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REVIEW ARTICLE

Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials

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Background. Meta-analyses have shown that high-frequency (HF) repetitive transcranial magnetic stimulation (rTMS) has antidepressant properties when compared with sham rTMS. However, its overall response and remission rates in major depression (MD) remain unclear. Thus, we have systematically and quantitatively assessed the efficacy of HF-rTMS for MD based on randomized, double-blind and sham-controlled trials (RCTs).

Method. We searched the literature from 1995 through to July 2012 using MEDLINE, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, SCOPUS, and ProQuest Dissertations & Theses. We used a random-effects model, odds ratios (ORs) and the number needed to treat (NNT).

Results. Data from 29 RCTs were included, totaling 1371 subjects with MD. Following approximately 13 sessions, 29.3% and 18.6% of subjects receiving HF-rTMS were classified as responders and remitters, respectively (compared with 10.4% and 5% of those receiving sham rTMS). The pooled OR was 3.3 ($p<0.0001$) for both response and remission rates (with associated NNTs of 6 and 8, respectively). Furthermore, we found HF-rTMS to be equally effective as an augmentation strategy or as a monotherapy for MD, and when used in samples with primary unipolar MD or in mixed samples with unipolar and bipolar MD. Also, alternative stimulation parameters were not associated with differential efficacy estimates. Moreover, baseline depression severity and drop-out rates at study end were comparable between the HF-rTMS and sham rTMS groups. Finally, heterogeneity between the included RCTs was not statistically significant.

Conclusions. HF-rTMS seems to be associated with clinically relevant antidepressant effects and with a benign tolerability profile.

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Key words: Acceptability, efficacy, major depression, meta-analysis, repetitive transcranial magnetic stimulation.

Introduction

Major depression (MD) is highly prevalent, has a high incidence and is associated with a substantial loss of quality of life, increased mortality rates, and enormous social and economic costs (Ebmeier *et al.* 2006). Moreover, MD is currently ranked third worldwide in disease burden, and is expected to rank first in high-income countries in 2030 (Mathers & Loncar, 2006).

While pharmacological interventions remain the cornerstone of the management of MD, they are often unable to yield adequate clinical improvements in a relatively large proportion of subjects. In fact, up to 20–30% of subjects suffering from MD remain significantly ill despite the use of multiple therapeutic approaches (Berlim *et al.* 2008) and, as demonstrated by the large Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, less than a third of them achieve remission within 12 weeks of starting a first-line antidepressant (Trivedi *et al.* 2006). Furthermore, medications, including antidepressants, are often associated with significant side effects such as metabolic abnormalities and sexual dysfunction (Lam *et al.* 2009).

In recent years, a variety of novel neuromodulation techniques targeting MD have emerged (George & Aston-Jones, 2010). Among these, repetitive

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transcranial magnetic stimulation (rTMS) is the most promising, as it allows for discrete and safe non-invasive modulation of cortical excitability and function (Rossi *et al.* 2009). More specifically, rTMS involves the induction of electric currents within the brain (up to a depth of 2 cm) produced by pulsating magnetic fields generated through a coil of wire near the scalp (Rosa & Lisanby, 2012). These induced currents can modulate nerve cell activity in relatively focused brain regions, with frequencies $\geqslant$5 Hz [i.e. high-frequency rTMS (HF-rTMS)] being generally associated with excitatory effects (George & Aston-Jones, 2010).

Meta-analyses have shown HF-rTMS applied over the left dorsolateral prefrontal cortex (DLPFC) to have antidepressant properties as indexed mainly by statistically significant pre- to post-treatment changes in depression scores when compared with sham rTMS (Ebmeier *et al.* 2006; Lam *et al.* 2008; Slotema *et al.* 2010). However, its overall response and remission rates in primary MD remain unclear, and this is particularly problematic as growing consensus in the literature suggests that interventions with a greater likelihood of attaining at least a clinical response (and ideally a remission) have clear advantages in terms of patients' long-term overall functioning and prognosis (Nierenberg & DeCecco, 2001; Keller, 2004; Rush *et al.* 2006). Furthermore, previous meta-analyses have usually combined studies with mixed patient populations (e.g. vascular/post-stroke depression, primary MD), and have often merged data from varying rTMS protocols (e.g. primed rTMS, bilateral rTMS, HF-rTMS over the left DLPFC and/or low frequency rTMS over the right DLPFC), while overlooking their dissimilar neurophysiological basis (Rossi *et al.* 2009; Sandrini *et al.* 2011). Also, the confounding effects of medication use (e.g. subjects who started HF-rTMS concomitantly with a new antidepressant compared with those who were previously on stable medication regimens or off medication) have been rarely accounted for. Finally, previous meta-analyses often lacked relevant details about their key methodological aspects (for additional information, please refer to the Supplementary material). Undoubtedly, these limitations may have contributed to the recent questioning about the therapeutic relevance of rTMS for MD (Ridding & Rothwell, 2007; Fitzgerald, 2010).

To summarize the best available evidence on the use of HF-rTMS for treating MD (considering the limitations of the previous meta-analyses), we have carried out a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials (RCTs). We assessed the following issues: (*a*) rates of response and remission following HF-rTMS treatment; (*b*) the utility of HF-rTMS as a monotherapy or as an augmentation strategy; (*c*) the differential efficacy of HF-rTMS in samples with unipolar MD *versus* in mixed samples with unipolar and bipolar MD and in patients with categorically defined treatment-resistant depression (TRD) *versus* in patients with a less resistant illness; (*d*) the impact of the strategy for managing missing data and of alternative stimulation parameters on the efficacy of HF-rTMS; and (*e*) its overall acceptability (as indexed by drop-out rates).

