Chen et al[60]; People's Republic of China	L	5 cm	20	90	F8	–	90	–	20	34	10	MagStim
	Hernandez-Ribas et al[61]; Spain	L	5 cm	15	100	F8	–	90	1,500	20	60	15	MagStim
	Spampinato et al[40]; Italy	L	5 cm	10	120	F8	70	45	3,000	–	26	20	MagStim
	Speer et al[62]; USA	L	5 cm	1 20	110	F8	–	45	1,600	1 40	– 28	15	Cadwell

Notes: *Mean values; [a]only the "standard rTMS" group is included in the current analysis (patients in the positron emission tomography [PET]-guided rTMS group received rTMS at individually-determined target positions on the left or on the right hemisphere); [b]since sham was applied bilaterally, only the active bilateral rTMS condition is included in the current analysis; [c]only the "conventional rTMS" group is included in the current analysis (patients in the sleep electroencephalogram [SEM]-modulated rTMS group received rTMS to the frontal, occipital, and temporal areas); [d]since sham was administered at 110% MT, only the active rTMS with 110% MT group is included in the current analysis; [e]since sham was administered unilaterally, only the unilateral rTMS group is included in the current analysis; [f]since sham was administered bilaterally, only the bilateral rTMS group is included in the current analysis. The left rTMS condition included sham to the right DLPFC. For the definition of location, 5 cm refers to 5 cm rostral (anterior) to the sagittal (parasagittal) plane.

Abbreviations: B, bilateral DLPFC; DLPFC, dorsolateral prefrontal cortex; F8, figure-of-eight shape; L, left DLPFC; MRI, magnetic resonance imaging; R, right DLPFC; rTMS, repetitive transcranial magnetic stimulation; TI, tangential with inactive coil; TS, tangential with sham coil containing embedded magnetic shield.

Table 3 Patient characteristics and depression scores in the active rTMS and sham groups in N=18 studies

Study diagnostic system; diagnosis	Data source	Mean age (all patients)	% female (all patients)	Treatment-resistance (failed trials)[A]	Bipolar depression (%)[B]	Psychotic depression (%)[C]	Medication[D]	Scale[E]	Mean ± SD (N) depression severity score				Mean ± SD (N) depression severity score	
									Baseline (pre)		Last session (post)[F]		Baseline – last session[F]	
									Sham	Active rTMS	Sham	Active rTMS	Sham	Active rTMS
George et al[46]; DSM-IV, MDD[a]	Tab 5	47	57 108/190	some (1–4)	–	–	–	HAMD24	27±5 (98)	26±5 (92)	23±7 (91)	22±9 (83)	4±6 (94)	4±8 (88)
								MADRS	30±6 (98)	29±7 (92)	28±9 (91)	25±11 (83)	2±8 (94)	4±10 (88)
Paillere Martinot et al[50]; DSM-IV, MDD	Auth	47	66 21/32	+ (≥2)	+ 28%	N/A	+	HAMD21	26±7 (14)	26±6 (18)	19±10 (14)	15±11 (18)	7±9 (14)	11±10 (18)
								MADRS	35±6 (14)	32±8 (18)	24±12 (14)	17±12 (18)	11±10 (14)	15±11 (18)
Pallanti et al[51]; DSM-IV, MDD	Tab 1B Fig 1B	48	58 23/40	+ (≥2)	N/A	–	+	HAMD21	29±4 (20)	29±6 (20)	28±4 (20)	22±4 (20)	1±4 (20)	7±5 (20)
Triggs et al[52]; DSM-IV, MDD	Tab 3 (all)	46	60 29/48	+ (≥2)	+ 4%	N/A	+	HAMD24	28±3 (14)	28±5 (34)	18±10 (14)	17±9 (34)	10±9 (14)	11±8 (34)
	Tab 3 R								27±3 (7)	27±5 (16)	13±7 (7)	14±8 (16)	14±6 (7)	13±7 (16)
	Tab 3 L								28±4 (7)	28±6 (18)	22±12 (7)	20±9 (18)	6±11 (7)	8±8 (18)
	Tab 3 (all)							BDI21	29±7 (14)	31±10 (34)	19±12 (14)	18±13 (34)	10±10 (14)	13±12 (34)
	Tab 3 R								31±6 (7)	32±9 (16)	15±10 (7)	15±13 (16)	16±9 (7)	17±12 (16)
	Tab 3 L								27±7 (7)	30±11 (18)	23±13 (7)	21±12 (18)	4±11 (7)	9±12 (18)
Zheng et al[41]; DSM-IV, MDE	Tab 1	27	35 12/34	+ (≥2)	–	–	+	HAMD17	25±3 (15)	25±3 (19)	23±3 (15)	14±5 (19)	2±3 (15)	11±4 (19)
								BDI21	21±4 (15)	21±4 (19)	20±5 (15)	14±5 (19)	1±5 (15)	7±5 (19)
Aguirre et al[53]; DSM-IV, MDD	Auth	47	68 23/34	some (≥1)	–	–	+	HAMD17	19±5 (15)	19±6 (19)	16±4 (15)	15±5 (19)	3±5 (15)	4±6 (19)
He et al[54]; DSM-IV, DYS/MDD	Auth	39	70 56/80	N/A	–	N/A	–	HAMD24	24±4 (43)	23±4 (37)	24±5 (43)	21±4 (37)	0±5 (43)	2±4 (37)
Lingeswaran[55]; DSM-IV, DYS/MDD	Tab 2 Tab 3	36	61 14/23	some	–	–	+	HAMD17	22±3 (14)	23±4 (9)	12±3 (14)	13±5 (9)	10±3 (14)	10±5 (9)
								MADRS	31±6 (14)	32±5 (9)	17±5 (14)	17±4 (9)	14±6 (14)	15±5 (9)
Ray et al[39]; ICD-10, MDE[b]	Tab 2 Auth	34	20 8/40	N/A	+ 30%	+ 68%	+ D1	HAMD17	29±6 (20)	30±4 (20)	20±6 (20)	4±5 (20)	10±5 (20)	25±6 (20)
Bakim et al[56]; DSM-IV, MDD	Tab 3 Tab 4	44	91 21/23	+ (≥2)	–	–	+	HAMD17	26±4 (12)	24±3 (11)	20±8 (12)	12±8 (11)	6±7 (12)	12±7 (11)
								MADRS	29±6 (12)	28±3 (11)	22±8 (12)	14±8 (11)	7±7 (12)	14±7 (11)

Blumberger et al[57]; DSM-IV, MDD[a]	Tab IV L	47	62 26/42	+ (≥2)	–	–	+	HAMD17	25±3 (18)	26±3 (19)	18±4 (18)	20±6 (19)	7±4 (18)	6±5 (19)
Fitzgerald et al[58]; DSM-IV/ICD-10, MDD[a]	Tab 2	43	52 22/42	+ (≥2)	–	N/A	+	HAMD17	23±2 (20)	24±4 (22)	23±5 (17)	22±6 (19)	0±4 (18)	2±5 (21)
								BDI-II	28±10 (20)	38±10 (22)	27±11 (16)	30±13 (19)	1±11 (18)	8±12 (21)
								MADRS	32±4 (20)	34±6 (22)	30±6 (17)	31±10 (19)	2±5 (18)	3±9 (21)
Huang et al[59]; DSM-IV, MDE	Tab 2 Tab 3	32	70 39/56	–	–	–	+D1	HAMD17	22±3 (28)	23±2 (28)	17±2 (28)	15±2 (28)	5±3 (28)	8±2 (28)
								MADRS	36±5 (28)	35±4 (28)	28±4 (28)	24±2 (28)	8±5 (28)	11±3 (28)
Peng et al[38]; DSM-IV, MDE	Tab 2	27	37 11/30	+ (≥2)	–	–	+	HAMD17	25±3 (13)	25±3 (17)	23±3 (13)	14±2 (17)	2±3 (13)	11±3 (17)
								BDI	22±2 (13)	21±2 (17)	20±2 (13)	14±3 (17)	2±2 (13)	7±3 (17)
Chen et al[60]; DSM-IV, MDD	Tab 1	46	55 11/20	+ (2)	N/A	+	+	HAMD17	25±2 (10)	24±2 (10)	12±1 (10)	10±2 (10)	13±2 (10)	14±2 (10)
								BDI-II21	38±2 (10)	31±4 (10)	26±5 (10)	24±4 (10)	12±4 (10)	7±4 (10)
Hernandez-Ribas et al[61]; DSM-IV, MDE	Tab 2	46	76 16/21	some (≥1)	+ 29%	–	+	HAMD21	17±2 (11)	20±4 (10)	10±5 (11)	9±5 (10)	7±4 (11)	11±5 (10)
Spampinato et al[40]; DSM-IV-TR, MDE	Tab III	53	36 8/22	+ (3)	–	–	+	HAMD21	20±2 (10)	22±2 (12)	17±1 (10)	10±6 (12)	3±2 (10)	12±5 (12)
								MADRS	26±1 (10)	28±2 (12)	20±3 (10)	12±8 (12)	6±3 (10)	16±7 (12)
Speer et al[62]; DSM-IV, MDE	Tab 1 (all) Tab 1 1 Hz Tab 1 20 Hz	42	54 13/24	+ (≥2)	+ 38%	N/A	–	HAMD28	24±5 (8)	32±10 (16)	29±6 (8)	29±9 (16)	–5±6 (8)	3±10 (16)
									24±5 (8)	29±8 (8)	29±6 (8)	25±7 (8)	–5±6 (8)	4±8 (8)
									24±5 (8)	36±11 (8)	29±6 (8)	32±10 (8)	–5±6 (8)	4±11 (8)

Notes: All studies included patients with a major depressive episode and/or disorder according to DSM-IV or ICD-10. The mean number of patients per group was used in the final calculations if patients dropped out throughout the study between baseline and final sessions (for example, in George et al[46]). 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). [A]Treatment-resistance: + are studies in which all (active and sham) patients failed (or showed intolerance to) ≥2 AD trials (of same or different class) of an adequate dose/length during current or lifetime episode; – are studies in which all patients failed 0–1 AD trials; "some" are studies in which patients failed ≥1 AD trials (these studies were excluded from all analyses because this category overlapped with the + and – category); [B]Bipolar depression (%): + are studies including any proportion of patients with bipolar disorder I and/or II at baseline; – means that all patients had unipolar depression (no history of bipolar disorder, mania, hypomania, Axis I disorders); [C]Psychotic depression (%): + are studies including any proportion of patients with psychotic features at baseline; – means that all patients had non-psychotic depression (no history of psychosis, Axis I disorders); [D]medication = antidepressants (+ means any proportion of patients/study received stable doses, +D1 means that antidepressants were started on day 1 concurrently with rTMS, – means that all patients were antidepressant-free but some might have received mood stabilizers); [E]it was assumed that the HAMD21 or BDI21 were used if no further information was provided; [F]the "last session" refers to the last stimulation session of the double-blind phase of a study. [a]Mean age and % female variables include patients who either withdrew before the end of study or were included in groups not included in the current study; [b]according to the correspondence with authors, the mean and SD scores for the post-rTMS condition of the study should be reversed for the active and sham groups (correct scores are reported in this table). All means that scores for all independent subgroups within studies were combined.