Methodology of the literature review

Search strategy

We identified articles for inclusion in this meta-analysis by:

(1) Screening the bibliographies of all meta-analyses on rTMS for MD published to date (McNamara *et al.* 2001; Burt *et al.* 2002; Kozel & George, 2002; Martin *et al.* 2002, 2003; Couturier, 2005; Herrmann & Ebmeier, 2006; Gross *et al.* 2007; Lam *et al.* 2008; Schutter, 2009, 2010; Slotema *et al.* 2010; Allan *et al.* 2011) as well as of all included RCTs;
(2) Searching Medline, EMBASE, PsycINFO, the Cochrane Central Register of Controlled Trials (CENTRAL), SCOPUS and ProQuest Dissertations & Theses (PQDT) from 1 January 1995 until 22 July 2012.

The search procedures (including syntaxes, parameters and results) are described in detail in the Supplementary material.

Study selection

Candidate studies (judged on the basis of their title and abstract) had to satisfy the following criteria (Higgins & Green, 2008):

(1) Study validity: random allocation; double-blind (i.e. patients and clinical raters blinded to treatment conditions); sham-controlled (i.e. coil angled on the scalp or use of a specific sham coil); parallel or crossover design (with only data from the initial randomization being used for the latter to avoid carryover effects); $\geqslant$5 subjects with MD randomized per study arm;
(2) Sample characteristics: subjects aged 18–75 years with a diagnosis of primary MD according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition or later (APA, 1994) or the International Classification of Diseases criteria (World Health Organization, 1992);
(3) Treatment characteristics: HF-rTMS ($\geqslant$5 Hz) over the left DLPFC given for $\geqslant$10 sessions;

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(4) Publication related: articles written in English.

Studies were excluded if they:

(1) Enrolled subjects with 'narrow' diagnoses (e.g. postpartum MD) or secondary MD (e.g. vascular depression);
(2) Started HF-rTMS concomitantly with a new antidepressant medication;
(3) Did not report rates of response and/or remission.

Data extraction

Data were recorded in a structured manner as follows:

(1) Sample characteristics: mean age, gender, treatment strategy (i.e. augmentation *versus* monotherapy), primary diagnosis, presence of TRD;
(2) Study design: strategy for managing missing data (i.e. intention-to-treat approach *versus* completers-only analyses);
(3) rTMS-related parameters: stimulation frequency and intensity (including the total number of stimuli delivered), number of treatment sessions, type of sham;
(4) Primary outcome measure: number of responders to treatment based on the RCTs' primary efficacy measure (defined as a $\geqslant$50% reduction in post-treatment scores on the Hamilton Depression Rating Scale (HAMD; Hamilton, 1960) or on the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) at the end of the blinded treatment;
(5) Secondary outcome measure: number of remitters based on the RCTs' primary efficacy measure (e.g. 17- or 21-item HAMD scores $\leqslant$7 or $\leqslant$8 (Rush *et al.* 2006), respectively, or MADRS scores $\leqslant$6 (Rush *et al.* 2006)) at the end of the blinded treatment;
(6) Acceptability of treatment: differential drop-out rates between the HF- and sham rTMS groups at the end of the blinded treatment.

Data synthesis

Analyses were performed using Comprehensive Meta-Analyses version 2.0 (Biostat, USA), and IBM SPSS version 20 (IBM Corp., USA).

We used a random-effects model because we assumed that the true treatment effects had probably varied between the included RCTs (Riley *et al.* 2011). If provided, intention-to-treat data, using a method such as 'last observation carried forward' (Fergusson *et al.* 2002), were preferred over data from completers. The efficacy of HF-rTMS for MD as well as its acceptability were investigated by odds ratios (ORs) (Deeks, 2002) and the number needed to treat (NNT). We considered a NNT $\leqslant$10 as clinically meaningful because such a treatment difference would be routinely encountered in day-to-day clinical practice (Citrome, 2011). We also performed cumulative analyses to retrospectively identify the point in time when HF-rTMS (compared with sham rTMS) first reached conventional levels of statistical significance in terms of higher response and remission rates (Egger *et al.* 2001). To rule out the presence of baseline differences in depressive symptoms between HF- and sham rTMS groups, we computed the pooled standardized mean difference (SMD) for subjects' baseline depression scores. Furthermore, we conducted subgroup analyses to assess the potential impact of the following study characteristics on effect size estimates for response and remission rates: (*a*) presence of TRD at baseline (i.e. <2 *versus* $\geqslant$2 failed antidepressant trials in the current depressive episode; Berlim & Turecki, 2007); (*b*) treatment strategy (i.e. monotherapy *versus* augmentation); (*c*) diagnosis (i.e. unipolar MD *versus* mixed samples with unipolar and bipolar MD); and (*d*) strategy for managing missing data (i.e. intention-to-treat approach *versus* completers-only analyses; papers lacking information on this issue were conservatively deemed to have employed the latter; Moher *et al.* 2010). Finally, we conducted meta-regression analyses (method of moments) to assess the potential impact of the following stimulation parameters on effect size estimates for response and remission rates: (*a*) frequency in Hz; (*b*) percentage of the resting motor threshold (%rMT), (*c*) number of sessions; and (*d*) total number of magnetic pulses.

Heterogeneity was assessed using the Q statistics and the I^2 index (Cooper *et al.* 2009). Values of $p<0.10$ for the former and >35% for the latter were deemed as indicative of study heterogeneity (Borenstein *et al.* 2009). Finally, we used funnel plots, Rosenthal's fail-safe N (Rosenthal, 1979), Egger's regression intercept (Egger *et al.* 1997) and Duval & Tweedie's trim-and-fill procedure (Duval & Tweedie, 2000) to test for the presence of publication bias (Borenstein *et al.* 2009; Cooper *et al.* 2009).

Results

Literature search

Of the 34 RCTs on HF-rTMS for MD included in the previous meta-analyses, 20 were selected for the present investigation (George *et al.* 1997; Berman *et al.* 2000; George *et al.* 2000; Garcia-Toro *et al.* 2001; Boutros *et al.* 2002; Padberg *et al.* 2002; Fitzgerald *et al.* 2003; Hoppner *et al.* 2003; Nahas *et al.* 2003; Holtzheimer *et al.* 2004; Koerselman *et al.* 2004;

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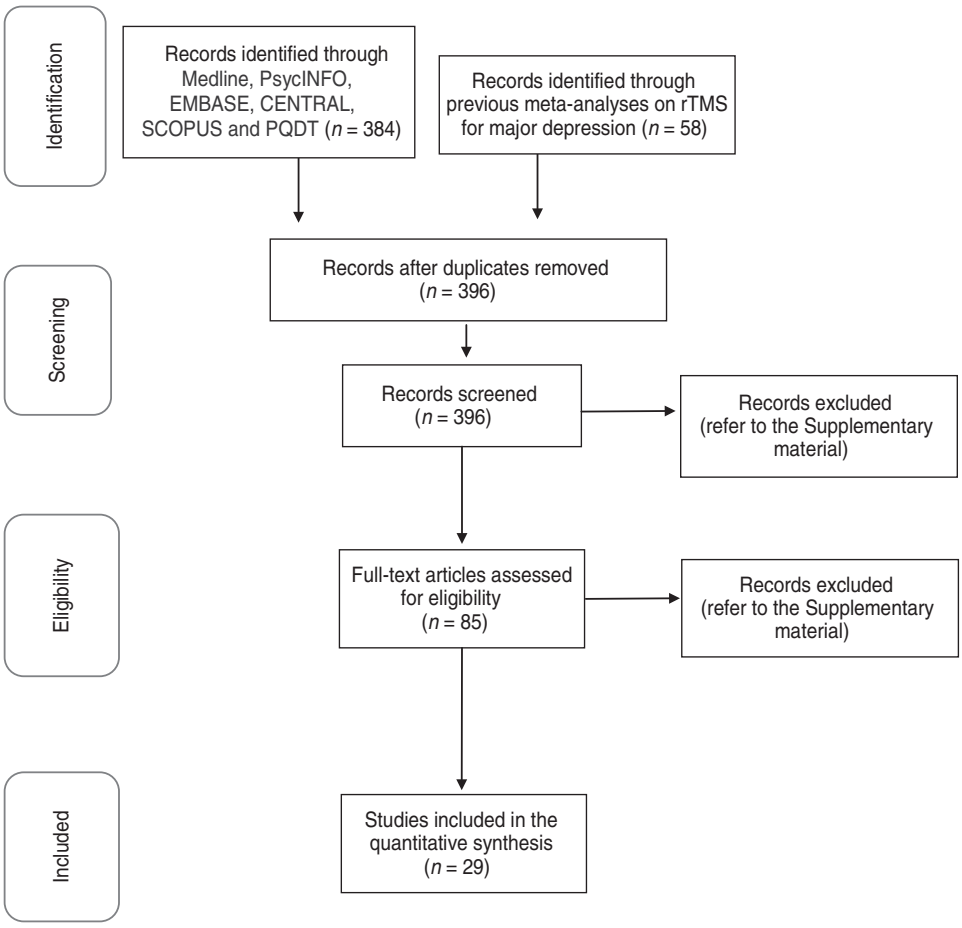

Fig. 1. Study selection procedures: PRISMA flowchart. CENTRAL, Cochrane Central Register of Controlled Trials; PQDT, ProQuest Dissertations & Theses; rTMS, repetitive transcranial magnetic stimulation.

Mosimann *et al.* 2004; Rossini *et al.* 2005; Su *et al.* 2005; Avery *et al.* 2006; Anderson *et al.* 2007; Loo *et al.* 2007; O'Reardon *et al.* 2007; Stern *et al.* 2007; Mogg *et al.* 2008). Also, we retrieved 15 RCTs on HF-rTMS for MD from Medline, PsycINFO, EMBASE, CENTRAL, SCOPUS and PQDT. Of these, nine met the eligibility criteria (George *et al.* 2010; Triggs *et al.* 2010; Zheng *et al.* 2010; Zhang *et al.* 2011; Blumberger *et al.* 2012; Fitzgerald *et al.* 2012; Hernández-Ribas *et al.* 2013; Bakim *et al.* in press). See Fig. 1 for a PRISMA flowchart (Moher *et al.* 2009), and the Supplementary material for a detailed description of the study selection procedures.

Included RCTs and subject characteristics

A total of 29 RCTs were included in our meta-analysis, totaling 1371 subjects with MD, of whom 730 were randomized to HF-rTMS (mean age=47.6, S.D.=7.1 years, 58.6% females), and 641 were randomized to sham rTMS (mean age=47.4, S.D.=6.7 years, 54.4% females) (Table 1). The mean number of HF-rTMS sessions and magnetic pulses delivered were 13.4 (S.D.=5.7) and 20922 (S.D.=17656), respectively, and 18 RCTs (62.1%) included subjects with treatment-resistant MD (i.e. $\geqslant$2 failed antidepressant trials in the current depressive episode; Berlim & Turecki, 2007). Finally, rTMS was offered as an augmentation treatment strategy in 21 out of 29 (72.4%) trials.

Response rates

Data relating to response rates were available from all 29 RCTs. Overall, 214/730 (29.3%) and 67/641 (10.4%) subjects receiving HF- or sham rTMS were classified as responders, respectively. The pooled OR was 3.3 [95% confidence interval (CI) 2.35–4.64, z=6.9, p<0.0001], indicating a significant difference in outcome favoring HF-rTMS (Fig. 2). The risk difference translated into a NNT of 6 (95% CI 4.4–6.8), meaning that about one in every six patients have clinically responded following HF-rTMS treatment (Citrome, 2011).