Abbreviations: AD, antidepressant; Auth, authors; BDI, Beck Depression Inventory; DYS, dysthymia; D1, antidepressants started on day 1; DLPFC, dorsolateral prefrontal cortex; Fig, Figure; HAMD, Hamilton Depression Rating Scale; L, left DLPFC; MADRS, Montgomery Åsberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; N/A, not reported or inadequate information; R, right DLPFC; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; ICD-10, International Statistical Classification of Diseases and Related Health Problems; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; Tab, Table.

analysis. These combined scores appear in rows labelled "all" in Table 3.

The meta-analysis was computed using Comprehensive Meta-Analysis 2.0 (CMA; Biostat Inc., Englewood, NJ, USA). If one study utilized multiple depression scales then multiple effect sizes based on each scale were computed; these effect sizes were combined into one effect size per study using an arithmetic mean. The effect size used in the current analysis was the standardized mean difference (Cohen's *d*) between depression scores at baseline to final after sham compared to active rTMS. The interpretation criteria for the absolute size of Cohen's *d* are: d=0.20–0.49 (small), d=0.50–0.79 (moderate), and $d \geq 0.80$ (large).[30]

The current study utilized the random-effects model of meta-analysis[29] with the inverse-variance weights (a sum of the within- and between-study variance).[31] The overall mean weighted effect size *d* of all studies was the sum of the product of all effect sizes and weights divided by the sum of all weights.[29] Negative values of *d* indicated that rTMS had antidepressant properties compared to sham.

The heterogeneity among the effect sizes was investigated using a *Q* statistic and an I^2 index (I^2=100%×(Q-df)/Q with df=k-1; k=number of studies).[29] The I^2 index shows the variability in effect sizes due to real (rather than chance) differences among studies and can be interpreted using the following criteria: 25% (little heterogeneity due to real differences among studies), 50% (moderate heterogeneity), and 75% (high heterogeneity).[32]

Sensitivity and moderator analyses

The stability of the overall mean weighted *d* over time was investigated as one study at a time was added to all previous studies (cumulative analysis) and as one study at a time was removed from the overall analysis (one study removed analysis). The moderator analyses (subgroup analyses and univariate meta-regressions) were used to test the influence of systematic differences among studies (clinical characteristics or patients and rTMS parameters) on the overall mean weighted *d*.

Publication bias analyses

Publication bias was assessed using methods available in CMA (Biostat). The Rosenthal's Fail-Safe N[33] was computed to find out the number of studies (theoretically missing from the current analysis) required to lower the overall mean weighted *d* to zero in the current analysis. The Duval and Tweedie's Trim-and-Fill analysis[34] was used to test if the so-called funnel plot of *d* versus standard error of the mean (SEM)/study[35] was symmetrical around the overall mean weighted *d* of all studies. Finally, the Begg and Mazumdar Rank Order Correlation (Kendall's *tau b*) between the standardized *d* versus SEM in each study,[36] and the Egger's regression of 1/SEM (predictor) on the standardized *d*, [37] were used to test whether smaller studies differ systematically (significantly) from the larger studies. It was assumed that publication bias might be present if the Fail-Safe N is low, the funnel plot is asymmetrical, Begg and Mazumdar Correlation is statistically significant, and/or the intercept of the regression line significantly deviates from zero, causing an asymmetry of the funnel plot.[29]

Results

An inspection of the weighted effect sizes *d* for each of the N=58 studies revealed that N=4 studies (all "new" studies)[38–41] were outliers in the current analysis. Specifically, weighted *d*s in these studies were statistically significantly higher than the overall mean weighted *d* of all other studies (Figures S1 and S2). As a consequence, the overall mean weighted *d* was inflated when these studies were included in the meta-analysis of the N=18 "new" studies (d=–0.80) compared to when these studies were removed from the analysis (N=14 "new" studies: d=–0.42; Table 4). Thus, these N=4 "new" studies were excluded and all subsequent analyses were computed using N=14 "new" studies.

One of the four studies[39] might have been an outlier because of the following methodological differences between this and all other studies: the use of a clinical interview for HAMD scale (rather than HAMD scale alone), depression diagnosed using ICD-10 (rather than DSM-IV), inclusion of high proportions of patients with bipolar (30%) and psychotic depression (68%; Table 3). The reasons why the other three studies might have been outliers are addressed in the Discussion section.

The N=14 "new" studies were conducted in nine countries (three each in the US and People's Republic of China; two in Spain; one each in France, Italy, Turkey, India, Canada, and Australia; Table 2). These studies were conducted on a total of N=659 patients in the active rTMS (N=340) and sham (N=319) groups. All patients had diagnoses of a major depressive episode and/or disorder according to DSM-IV or ICD-10 (Table 3). There was little evidence that the

Table 4 Results of the random-effects meta-analysis of the N=14 "new" studies (2010–2013) and all N=54 studies: N=40 "old" studies (1997–2008) and N=14 "new" studies

	N studies (%)	*d* (95% CI)	$P_{two-tailed}$
Overall mean weighted *d*			
"old 40" studies (1997–2008)	40	–0.54 (–0.68, –0.41)	<0.001*
"new 18" studies (2010–2013)	18	–0.80 (–1.16, –0.44)	<0.001*
"new 14" studies, outliers excluded	14	–0.42 (–0.66, –0.18)	<0.001*
"old 40" versus "new 14" studies			0.151
"New" N=14 studies	2010–2013		
Total N patients	rTMS/sham	659 (340/319)	
Heterogeneity	$Q(df)$; $P_{two-tailed}$; I^2	$Q(df\ 13)=25.9$; $P=0.018$*; $I^2=50\%$	
Rosenthal's Fail-safe N for $P>0.05$	N–studies needed to reduce the overall mean weighted *d* to 0	N=71 (N=5 studies missing for every study included in the current analysis)	
Duval and Tweedie's trim-and-fill analysis	Funnel plot symmetrical? N studies missing on either side of the overall mean weighted *d*	Yes None	
Begg and Mazumdar rank order correlation	τ; $P_{two-tailed}$	–0.09; $P=0.661$	
Egger's regression	Intercept; $P_{two-tailed}$	–1.21; $P=0.276$	

Note: *$P<0.05$.
Abbreviations: CI, confidence interval; *d*, standardized mean difference (effect size); *df*, degrees of freedom; rTMS, repetitive transcranial magnetic stimulation; τ, Kendall's correlation coefficient tau b with continuity correction.

publication bias systematically affected the results of the current analysis (Table 4).

There was a moderate antidepressant effect of rTMS because the change in mean depression scores from baseline to final was significantly higher after rTMS compared to sham in the N=14 "new" studies (*d*=–0.42; Table 4 and Figure 2). The "new" studies did not show a superior antidepressant effect of rTMS compared to the "old" studies because the overall mean weighted *d* did not significantly differ between the two groups of studies ("old" *d*=–0.54 versus "new" *d*=–0.42; *P*=0.151; Table 4).

The 50% heterogeneity in the effect sizes among the N=14 "new" studies (Table 4) was probably due to methodological differences among these studies in terms of depression scales used (HAMD in all N=14 studies, MADRS in N=6 studies, and BDI in N=3 studies), clinical characteristics of patients (Table 3), and different parameters of rTMS (Table 2). Some of the N=14 "new" studies did not report the above characteristics (Tables 2 and 3) and thus the percentage scores shown below are computed based on studies with valid responses only.

The N=40 "old" studies and the N=14 "new" studies were conducted on mostly middle-aged patients (aged 40 years old and above). Similarly to the "old" studies, 50% of the "new" studies utilized 60% or more female patients per study.

Like the "old" studies, most of the "new" studies were conducted on patients with (Table 3):

- treatment-resistance, defined as a failure to respond to or tolerate ≥2 antidepressant trials (N=8/9, 89% of studies),
- non-psychotic depression (N=8/9, 89% of studies), and
- concurrent antidepressant treatment (N=11/14, 79% of studies). Of these N=11 studies, most included patients on stable doses of antidepressants (N=10/11 studies). Antidepressants were started on day 1 of the study in only N=1/11 studies.

In contrast to the majority of "old" studies that had included any proportions of bipolar patients, the "new" studies were mostly conducted on patients with unipolar depression (N=8/12, 67% of studies).

The current results also suggest that similar properties of rTMS have been used over the last 16 years of research on depression (in studies published in 1997–2013). Similarly to the "old" studies, the most commonly utilized rTMS parameters among the "new" studies were: 10 Hz frequency of stimulation (N=5/14, 36% of studies), 110% motor threshold stimulation (N=4/13, 41% of studies), 800 or 1,600 stimuli/session (N=4/10, 40% of studies), 20 trains/session (N=6/13, 46% of studies), a 70 mm stimulating coil diameter (N=4/5, 80% of studies), and a figure-of-eight shape of the stimulating

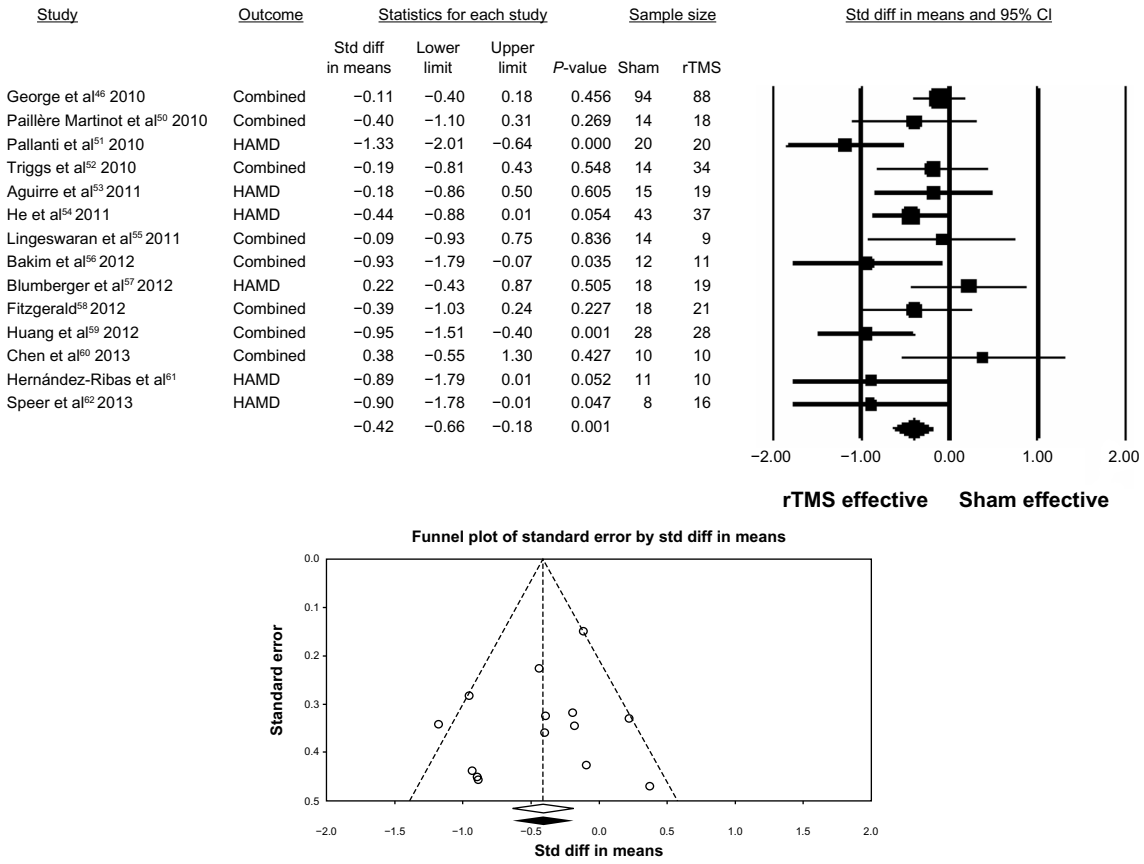

Figure 2 Random-effects meta-analysis of N=14 "new" studies (2010–2013) comparing the change in mean depression scores on HAMD, BDI, and/or MADRS (baseline – final), after rTMS versus sham.

Notes: In the studies by Triggs et al[52] and Speer et al,[62] rTMS was administered using different properties into different subgroups of patients in a study and the depression scores for such subgroups were combined. The mean number of patients per group was used in the final calculations if patients dropped out throughout the study between baseline and final sessions. The forest plot (top) shows the weighted effect size *d* (box) and its 95% CI (vertical line through the box) for each study in the analysis ("combined" indicates that more than one depression scale was used in a study and the effect sizes according to the multiple scales were combined). The diamond depicts the overall mean weighted *d* of all studies and its 95% CI (width of the diamond). The mean depression scores (baseline – final) were significantly reduced after rTMS compared to sham (overall mean weighted *d*=–0.41, 95% CI: –0.64, –0.18). The funnel plot (bottom) shows the effect sizes *d* plotted versus SEM for each study in the analysis. The plot was symmetrical around the overall mean weighted *d* suggesting that publication bias had little effect on the results of the current meta-analysis.

Abbreviations: BDI, Beck Depression Inventory; CI, confidence interval; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; SEM, standard error of mean; Std diff, standardized mean difference *d*.

coil (N=13/13 studies). In contrast to the 10 rTMS sessions most commonly used among the "old" studies, the "new" studies most often utilized longer paradigms of 15 sessions (N=6/14, 43% of studies).

Interestingly, even though the new "sham-coils" improve the blinding of studies and prevent stimulation of the brain due to an inbuilt magnetic shield, these coils have not been commonly used in the "new" studies yet (possibly due to a high cost of replacing the older stimulators with the newest ones). In fact, similarly to the "old" studies, the most common sham practice among the "new" studies was to tilt the active coil by a 90° angle from the scalp (N=6/14, 43% of studies).

Finally, just like the "old" studies, the left-fast rTMS (>1 Hz) of the DLPFC was the most common combination of the location-frequency of rTMS among the "new" studies (N=10/14, 71% of studies), followed by the bilateral or sequential rTMS (N=3/14, 21% of studies), and the left-slow (≤1 Hz), right-slow, and right-fast rTMS that were utilized in one study (7%) each.

Since there were too few "new" studies, we have combined all "old" and "new" studies (total N=54) to conduct moderator and subgroup analyses. The results of these analyses are shown in Table 5.

The overall mean weighted *d*=–0.51 in all N=54 studies suggests that rTMS was only moderately better than sham at reducing depression scores over the last 16 years in a total of 2,242 patients in 17 countries (Table 5; Figure S3; Table S3). Even though only moderate, this overall effect size became stable around –0.50 to –0.54 over the last 8 years as studies were removed from the analysis one at a time (Figure S4), or cumulatively added to the analysis (Figure S5).

Univariate comparisons of subgroups of studies based on common study properties showed that no one specific characteristic was superior in terms of producing higher

Table 5 Random-effects subgroup analyses and meta-regressions of the change in depression scores (baseline – final) after rTMS compared to sham in N=54 sham-controlled studies published in 1997 – August 2013

Studies	N studies (%)[a]	*d* (95% CI)	$P_{two-tailed}$
All studies (1997–2013)	54	–0.51 (–0.63, –0.39)	<0.001*
Subgroups			
Location-frequency[b]	54		
Left-slow (≤1 Hz)	4 (7%)	–0.61 (–1.21, –0.01)	0.046*
Left-fast (>1 Hz)	43 (80%)	–0.49 (–0.63, –0.34)	<0.001*
Right-slow	6 (11%)	–1.01 (–1.61, –0.42)	0.001*
Right-fast	1 (2%)	0.03 (–0.86, 0.92)	0.948
Bilateral or sequential (left then right)	7 (13%)	–0.55 (–0.82, –0.29)	<0.001*
Treatment resistance	27		
Yes (all failed ≥2 AD trials)	21 (78%)	–0.52 (–0.70, –0.35)	<0.001*
No (all failed 0–1 AD trials)	6 (22%)	–0.80 (–1.02, –0.50)	<0.001*
Yes versus no[c]			0.108
Concurrent medication	54		
YES (any % of patients)	42 (78%)	–0.51 (–0.63, –0.38)	<0.001*
Stable dose	35 (83%)	–0.51 (–0.65, –0.36)	<0.001*
Started on day 1	7 (17%)	–0.50 (–0.77, –0.23)	<0.001*
NO (all patients)	12 (22%)	–0.56 (–0.84, –0.28)	<0.001*
YES versus NO[c]			0.229
Bipolar depression	42		
YES (any % of patients)	23 (55%)	–0.44 (–0.60, –0.28)	<0.001*
NO (all patients)	19 (45%)	–0.54 (–0.72, –0.34)	<0.001*
YES versus NO[c]			0.921
Psychotic depression	28		
YES (any % of patients)	5 (18%)	–0.51 (–1.14, 0.13)	0.117
NO (all patients)	23 (82%)	–0.58 (–0.77, –0.40)	<0.001*
YES versus NO[c]			0.745
Coil-type	51		
F8	47 (92%)	–0.52 (–0.65, –0.38)	<0.001*
Circular	4 (8%)	–0.62 (–1.05, –0.19)	0.005*
F8 versus circular[c]			0.561
Coil angle sham	54		
0° (inactive coil)	5 (9%)	–0.36 (–0.64, –0.07)	0.015*
0° (sham coil)	10 (19%)	–0.63 (–0.92, –0.34)	<0.001*
45°	18 (33%)	–0.40 (–0.57, –0.22)	<0.001*
90°	21 (39%)	–0.56 (–0.77, –0.35)	<0.001*
0° (sham coil) versus 45°			0.757
0° (sham coil) versus 90°			0.150

	N studies	T^2_{total}	T^2_{model}	R^2	*B*	$P_{two-tailed}$
Meta-regression predictors[d]						
% female patients	53	0.046	0.022	0.52	–0.01	0.002*
Stimuli/session	33	0.043	0.004	0.91	0.0002	<0.001*
Trains/session[e]	48	0.071	0.044	0.38	0.007	0.013*

Notes: Total patients in N=54 studies totaled N=2,242 (rTMS N=1,184, sham N=1,058). [a]The percent values are reported based on the number of studies that reported a particular characteristic; [b]effect sizes in subgroups based on location-frequency of rTMS were not compared statistically because some studies used multiple active rTMS groups but the same sham groups, and thus the subgroups were not independent; [c]subgroups were compared using the mixed-effect model; random-effects model was used to compute the overall mean weighted *d* in each subgroup and overall mean weighted *d* of subgroups were compared using the fixed-effect model because the number of subgroups was fixed; [d]proportion of the between-study variance in weighted *d* explained by the predictor was computed as $R^2=1-(T^2_{model}/T^2_{total})$, where T^2_{model} is the between-study variance in the weighted *d* (outcome) unexplained by the regression model containing the predictor and T^2_{total} is the within- and between-study variance;[29] [e]following the Bonferroni correction for multiple regressions (new significance threshold of 0.05/7=0.007), the regression of trains/session on weighted *d* became non-significant. *$P<0.05$.
Abbreviations: AD, antidepressant; CI, confidence interval; rTMS, repetitive transcranial magnetic stimulation.

antidepressant effects. For example, except for the right-fast rTMS of the DLPFC that was utilized in only one study, all combinations of the location-frequency of rTMS were effective at significantly reducing depression scores compared to sham (Table 5). There was a non-significant trend toward higher overall mean weighted effect sizes in studies with non-treatment resistant patients compared to those with treatment-resistant patients (Table 5). rTMS was also similarly effective in studies with unipolar depression compared to studies with generally low proportions of

bipolar patients (Table 5). However, it remains unclear if the antidepressant properties of rTMS extend to psychotic depression because there were too few studies with low proportions of patients with psychotic depression in the current analysis (N=5; Table 5).