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Heterogeneity between RCTs did not exceed that expected by chance [Q_{29}=28.9, degrees of freedom (df)=28, p=0.42, I^2=2.97], implying that the variance among the effect sizes was not greater than expected by sampling error. The fail-safe N was 321, indicating that at least 321 unpublished or missing null findings would be needed to render the clinical effect of active HF-rTMS in terms of response statistically non-significant (i.e. $p \geqslant 0.05$). Additionally, the associated funnel plot was reasonably symmetrical (Fig. 3). Publication bias was assessed more conservatively with Egger's regression intercept, which was 0.45 (df=27, t=1.1, two-tailed p=0.28), suggesting a low risk of publication bias. In the more conservative Duval and Tweedie's trim-and-fill procedure, two of the RCTs with the highest ORs were trimmed and filled on the opposite side of zero, resulting in a corrected pooled OR of 3.16 (95% CI 2.18–4.6, Q_{adj}=34.59).

Remission rates

Data relating to remission rates were available from 15 RCTs. Overall, 96/516 (18.6%) and 23/459 (5%) subjects receiving HF- or sham rTMS were classified as remitters, respectively. The pooled OR was 3.3 (95% CI 2.04–5.32, z=4.88, p<0.0001) (Fig. 4). The risk difference translated into a NNT of 8 (95% CI 5.8–10.5).

Heterogeneity between RCTs did not exceed that expected by chance (Q_{15}=8.05, df=14, p=0.89, I^2=0). The associated funnel plot was reasonably symmetrical (Fig. 5), the fail-safe N was 67, and Egger's regression intercept was 0.3 (df=13, t=0.73, two-tailed p=0.48), suggesting a low risk of publication bias. In the Duval and Tweedie's trim-and-fill procedure, one RCT was trimmed and filled on the opposite side of zero, resulting in a corrected pooled OR of 3.13 (95% CI 1.95–5, Q_{adj}=9.82).

HF-rTMS for MD: acceptability

No differences on drop-out rates were observed at study end between HF- and sham rTMS groups (7.5% *v.* 7.6%, respectively) (OR=0.97, z=–0.14, p=0.89) (Fig. 6). Furthermore, heterogeneity between RCTs did not exceed that expected by chance (Q_{22}=14.5, df=21, p=0.84, I^2=0). Finally, no differential drop-out rates were observed when HF-rTMS was used as an augmentation strategy or as a monotherapy for MD (Q=0.1, df=1, p=0.76). For the associated forest plots, please refer to the Supplementary material.

Efficacy of HF-rTMS for MD: presence of TRD

There were no significant differences in terms of efficacy between HF-rTMS used in samples with categorically defined TRD or in samples including less treatment-resistant patients (response: Q=0.95, df=1, p=0.33; remission: Q=0.39, df=1, p=0.53). For the associated forest plots, please refer to the Supplementary material.

Efficacy of HF-rTMS for MD: augmentation versus monotherapy

There were no significant differences in terms of efficacy between HF-rTMS used as an augmentation strategy or as monotherapy for MD (response: Q=0, df=1, p=0.95; remission: Q=0.01, df=1, p=0.91). For the associated forest plots, please refer to the Supplementary material.

Efficacy of HF-rTMS for MD: primary diagnosis

There were no significant differences in terms of efficacy between HF-rTMS used in samples with primary unipolar MD or in mixed samples with unipolar and bipolar MD (response: Q=0.39, df=1, p=0.39; remission: Q=0.11, df=1, p=0.74). For the associated forest plots, please refer to the Supplementary material.

Efficacy of HF-rTMS for MD: missing data management

There were no significant differences in terms of efficacy between RCTs using an intention-to-treat approach or a completers-only analysis (response: Q=1, df=1, p=0.32; remission: Q=2.67, df=1, p=0.10). For the associated forest plots, please refer to the Supplementary material.

Efficacy of HF-rTMS for MD: stimulation parameters

Meta-regressions have shown no significant association between alternative rTMS-related parameters and estimates of response and remission rates: frequency (response: coefficient=0.06, S.E.=0.04, z=–0.12, p=0.9; remission: coefficient=0.02, S.E.=0.07, z=0.27, p=0.79),%rMT (response: coefficient=–0.009, S.E.=0.014, z=–0.62, p=0.53; remission: coefficient=–0.005, S.E.=0.02, z=–0.28, p=0.78), total number of sessions (response: coefficient=–0.001, S.E.=0.02, z=–0.05, p=0.93; remission: coefficient=–0.003, S.E.=0.028, z=–0.12, p=0.9), and total number of magnetic pulses (response: coefficient=<0.0001, S.E.=<0.0001, z=–0.88, p=0.39; remission: coefficient=<0.0001, S.E.=<0.0001, z=–0.18, p=0.86). For the associated regression scatter plots, please refer to the Supplementary material.

Cumulative analyses

RCTs on HF-rTMS for MD showed it to be significantly superior to sham rTMS in terms of response and

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Table 1. *Included randomized, double-blind and sham-controlled trials on high-frequency rTMS for major depression: main characteristics*