According to the current results, the antidepressant effect of rTMS was probably not secondary to concurrent antidepressants. Table 5 shows that depression was reduced after rTMS compared to sham in studies with patients who were medication-free or started on antidepressants concurrently with rTMS on day 1 of a study. Overall mean weighted effect sizes did not differ statistically between studies with medicated versus medication-free patients (Table 5).

The current study also shows that depression was reduced after rTMS compared to sham using both stimulating coil shapes (figure-of-eight or circular) and various sham designs. Although studies using sham coils produced the highest overall mean weighted effect size (d=–0.63; Table 5) compared to all other sham designs, more than N=10 studies using sham coils are needed to statistically confirm the superiority of this blinding method. Compared to sham coils, tilting of active coils at 45° or 90° from the scalp was the most commonly used sham practice in studies published until August 2013 (Table 5). The most commonly used stimulators were the MagStim (UK; N=28/54, 52% of studies) and the MagPro (USA; N=10/54, 18% of studies) models.

Finally, seven univariate meta-regressions were conducted to find out if any demographic characteristics of patients (mean age/study and proportion of female patients/study) or rTMS parameters (frequency of stimulation, motor threshold, total number of sessions, stimuli/session, trains/session) could predict a change in the effect sizes weighted according to the random-effects model. Two regressions showed that the antidepressant effect of rTMS was superior in studies with more female patients and fewer stimuli per session (Table 5; Figure 3). However, a change in weighted ds could not be significantly predicted using the mean age of all patients per study, frequency of stimulation, motor threshold, or a total number of sessions as predictors. Predictors "stimuli/session" and "% female patients" explained 91% and 52% of the between-study variability in effect sizes, respectively.

Discussion

The current meta-analysis conducted on N=54 studies published in 1997–2013 showed that rTMS has a short-term antidepressant effect that is superior in studies with more female patients and fewer stimuli per session (Table 5 and Figure 3). The most commonly used characteristics of patients and rTMS parameters in the sham-controlled studies over the last 16 years (1997–2013) included in the current analysis were: at least 60% female patients/study in half of all studies (range: 22%–92%); mostly middle-aged or older patients (range of the mean age of all patients per study: 39–62 years); fast (>1 Hz) stimulation of the left DLPFC; frequency of 10 Hz; 110% motor threshold; figure-of-eight coil with 70 mm diameter; 1,600 stimuli/session; 20 trains/session; and 10 sessions/study (although the more recent studies published after 2008 most commonly used longer protocols of 15 sessions/study). The most commonly used sham strategy was tilting of the active coil at the 90° angle from scalp (Table 5). Most of the studies to date included proportions of patients with treatment resistance, on concurrent antidepressants (particularly at the stable dose), with bipolar and non-psychotic depression (Table 5).

It is likely that sex plays a role in the short-term response to the left-fast rTMS because 80% of all studies in the current meta-analysis utilized this combination of rTMS parameters (Table 5). This result confirms another univariate finding that out of patients who failed to respond to a 4-week, double-blind phase of rTMS in a large RCT,[42] only females showed a superior response to rTMS during the extension (open-label) phase of the study.[5] However, such a response to treatment was probably related to a combination of factors rather than sex alone. This is because the patients in the RCT were unipolar, non-psychotic, medication-free, moderately–severely treatment-resistant, and required more than four weeks of treatment to respond to rTMS.[5] Another open-label study also showed that the improved response to rTMS in females depended on younger (premenopausal) age and the ovarian hormonal levels.[43] Such a result is not surprising because depression has a strong hormonal component.[44,45] Thus, it can be speculated that the superior effect of sex in our meta-analysis was also due to younger age of female patients, and other factors (such as less severe unipolar depression and/or medication-free status). However, such confounding factors can be investigated only to a limited extent in meta-analyses that are computed on data. It should be possible to compute multiple meta-regressions on group data as new studies using rTMS become available in the future, providing that these studies report the characteristics of their patients and/or rTMS properties used.

The second important finding in the current meta-analysis is that the short-term antidepressant properties of rTMS were observed in studies using fewer stimuli per session according to a univariate meta-regression (Table 5 and Figure 3).

Other meta-analyses showed that the efficacy of rTMS was not associated with the number of stimuli/session nor total stimuli.[14,19,20,23] The initial negative correlation between the effect sizes and the total number of stimuli in one meta-analysis[20] was attributed to one large RCT only.[42] Similarly, this and another large RCT[42,46] contributed to the additional significant univariate meta-regression of the total number of stimuli (computed as "stimuli per session" × "total sessions" per study based on the data shown in Table 2) on weighted *d* in the current analysis (Figure S6). However, the meta-regression of stimuli/session on weighted *d* remained unchanged after the removal of the same two RCTs[42,46] in the current analysis (Figure S7). In general, the findings from the two largest RCTs[42,46] suggest that the initially non-responsive patients appear to indeed require more than 15 rTMS sessions with a high number (3,000) of stimuli/session to show a response to rTMS. However, the results of the current meta-analysis suggest that the short-term response to rTMS (during the double-blind phase of the study) might require fewer stimuli per session. Again, based on the current results, it can only be speculated that particularly the less treatment-resistant female patients require fewer stimuli per session in the short (up to 10 sessions), left-fast rTMS paradigms to demonstrate the antidepressant response to rTMS.

Interestingly, some evidence in support of the speculation above can be found in three of the four studies classified as outliers in the current analysis. Specifically, a large antidepressant effect of rTMS was observed in the total of N=86 patients (63%–65% males) on concurrent antidepressants, with unipolar, non-psychotic depression, and with moderate–severe treatment-resistance using long (20 sessions), left-fast paradigms with a high number (3,000) of stimuli/session.[38,40,41] Therefore, in contrast to female patients, male patients with more severe major depression might require longer, left-fast paradigms with more stimuli per session to show an antidepressant response to rTMS during the double-blind phases of studies. Furthermore, such a sex-dependent effect could also explain why the two largest RCTs to date, with similar study characteristics to those in the three outlier studies, have demonstrated only small antidepressant effects of rTMS in mostly female (medication-free) patients: *d*=–0.30 in N=301 patients[42] (Figure S1) and *d*=–0.11 in N=190 patients[46] (Figure 2). Such small effect sizes might have resulted from a high quality of blinding (with sham coils) in the RCTs compared to the large effect sizes using tilted active coils in the outlier studies. Thus, future primary studies should investigate the effects of rTMS separately in both sexes controlling for severity of treatment resistance and the number of stimuli/session in the left-fast rTMS paradigms.

The significant reduction in depression scores after rTMS associated with fewer stimuli per session raises the question of whether or not the brain can be "overstimulated" during rTMS leading to a reduction in the antidepressant properties of this method. One mechanism of such an "overstimulation" could be related to the firing properties of neurons. In general, voltage-gated sodium channels are key players in membrane excitation and the production of action potentials. The classical model of sodium channel gating described by Hodgkin and Huxley suggests that a voltage-gated mechanism mediates the activation (opening of sodium channels) as well as inactivation following a refractory period during which no excitation can occur.[47] A strong depolarization involving a large number of neurons can inactivate sodium channels and thereby prevent further excitation for a prolonged period of time. Since neurons need to recover from firing before being able to produce new action potentials, stimulating the brain with too many stimuli might lead to a neural saturation (inability of most neurons to produce new action potentials) and consequently a reduction in antidepressant properties of rTMS. In practical terms, using shorter sessions with fewer stimuli could be less costly as well as time consuming for patients and administrators.

Univariately, the mean age of all patients (rather than age of individual patients) was not related to a better antidepressant outcome of rTMS in the current and past meta-analyses[14,20] possibly due to the use of group data. Similarly, effect sizes were unrelated to severity of treatment-resistance or presence versus absence of treatment-resistant patients in other meta-analyses.[14,16,17,20] In our analysis there was only a trend toward higher antidepressant effect of rTMS in (very few) studies with non-treatment-resistant patients compared to studies with treatment-resistant patients (Table 5). The reason for this result could be that we have not controlled for severity of illness in our meta-analysis. Furthermore, our classification of studies into subgroups was also not optimal for unipolar versus bipolar and psychotic versus non-psychotic depression. In general, very few patients had such diagnoses per study (Table 3). Thus, there was no difference in effect sizes between groups of studies with all unipolar and all non-psychotic patients compared to studies with mostly unipolar and mostly non-psychotic patients, respectively (Table 5). Other meta-analyses have also found no differences in effect sizes or response and remission rates between studies with unipolar compared to bipolar patients.[14,23] While effect sizes were higher in studies

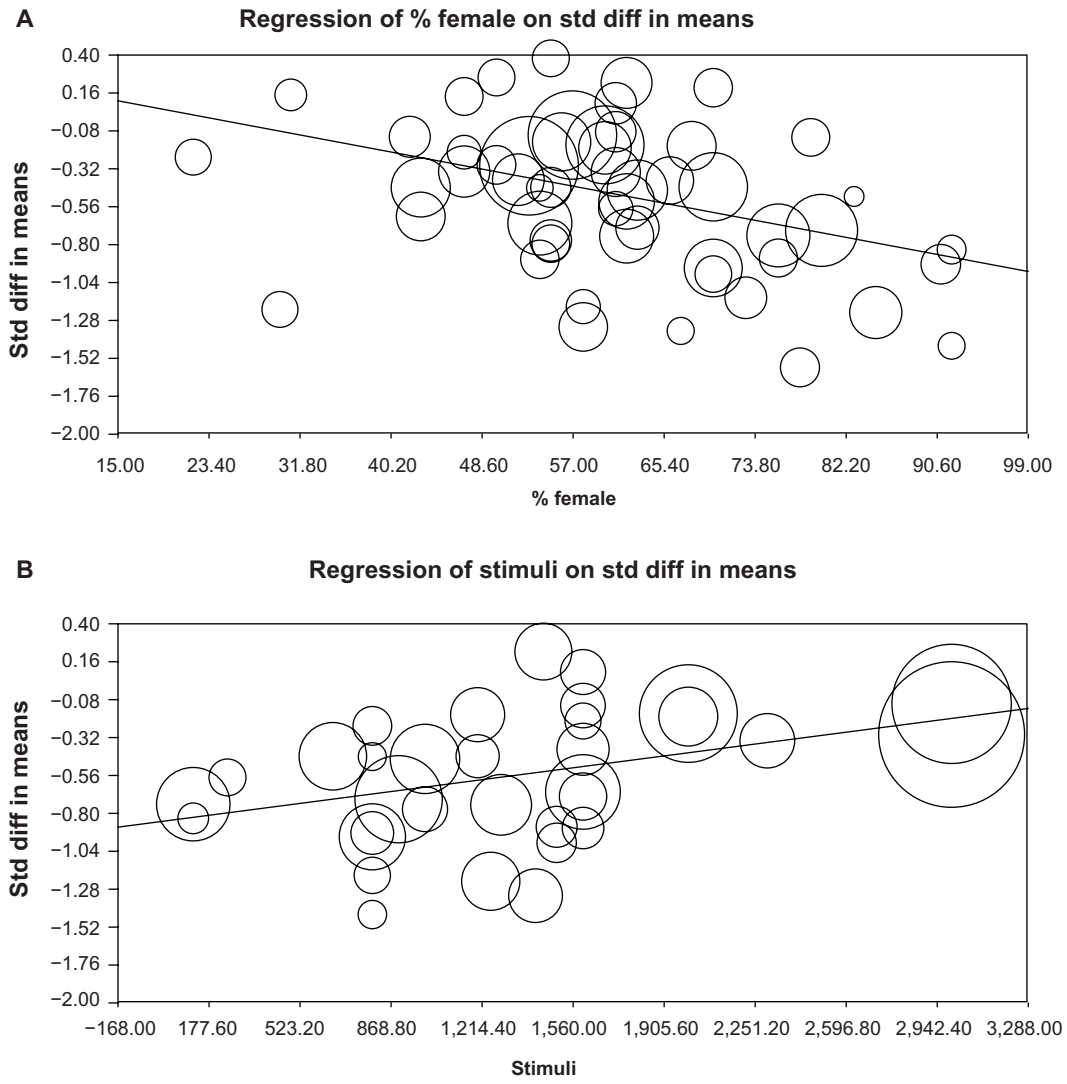

Figure 3 Univariate random-effects meta-regressions of various study characteristics used as predictors (proportion of female patients/study and stimuli/session) on the weighted effect sizes *d* (the outcome) in studies published in 1997–2013.
Notes: The figures are scatterplots of the outcome (weighted *d*/study; Y-axes) versus predictors (X-axes): (**A**) proportion of female patients/study and (**B**) stimuli/session. Depression scores (baseline – final) were significantly reduced after rTMS compared to sham in studies with more female patients and less stimuli/session.
Abbreviations: rTMS, repetitive transcranial magnetic stimulation; Std diff, standardized mean difference *d*.

with non-psychotic versus psychotic patients in one meta-analysis,[19] such result was not confirmed by another meta-analysis,[14] possibly due to including studies with unknown psychosis status in the non-psychotic group.

The short-term antidepressant effect of rTMS was not secondary to concurrent antidepressants in the current analysis. Specifically, it was observed in studies with patients who were all medication-free or who started on antidepressants concurrently with rTMS (Table 5). However, the current analysis did not confirm the finding from other meta-analyses that the short-term response to rTMS was higher[23] or tended to be higher[19] in studies using rTMS as monotherapy versus an add-on therapy. The reason for this result might be that we have not controlled for proportions of patients on concurrent antidepressants in the add-on studies.

According to our results depression severity was reduced after rTMS compared to sham in studies using different rTMS properties, such as different stimulating coils (figure-of-eight or circular), different sham paradigms, and different combinations of the location (right or left) and frequency (slow or fast) of DLPFC stimulation (Table 5). Although blinding is facilitated by the use of shielded sham coils that resemble active coils visually and produce similar auditory effects while not stimulating the brain,[48] these coils were still not commonly used compared to tilting of active coils (possibly due to high costs of replacing the older with newer

equipment). Furthermore, except for five studies, all other studies used the "5 cm rule" to define the position of the DLPFC (Table 2) in the current analysis. Even though it is so frequently used, the "5 cm rule" is less accurate than the 10–20 EEG (electroencephalogram) system and the magnetic resonance image (MRI)-guided neuronavigation.[49] Therefore, the antidepressant properties of rTMS could be further strengthened by the use of either MRI or the F5 location of the EEG system.[49]

The moderate effect sizes in the current and most other meta-analyses on this topic could be related to statistical methods of computing the effect sizes and performing a meta-analysis. The magnitude of effect sizes in individual studies might largely depend on the blinding quality of studies and the computation of effect sizes. Therefore, assuming that baseline depression scores are similar, the well-blinded studies could have smaller standardized differences in mean depression scores between rTMS and sham groups. This is because patients could respond to rTMS (due to its antidepressant properties) and to sham (due to placebo effect) in well-blinded studies. In contrast, the poorly-controlled studies in which patients and/or administrators guess the treatment allocation could show larger effect sizes. This time patients could respond to rTMS (guessing that they receive the real treatment) but not to sham (guessing that they receive the inactive treatment). This scenario is possible because patients can easily inform themselves about the method from the social media, for instance by watching industry-sponsored videos on YouTube directed toward the general population.

Furthermore, the past meta-analyses in this field used two general approaches to computing the effect sizes: the mean depression scores were compared before versus after rTMS or sham (in some studies controlling for baseline depression scores) using standardized mean differences (Cohen's *d* or Hedges' *g*), or proportions of patients who remitted after rTMS or sham versus baseline were compared using the odds ratios. None of these approaches of computing effect sizes is ideal from the statistical point of view. Mean scores could be skewed in studies with small sample sizes (<30 patients). Thus, the "true average" depression score would be shown more accurately using the mode (most commonly occurring depression score in the rTMS versus sham groups) or the median rather than the skewed mean. On the other hand, the odds ratios are also problematic because they rely on classifying patients into two groups (non-depressed versus depressed) based on a subjective cut-off on a depression scale. As a result, a patient with a score of 17 on a specific scale might be classified as "non-depressed" while another one with a score of 18 might already fall into the "depressed group" regardless of such a low difference between their scores. Furthermore, the odds ratios computed from each primary study would need to be based on the same cut-off for presence/absence of depression to reliably combine the results of these studies in meta-analysis. Therefore, the "all or nothing" classification of patients according to the odds ratio might be reliable and valid when large differences among patients' scores occur and thus the group membership can be reliably justified. Despite the limitations above, the advantage of mean scores is that they show the severity of depression without needing a specific cut-off to classify patients into groups.

Furthermore, different methods of weighing of studies and meta-analysis were utilized in the meta-analyses to date. The weights in the current meta-analysis were computed based on variance. Therefore, studies with higher variability of scores (due to rTMS being effective at reducing depression in only some, but not all, patients) had lower weights and thus lower influence on the overall mean weighted effect size. However, other methods of meta-analysis advocate the use of other weighing methods, such as the sample size, and correcting the effect sizes in individual studies for study-related artifacts before conducing any meta-analysis.[29] Despite all the statistical differences, most of the past 17 meta-analyses (published 2001–2013) and the current meta-analysis report similar (moderate) weighted effect sizes (standardized mean differences or odds ratios). Therefore, it is likely that the true effect of rTMS is either only moderate or indeed even higher in clinical practice considering the statistical limitations described above.

Although no strong evidence for publication bias was detected in the current study (Table 4), the sources included in our analysis were biased toward studies published in peer-reviewed journals and written in the English language. Such an apparent bias in selection of sources was not related to the systematic search strategy (Table 1). Our search was conducted for any type of resource (published or not published) in any language (because the authors of this study are multilingual speakers of six different languages). Instead, it appears that the majority of sources on this topic on PsycInfo and Medline were indeed published in peer-reviewed journals and written in English (or at least included a title and an abstract written in English). Therefore, such a linguistic bias is probably related to the fact that PsycInfo and Medline mostly store published sources and these sources are most often written in English. However, the results of our

analysis are generalizable beyond the English-speaking world because the N=54 studies were conducted in a total of 17 countries around the world (for the list see Table S3). According to the File Drawer Problem[33] studies with statistically significant results are more likely to be published while those with non-significant results remain in "file drawers" and are never published. Even though such so-called "gray (unpublished) literature" was not included, only 50% of all studies in the current meta-analysis reached the traditional significance level (Figure S3). Furthermore, no checklist for the quality of studies was used in the current analysis. Instead, the quality of studies was assessed indirectly by weighing the effect sizes based on variability of scores within and between studies. It was assumed that studies with low variability of scores were of higher quality and thus contributed more weight to the overall mean weighted effect sizes and vice-versa.

Conclusion

In conclusion, the results of the current study suggest that the short-term antidepressant properties of rTMS are not secondary to concurrent antidepressants and might depend on sex and the number of stimuli per session. Depending on degree of treatment-resistance and age, male and female patients with unipolar depression might require paradigms with different properties (number of stimuli per session, total number of sessions, left-fast or other combinations of location-frequency of stimulation) to show comparable antidepressant effects. While the clinical efficacy of the fast rTMS of the left DLPFC seems to be widely accepted, the right-slow and bilateral or sequential paradigms appear to be promising alternatives in the short-term treatment of acute major depression.

Author contributions

VA conducted the systematic search and assessed all studies for inclusion with KKK. The data were independently extracted by KKK and SKR (studies up to 2008), and KKK and VA (2009–2013). VA performed the pilot analyses in SPSS/CMA, while KKK performed the final analyses in SPSS/CMA and wrote the manuscript. All authors critically revised the manuscript.