	Active rTMS group			Sham rTMS group				Active/sham rTMS parameters							
Study	*n*	Age, years (S.D.)	Female/ male, *n*	*n*	Age, years (S.D.)	Female/ male, *n*	Type	Frequency, Hz	%rMT	Sessions, *n*	Total pulses	UD/BD	Treatment strategy	Missing data approach	TRD?
George *et al.* (1997)	7	42.4 (15.5)	6/1	5	41 (8.28)	5/0	45°	20	80	10	8000	11/1	Monotherapy[a]	N.A.	N/A
Berman *et al.* (2000)	10	45.2 (9.5)	2/8	10	39.4 (10.8)	4/6	30–45°	20	80	10	8000	19/1	Monotherapy	ITT	Yes[b]
George *et al.* (2000)	20	42.2 (10.8)	13/7	10	48.5 (8)	6/4	45°	5/20	100	10	16000	21/9	Monotherapy	N.A.	N/A
Garcia-Toro *et al.* (2001)	18	50 (11)	8/10	17	51.5 (15.9)	7/10	90°	20	90	10	12000	35/0	Augmentation	N.A.	Yes[c]
Boutros *et al.* (2002)	12	49.4 (8)	4/8	9	52 (7)	1/8	90°	20	80	10	8000	21/0	Augmentation	ITT	Yes[c]
Padberg *et al.* (2002)	20	61.2 (4.6)	13/7	10	52.7 (5.7)	8/2	90°	10	95	10	15000	30/0	Augmentation	N.A.	Yes[c]
Fitzgerald *et al.* (2003)	20	42.2 (9.8)	8/12	20	49.1 (14.2)	11/9	45°	10	100	10	10000	35/5	Augmentation	N.A.	Yes[c]
Hoppner *et al.* (2003)	11	60.4 (7)	8/3	10	56.4 (13.2)	7/3	90°	20	90	10	8000	21/0	Augmentation	N.A.	N/A
Nahas *et al.* (2003)	11	42.4 (7.3)	7/4	12	43.4 (9.3)	7/5	45°	5	110	10	16000	0/23	Augmentation	N.A.	N/A
Holtzheimer *et al.* (2004)	7	40.4 (8.5)	4/3	8	45.4 (4.9)	3/5	90°	10	110	10	16000	15/0	Monotherapy	ITT	Yes[c]
Koerselman *et al.* (2004)	26	51 (15.4)	12/14	26	52 (13.2)	17/9	45°	20	80	10	8000	52/0	Augmentation	N.A.	N/A
Mosimann *et al.* (2004)	15	60 (13.4)	5/10	9	64.4 (13)	5/4	90°	20	100	10	16000	20/4	Augmentation	N.A.	Yes[c]
Rossini *et al.* (2005)	37	55.7 (9.9)	27/10	17	56.3 (12.6)	11/6	90°	15	100	10	6000	37/17	Augmentation	N.A.	Yes[c]
Su *et al.* (2005)	20	43.4 (11.3)	15/5	10	42.6 (11)	7/3	90°	5/20	100	10	16000	25/5	Augmentation	N.A.	Yes[c]
Avery *et al.* (2006)	35	44.3 (10.3)	21/14	33	44.2 (9.7)	16/17	90°	10	110	15	24000	68/0	Monotherapy[d]	ITT	Yes[c]
Anderson *et al.* (2007)	11	48 (8)	7/4	14	46 (12)	9/5	Sham coil	10	110	15	12000	25/0	Augmentation	ITT	Yes[e]
Loo *et al.* (2007)	19	49.8 (2.5)	10/9	19	45.7 (15)	8/11	Sham coil	10	110	20	30000	34/4	Augmentation[f]	ITT	Yes[c]

O'Reardon *et al.* (2007)	155	47.9 (11)	86/69	146	48.7 (10.6)	74/72	Sham coil	10	120	30	90000	301/0	Monotherapy	ITT	Yes[b]
Stern *et al.* (2007)	10	53.2 (12)	6/4	15	53.3 (9)	9/6	90°	10	110	10	16000	25/0	Monotherapy	N.A.	Yes[b]
Mogg *et al.* (2008)	29	55 (18)	16/13	30	52 (15.5)	21/9	Sham coil	10	110	10	10000	58/1	Augmentation	ITT	N/A
George *et al.* (2010)	92	47.7 (10.6)	58/34	98	46.5 (12.3)	50/48	Sham coil	10	120	15	45000	190/0	Monotherapy	ITT	Yes[b]
Palliere-Martinot *et al.* (2010)	18	48.2 (7.8)	11/7	14	46.6 (10.3)	10/4	Sham coil	10	90	10	16000	23/9	Augmentation	ITT	Yes[c]
Triggs *et al.* (2010)	18	46.7 (15.3)	14/4	7	41.9 (14.1)	2/5	Sham coil	5	100	10	20000	25/0	Augmentation	N.A.	Yes[c]
Zheng *et al.* (2010)	19	26.9 (6.2)	7/12	15	26.7 (4.3)	5/10	45°	15	110	20	60000	34/0	Augmentation	N.A.	Yes[c]
Blumberger *et al.* (2012)	24	48.9 (13.4)	14/12	22	45.8 (13.4)	14/6	90°	10	100[g]	15	21750	46/0	Augmentation	ITT	Yes[c]
Zhang *et al.* (2011)	14	50.8 (13.3)	3/11	14	43.8 (13.9)	5/9	180°	10	110	20	30000	28/0	Augmentation	N.A.	Yes[c]
Bakim *et al.* (in press)	23	40.9 (9.1)	20/23	12	44.4 (10.2)	11/1	45°	20	80/110	30	24000	35/0	Augmentation	N.A.	Yes[c]
Fitzgerald *et al.* (2012)	24	43.4 (12.7)	15/9	20	44.9 (15.7)	8/12	45°	10	120	15	22500	44/0	Augmentation	N.A.	Yes[c]
Hernández-Ribas *et al.* (2013)	10	42.6 (5.6)	8/2	11	50.1 (8.1)	8/3	90°	15	100	15	22500	15/6	Augmentation	N.A.	Yes[b]

rTMS, Repetitive transcranial magnetic stimulation; S.D., standard deviation; %rMT, percentage of the resting motor threshold; UD, unipolar major depression; BD, bipolar depression (type I or II); TRD, treatment-resistant depression; N.A., information not available; ITT, intention to treat; MDE, major depressive episode.

[a] Only three subjects continued with stable medication regimens.

[b] Failure to respond to $\geqslant$1 antidepressant in the current or previous MDE.

[c] Failure to respond to $\geqslant$2 antidepressants in the current MDE.

[d] 31% (n=11) of the subjects maintained stable dosages of antidepressants during the study and 69% (n=24) were off medication.

[e] No explicit criteria for TRD.

[f] Of the subjects, 55.3% (21/38) kept a stable medication regimen.