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Disclosure

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Supplementary materials

Table S1 A list of N=40 "old" studies on the association between rTMS from our previous meta-analysis (unpublished). These studies were included in sensitivity and moderator analyses in the current study

Author, year, country
George et al,[1] 1997, USA
Avery et al,[2] 1999, USA
Kimbrell et al,[3] 1999, USA
Klein et al,[4] 1999, Israel
Loo et al,[5] 1999, Australia
Padberg et al,[6] 1999, Germany
Berman et al,[7] 2000, USA
Eschweiler et al,[8] 2000, Germany
George et al,[9] 2000, USA
Garcia-Toro et al,[10] 2001, Spain
Garcia-Toro et al,[11] 2001, Spain
Manes et al,[12] 2001, USA
Boutros,[13] 2002, USA
Padberg et al,[14] 2002, Germany
Fitzgerald et al,[15] 2003, Australia
Höppner et al,[16] 2003, Germany
Loo et al,[17] 2003 Australia
Nahas et al,[18] 2003, USA
Buchholtz et al,[19] 2004, Denmark
Hausmann et al,[20] 2004, Austria
Holtzheimer et al,[21] 2004, USA
Kauffmann et al,[22] 2004, USA
Koerselman et al,[23] 2004, the Netherlands
Mosimann et al,[24] 2004, Switzerland
Poulet et al,[25] 2004, France
Rossini et al,[26] 2005, Italy
Rumi et al,[27] 2005, Brazil
Su et al,[28] 2005, Taiwan
Avery et al,[29] 2006, USA
Fitzgerald et al,[30] 2006, Australia
Garcia-Toro et al,[31] 2006, Spain
Januel et al,[32] 2006, France
Anderson et al,[33] 2007, UK
Bortolomasi et al,[34] 2007, Italy
Herwig et al,[35] 2007, Germany/Austria
Loo et al,[36] 2007, Australia
O'Reardon et al,[37] 2007, USA, Australia, Canada
Stern et al,[38] 2007, USA
Bretlau et al,[39] 2008, Denmark
Mogg et al,[40] 2008, UK

Abbreviation: rTMS, repetitive transcranial magnetic stimulation.

Table S2 A list of N=50 studies on the association between rTMS and depression assessed in full-length and reasons for exclusion from the current meta-analysis

Author, year	Included/reason for exclusion
Aguirre et al,[41] 2011	Included (additional data provided by authors)
Avery et al,[42] 2007	No new data (data from Avery et al,[29] 2006)
Baeken et al,[43] 2010	Cross-over design, only one session
Bakim et al,[44] 2012	Included
Bares et al,[45] 2009	No sham (rTMS and placebo medication versus sham and venlafaxine)
Blumberger et al,[46] 2012	Included
Brakemeier et al,[47] 2007	No sham
Brakemeier et al,[48] 2008	No sham
Chen et al,[49] 2013	Included
Cohen et al,[50] 2009	No sham
Dell'Osso et al,[51] 2009	No sham
Fitzgerald et al,[52] 2012	Included
Furtado et al,[53] 2012	No sham
Galletly et al,[54] 2012	No sham
George et al,[55] 2010	Included
Hadley et al,[56] 2011	No sham
He et al,[57] 2011	Included (additional data provided by authors)
Herbsman et al,[58] 2009	No new data (data from Avery et al,[29] 2006)
Hernández-Ribas et al,[59] 2013	Included
Herwig et al,[60] 2010	No new data (data from Herwig et al,[35] 2007)
Höppner et al,[61] 2010	No new data (data from Herwig et al,[35] 2007)
Hoy et al,[62] 2012	No sham
Huang et al,[63] 2008	No sham
Huang et al,[64] 2012	Included
Jacob et al,[65] 2008	Inadequate data reported (SD values missing on Figure 1)
Kozel et al,[66] 2011	No new data (data from O'Reardon et al,[37] 2007)
Kreuzer et al,[67] 2012	rTMS after sleep deprivation
Lingeswaran et al,[68] 2011	Included

(*Continued*)

Table S2 (*Continued*)

Author, year	Included/reason for exclusion
Lisanby et al,[69] 2009	No new data (data from O'Reardon et al,[37] 2007)
Myczkowski et al,[70] 2012	Depression secondary to birth (postpartum depression)
Nongpiur et al,[71] 2011	No sham (primed all conditions with right 1 Hz stimulation)
Paillère Martinot et al,[72] 2010	Included (additional data provided by authors)
Pallanti et al,[73] 2010	Included (week 3 data extrapolated from Figure 1)
Peng et al,[74] 2012	Included
Ray et al,[75] 2011	Included
Rosenquist et al,[76] 2013	No new data (data from O'Reardon et al,[37] 2007)
Schrijvers et al,[77] 2012	No sham (one single sham session followed by active treatment)
Schutter et al,[78] 2009	DLPFC not stimulated (parietal cortex stimulated)
Schutter et al,[79] 2010	No new data (data from Schutter et al,[78] 2009)
Simpson et al,[80] 2009	No new data (data from O'Reardon et al,[37] 2007)
Spampinato et al,[81] 2013	Included
Speer et al,[82] 2009	Inadequate data reported (baseline scores/group missing)
Speer et al,[83] 2013	Included
Tamas et al,[84] 2007	Inadequate data reported (HAMD scores missing)
Triggs et al,[85] 2010	Included
Trojak et al,[86] 2011	Case study
Ullrich et al,[87] 2012	No sham (sham was the active left-slow stimulation of the DLPFC)
Zarkowski et al,[88] 2009	No sham
Zheng et al,[89] 2010	No new data (same cases as in Zheng et al,[90] 2010)
Zheng et al,[90] 2010	Included

Note: A total of N=18/50 studies were included in the final meta-analysis.
Abbreviations: DLPFC, dorsolateral prefrontal cortex; HAMD, Hamilton Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation;

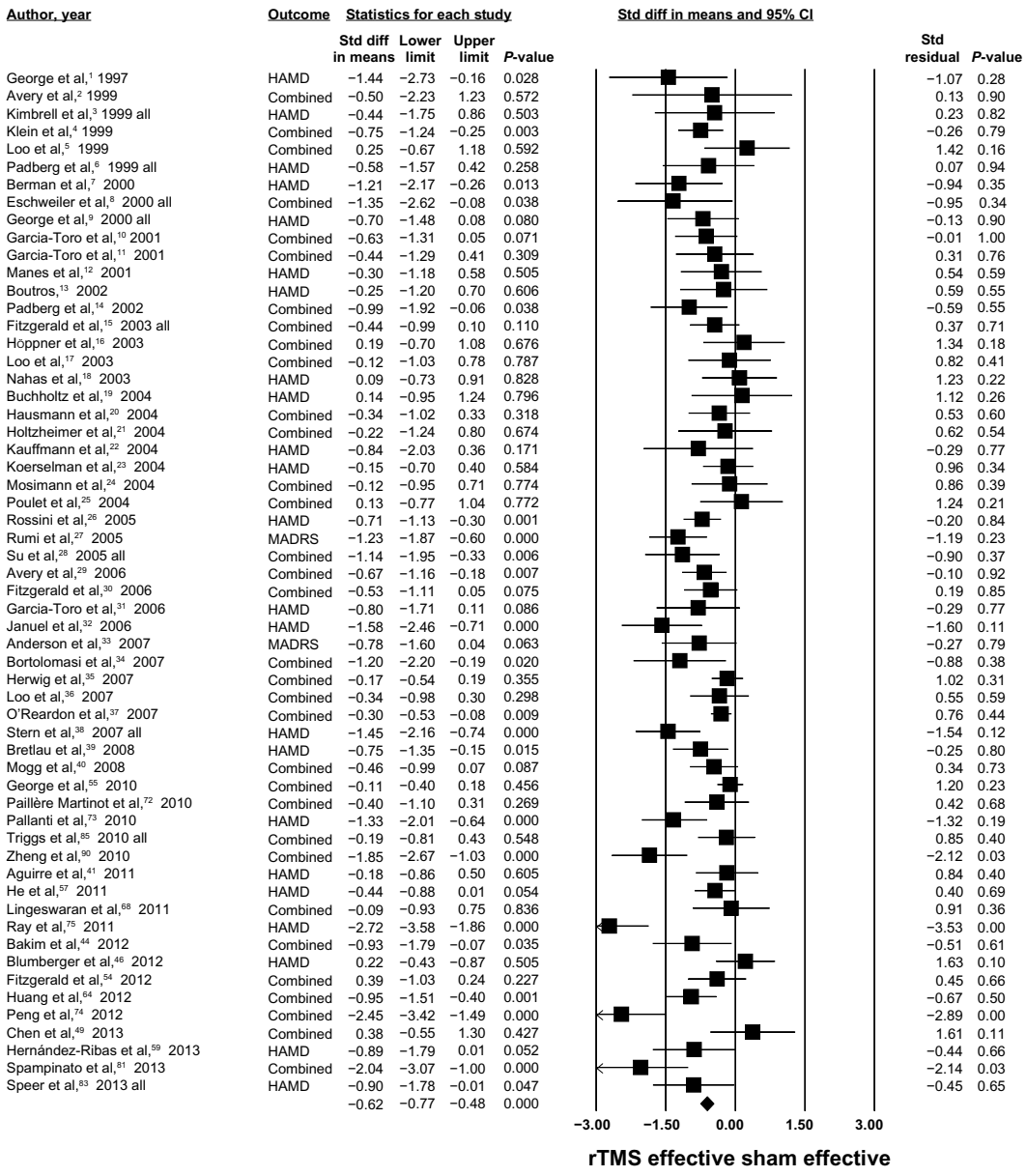

Figure S1 Random-effects meta-analysis of N=58 studies with standardized residuals and their *P*-values.

Notes: "All" indicates that rTMS was administered using different properties into different subgroups of patients in a study and the depression scores for such subgroups were combined. "Combined" indicates that more than one depression scale was used in a study and the effect sizes according to the multiple scales were combined). According to the *P*-values, 4/18 "new" studies were classified as outliers: Zheng et al 2010,[90] Ray et al 2011,[75] Peng et al 2012,[74] and Spampinato et al 2013.[81] These studies were excluded from all subsequent analyses.

Abbreviations: CI, confidence interval; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; Std diff, standardized mean difference *d*; Std, standardized.