[g] 120% of the rMT in subjects older than 60 years old.

Study name	Odds ratio	Lower limit	Upper limit	*z*	*p*	Active rTMS	Sham rTMS	Relative weight
	Statistics for each study							
George *et al.* (1997)	2.538	0.085	75.765	0.538	0.591	1/7	0/5	0.99
Berman *et al.* (2000)	3.316	0.120	91.601	0.708	0.479	1/10	0/10	1.04
George *et al.* (2000)	17.348	0.895	336.226	1.887	0.059	9/20	0/10	1.30
Garcia-Toro *et al.* (2000)	7.083	0.731	68.607	1.690	0.091	5/17	1/18	2.19
Boutros et al. (2002)	1.167	0.151	9.006	0.148	0.882	3/12	2/9	2.70
Padberg *et al.* (2002)	7.452	0.371	149.546	1.313	0.189	5/20	0/10	1.27
Fitzgerald *et al.* (2003)	1.000	0.019	52.977	0.000	1.000	1/20	1/20	0.73
Hoppner *et al.* (2003)	1.000	0.173	5.772	0.000	1.000	5/10	5/10	3.63
Nahas *et al.* (2003)	1.143	0.205	6.366	0.152	0.879	4/11	4/12	3.78
Holtzheimer *et al.* (2004)	2.800	0.196	40.057	0.758	0.448	2/7	1/8	1.61
Koerselman *et al.* (2004)	1.000	0.019	52.362	0.000	1.000	1/26	1/26	0.73
Mosimmann *et al.* (2004)	1.966	0.072	53.478	0.401	0.688	1/15	0/9	1.05
Rossini *et al.* (2005)	12.190	1.460	101.804	2.309	0.021	16/37	1/17	2.50
Su *et al.* (2005)	13.500	1.421	128.258	2.266	0.023	12/20	1/10	2.23
Avery *et al.* (2006)	7.104	1.437	35.120	2.405	0.016	11/35	2/33	4.35
Anderson *et al.* (2007)	15.600	1.481	164.376	2.287	0.022	6/11	1/14	2.04
Loo *et al.* (2007)	2.462	0.514	11.799	1.126	0.260	6/19	3/19	4.51
O'Reardon *et al.* (2007)	2.230	1.204	4.130	2.550	0.011	37/155	18/146	23.98
Stern *et al.* (2007)	31.000	1.462	657.278	2.204	0.028	5/10	0/15	1.22
Mogg *et al.* (2008)	4.105	0.978	17.229	1.930	0.054	9/28	3/29	5.34
George *et al.* (2010)	3.338	1.151	9.680	2.220	0.026	14/92	5/98	9.35
Palliere-Martinot *et al.* (2010)	4.583	0.945	22.235	1.889	0.059	10/18	3/14	4.45
Triggs *et al.* (2010)	0.714	0.099	5.178	−0.333	0.739	4/18	2/7	2.87
Zheng *et al.* (2010)	24.000	2.574	223.790	2.790	0.005	12/19	1/15	2.27
Blumberger *et al.* (2012)	0.429	0.036	5.126	−0.669	0.503	1/22	2/20	1.84
Zhang *et al.* (2011)	2.400	0.524	10.992	1.128	0.259	8/14	5/14	4.77
Bakim *et al.* (in press)	18.000	2.937	110.307	3.125	0.002	18/23	2/12	3.41
Fitzgerald *et al.* (2012)	0.830	0.016	43.775	−0.092	0.927	1/24	1/20	0.73
Hernández-Ribas *et al.* (2013)	6.222	0.936	41.382	1.891	0.059	7/10	3/11	3.13
	3.306	2.354	4.643	6.899	0.000	214/730	67/641	

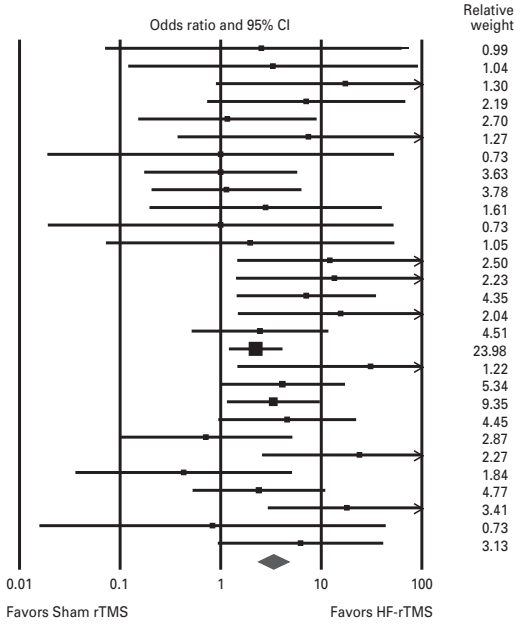

Fig. 2. Meta-analysis of high-frequency (HF) repetitive transcranial magnetic stimulation (rTMS) *versus* sham rTMS for major depression: response rates. CI, Confidence interval.