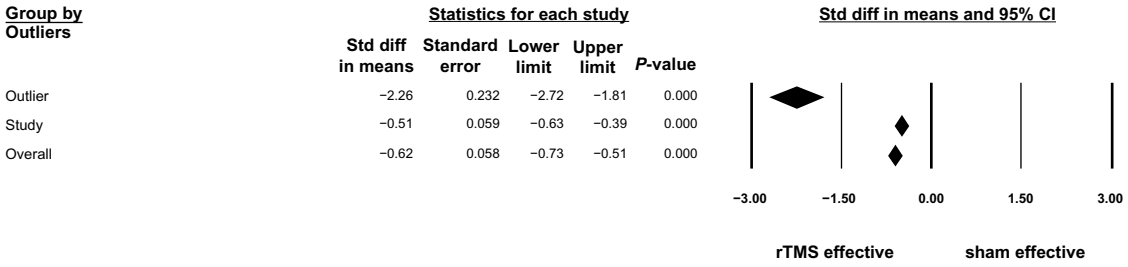

Figure S2 Forest plot showing the comparison of the N=4 outliers with N=54 studies.
Notes: Subgroup analysis using the mixed-effects model revealed that the overall mean weighted effect size *d* was significantly higher in the N=4 outlier studies (*d*=–2.26) compared to the N=54 studies (*d*=–0.51): $Q(df\ 1)=58.3$, $P<0.001$. The variability of the weighted effect sizes was high among the N=4 outlier studies (SEM =0.23) compared to the N=54 studies (SEM =0.06).
Abbreviations: CI, confidence interval; rTMS, repetitive transcranial magnetic stimulation; SEM, standard error of mean; Std diff, standardized mean difference *d*.

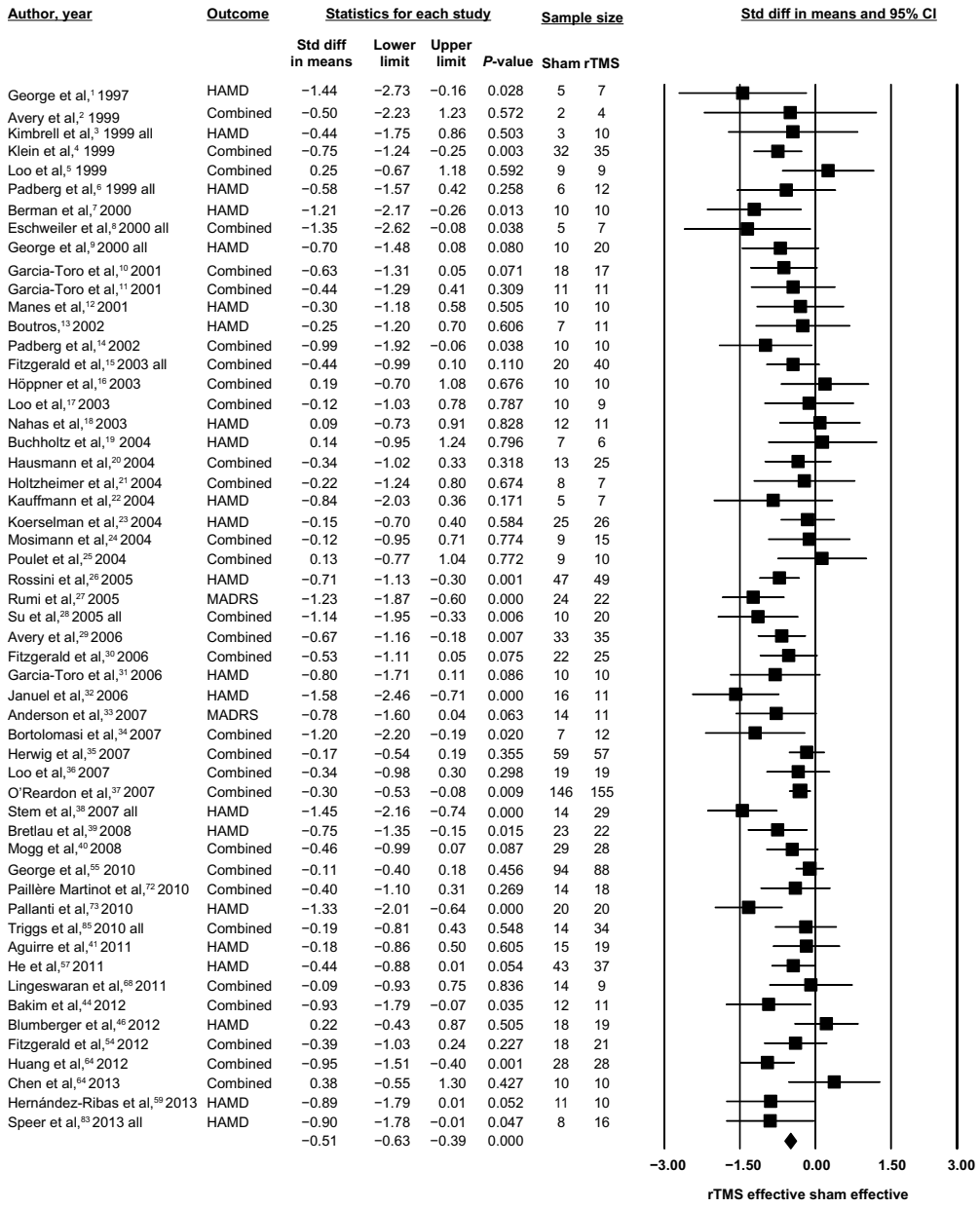

Figure S3 Random-effects meta-analysis of N=54 studies.

Notes: "All" indicates that rTMS was administered using different properties into different subgroups of patients in a study and the depression scores for such subgroups were combined. "Combined" indicates that more than one depression scale was used in a study and the effect sizes according to the multiple scales were combined). The mean number of patients per group was used in the final calculations if patients dropped out throughout the study between baseline and final sessions.

Abbreviations: CI, confidence interval; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; Std diff, standardized mean difference *d*.

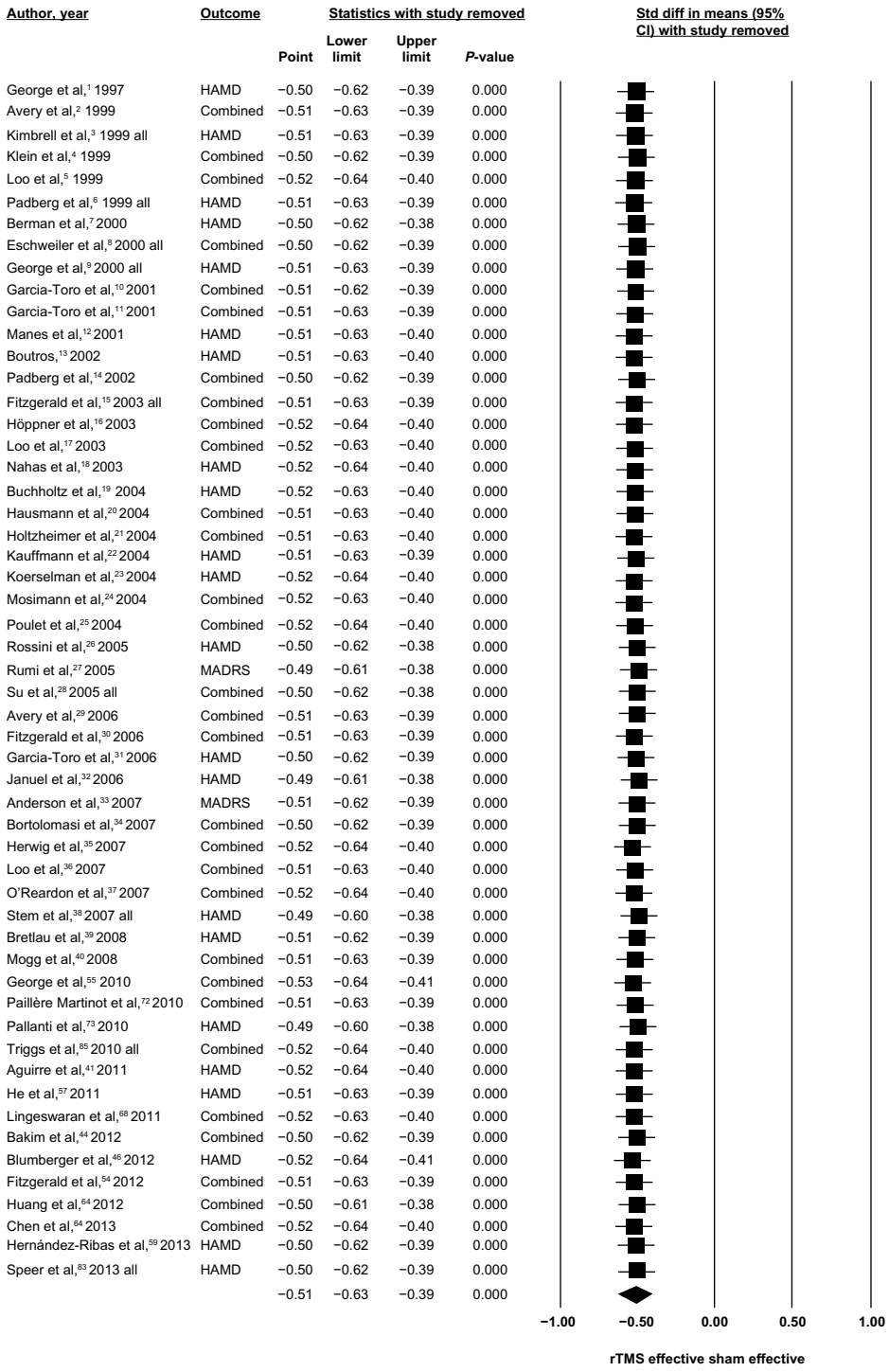

Figure S4 One study removed analysis (N=54 studies).

Notes: "All" indicates that rTMS was administered using different properties into different subgroups of patients in a study and the depression scores for such subgroups were combined. "Combined" indicates that more than one depression scale was used in a study and the effect sizes according to the multiple scales were combined). "Point" refers to the overall mean weighted *d* of all studies except for the study listed in each row.

Abbreviations: CI, confidence interval; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; Std diff, standardized mean difference *d*.