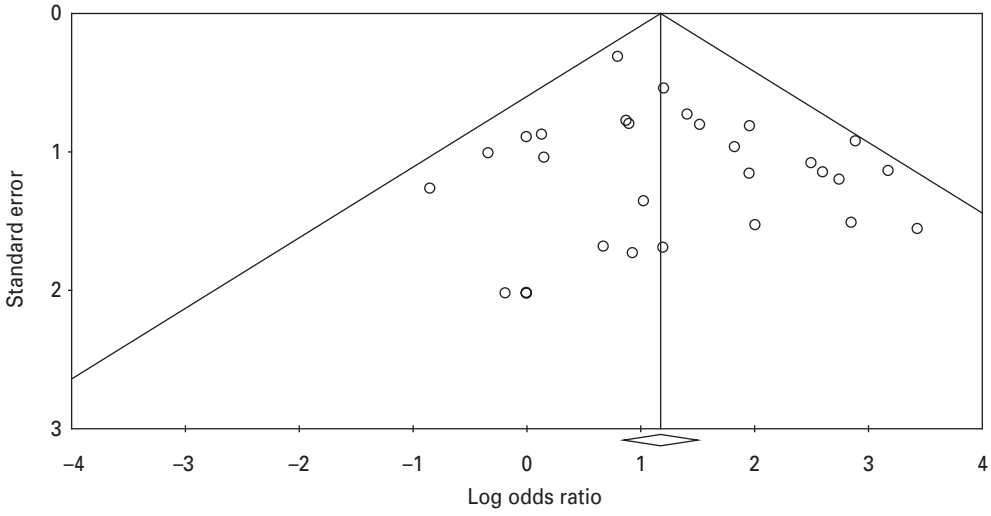

Fig. 3. Funnel plot of standard error by log odds ratio: response rates.

remission rates by the years 2002–2003 and 2005, respectively. Further studies essentially narrowed the CI around relatively similar OR estimates. For the associated forest plots, please refer to the Supplementary material.

HF- versus sham rTMS: baseline depression severity

No differences on mean baseline depression scores for HF- and sham-rTMS groups were found (SMD=–0.001, z=–0.02, p=0.98), thus ruling out illness severity at baseline as a confounding factor. Heterogeneity between RCTs did not exceed that expected by chance (Q_{28}=33.9, df=27, p=0.17, I^2=20.4). For the associated forest plot, please refer to the Supplementary material.

Discussion

To our knowledge, this is the first (and largest overall) meta-analysis to investigate response, remission and drop-out rates following HF-rTMS for primary MD. Briefly, our results show that this neuromodulation technique is significantly more effective than sham

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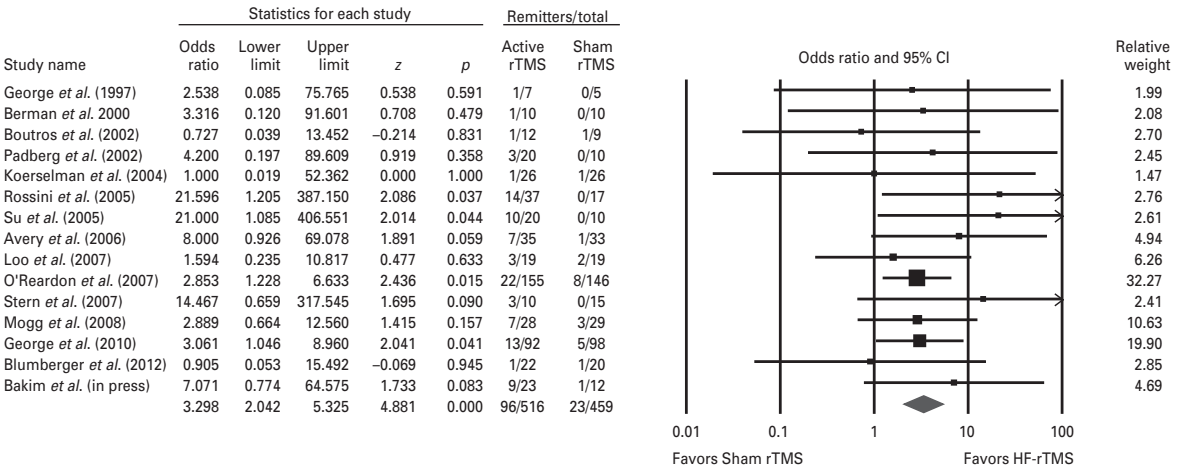

Fig. 4. Meta-analysis of high-frequency (HF) repetitive transcranial magnetic stimulation (rTMS) *versus* sham rTMS for major depression: remission rates. CI, Confidence interval.

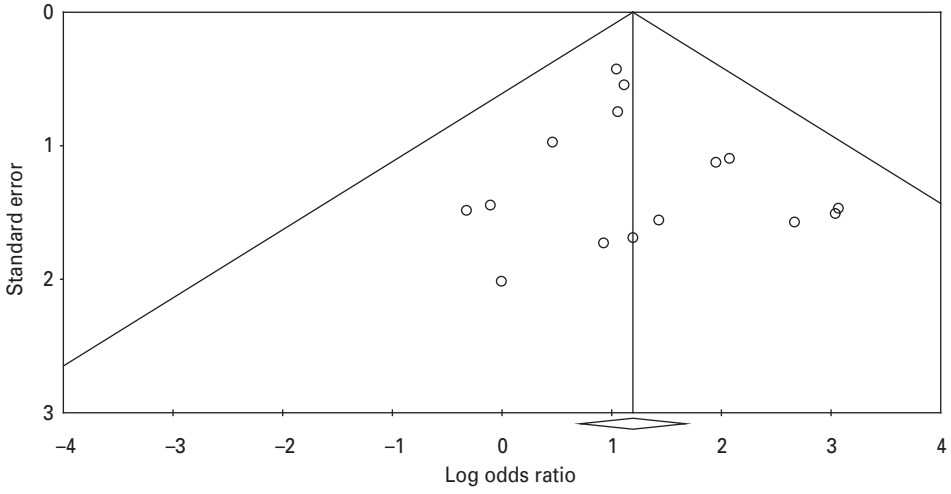

Fig. 5. Funnel plot of standard error by log odds ratio: remission rates.

rTMS in terms of both response and remission rates [with pooled ORs of 3.3 for each and clinically relevant NNTs (Citrome, 2011) of 6 and 8, respectively]. Furthermore, HF-rTMS seems to be equally effective as an augmentation strategy or as a monotherapy for MD, when it is used in patients with categorically defined TRD or in patients with less resistant depressive illness, and in samples with primary unipolar MD or in mixed samples with unipolar and bipolar MD. Moreover, alternative stimulation parameters were not associated with differential efficacy estimates. Finally, HF- and sham rTMS groups did not differ in terms of baseline depressive symptomatology and drop-out rates at study end.