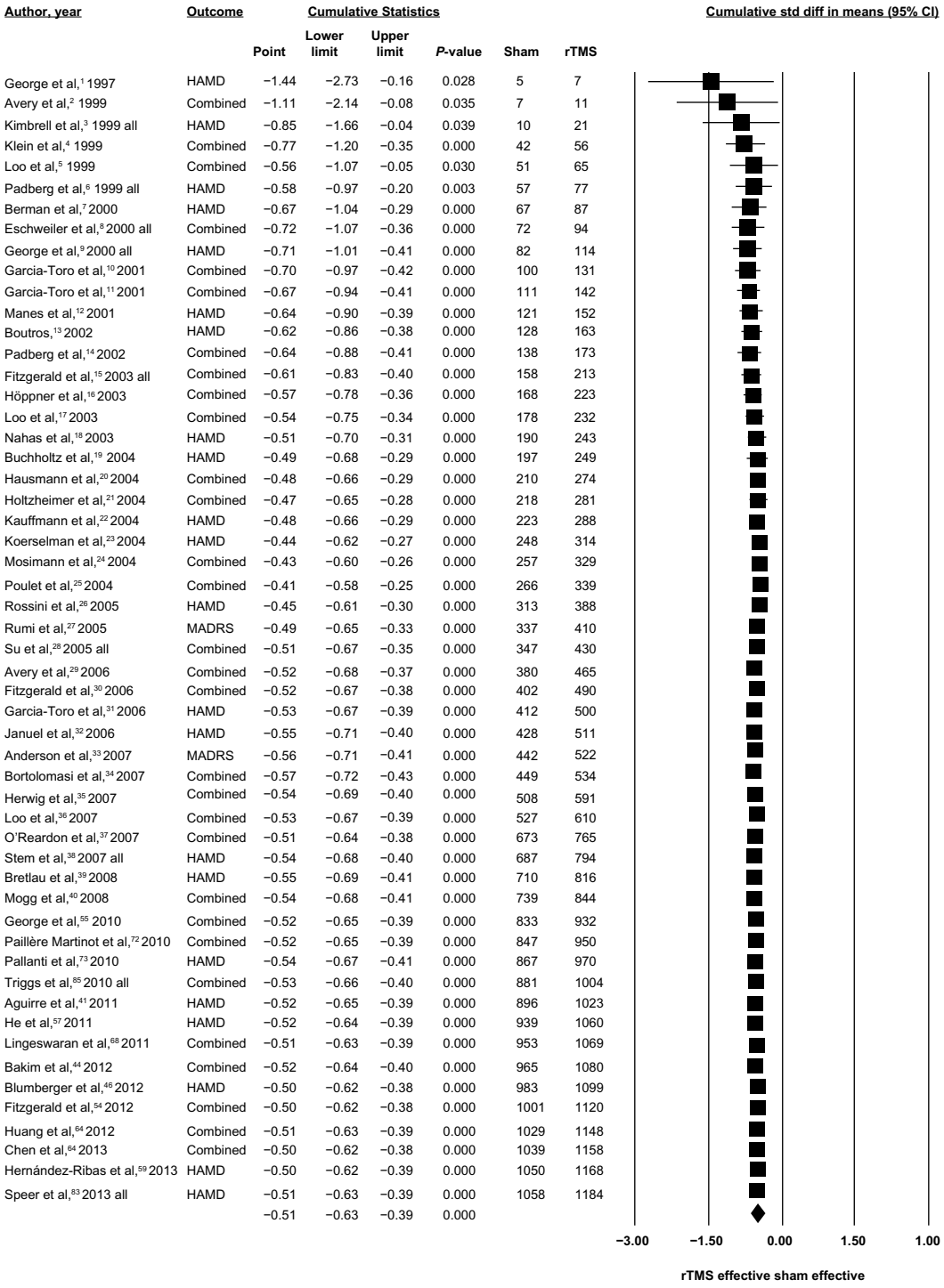

Figure S5 Cumulative meta-analysis (N=54 studies).

Notes: "All" indicates that rTMS was administered using different properties into different subgroups of patients in a study and the depression scores for such subgroups were combined. "Combined" indicates that more than one depression scale was used in a study and the effect sizes according to the multiple scales were combined). "Point" refers to the overall mean weighted *d* of all studies before and including the study listed in each row.

Abbreviations: CI, confidence interval; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; Std diff, standardized mean difference *d*.

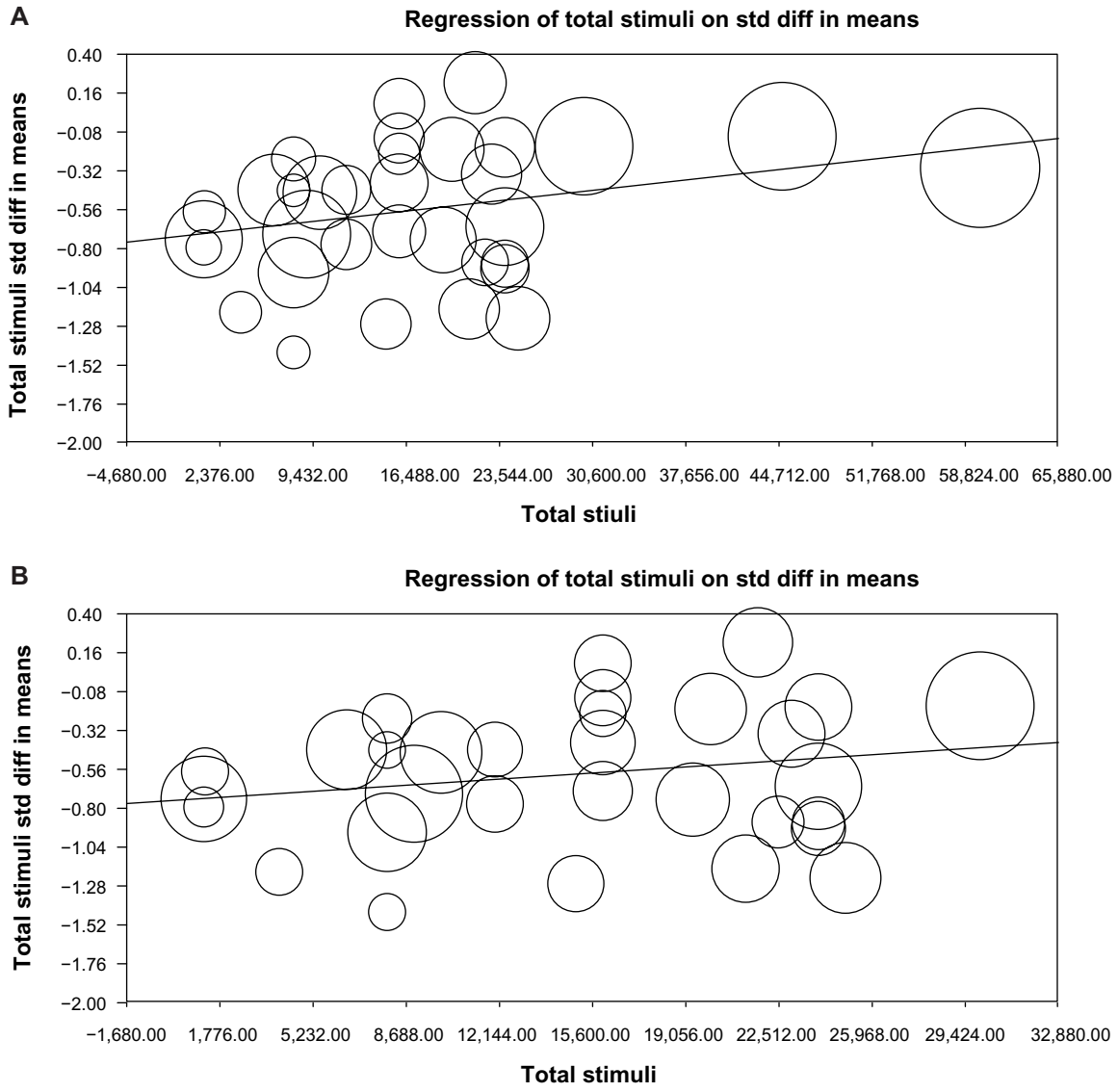

Figure S6 Univariate meta-regression of the total stimuli/study on the effect size *d* weighted according to the random-effects model.
Notes: Total stimuli = stimuli/session × total number of sessions. (**A**) The top figure shows the results of a significant meta-regression (slope *P*=0.015) in N=33 studies. However, the significance of this regression was due to two largest RCTs by O'Reardon et al[37] and George et al[55] (depicted as two largest circles on the right-hand side of (**A**). (**B**) These two RCTs are removed from the analysis in the bottom figure (slope, *P*=0.208).
Abbreviations: RCT, randomized controlled trial; std diff, standardized mean difference *d*.

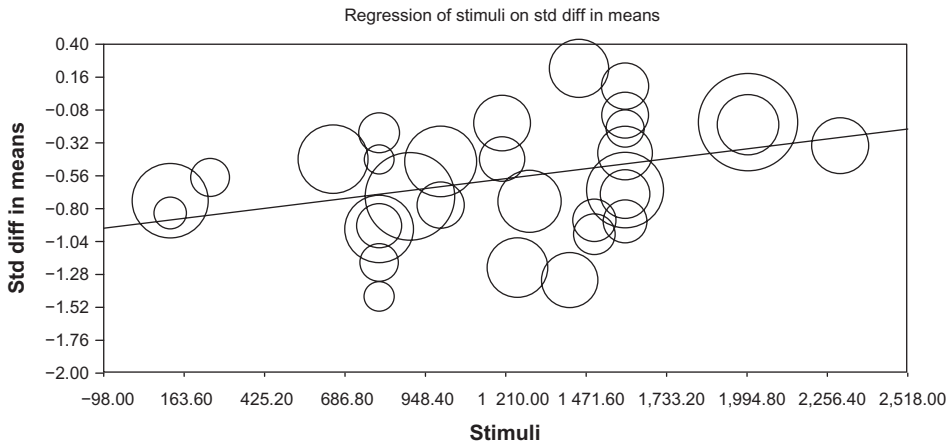

Figure S7 Univariate meta-regression of the stimuli/session on the effect size *d* weighted according to the random-effects model (two largest RCTs removed).
Notes: The slope of meta-regression conducted on N=31 studies remained positive and statistically significant (*P*=0.018) following the removal of O'Reardon et al[37] and George et al[55] studies.
Abbreviations: RCT, randomized controlled trial; std diff, standardized mean difference *d*.

Table S3 Location (country) where the N=54 studies published from 1997 to August 2013 were conducted

Rank	Country	Number of studies
1	USA	16
2	Australia	7
3	Spain	6
4	Germany	4
5	People's Republic of China, France, Italy	3 each
6	Austria, Canada, Denmark, UK	2 each
7	Brazil, India, the Netherlands, Switzerland, Taiwan, Turkey	1 each

Note: N does not add up to 54 because some studies were conducted in more than one country.

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