Overall, HF-rTMS seems to be an acceptable treatment for MD, and is associated with clinically relevant antidepressant effects (especially considering that it has been mostly investigated in samples with TRD). This notion is further strengthened by the fact that the observed effect sizes for HF-rTMS are comparable with those reported for several commercially available antidepressants and augmenting medications. For example, a recent meta-analysis of 122 trials on antidepressants for MD (mostly in non-TRD samples) found a pooled drug–placebo rate ratio for response to treatment of 1.42 (95% CI 1.38–1.48) and a corresponding NNT of 8 (95% CI 7.1–9.1) (Undurraga & Baldessarini, 2012); our estimate, when converted to rate ratio, is 2.2 (95% CI 1.72–2.83). Moreover, a recent meta-analysis on the use of atypical antipsychotics as augmenting agents for TRD has shown that the ORs for response and remission with drug *versus* placebo were 1.69 (95% CI 1.46–1.95) and 2.00 (95% CI 1.69–2.37), respectively (Nelson & Papakostas, 2009). Furthermore, our findings resemble those reported by the large and representative STAR*D study in which

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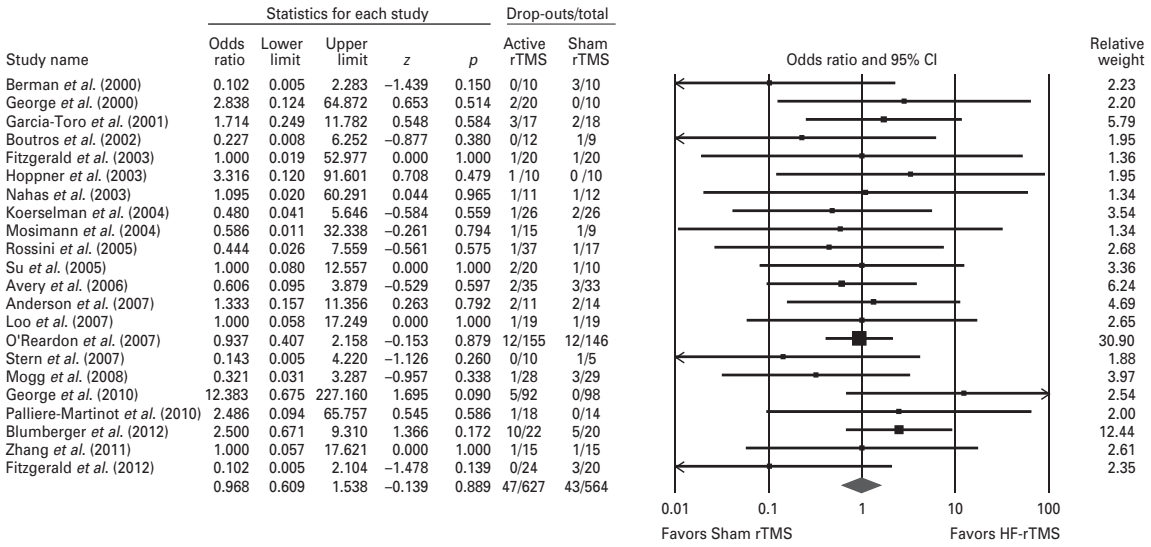

Fig. 6. Meta-analysis of high-frequency (HF) repetitive transcranial magnetic stimulation (rTMS) *versus* sham rTMS for major depression: drop-out rates. CI, Confidence interval.

remission rates after lithium carbonate or triiodothyronine augmentation of a second unsuccessful antidepressant course were 20.4% (Nierenberg *et al.* 2006). More specifically, HF-rTMS in the current meta-analysis was associated with remission rates of 18.6% in depressed individuals who had often not responded to at least two antidepressant trials in the current episode.

It is difficult to compare our findings with those of previous meta-analysis as their main outcome measures and methodology differed significantly from ours. For example, we included a homogeneous set of RCTs in terms of the stimulation protocol used (i.e. HF-rTMS over the left DLPFC). Furthermore, our use of clinically relevant outcome measures such as response and remission rates is in line with current guidelines on the assessment of treatment efficacy in MD (Rush *et al.* 2006), and is clearly more useful and understandable for healthcare professionals and administrators, as well as for patients and their relatives, than traditional effect sizes such as Cohen's *d* or Hedges' *g* (Fritz *et al.* 2012). All but one previous meta-analysis (Lam *et al.* 2008) has reported response and remission rates following rTMS for MD, although in this study the focus was on treatment-resistant cases, diverse stimulation protocols were combined (e.g. HF-, bilateral and low-frequency rTMS) and significant heterogeneity between the included RCTs (e.g. I^2 >30%) was observed (Lam *et al.* 2008).

As the therapeutic use of HF-rTMS involves several variables, it is possible that the optimum treatment protocol is yet to be determined (Wassermann & Zimmermann, 2012). However, based on our findings, we could not show that the optimization of parameters such as frequency,%rMT, and number of sessions/total magnetic stimulation produced higher efficacy estimates. In other words, intensive HF-rTMS protocols are not necessarily more effective for MD than less intensive ones, and this might have implications for the 'real-world' delivery of this neuromodulation treatment. More broadly, and in light of our main results, we propose that future studies on HF-rTMS for MD should move away from establishing the efficacy of current stimulation protocols against sham rTMS – which we believe has now been firmly demonstrated – and focus instead on new ways of improving its therapeutic effects, tolerability and availability. For instance, new stimulation protocols and devices, such as theta burst stimulation (Chistyakov *et al.* 2010) and the H-coil (Levkovitz *et al.* 2010), respectively, and the application of baseline electrophysiological and/or neuroimaging evaluations to determine whether HF-rTMS will be effective for individual patients (Arns *et al.* 2012) have already yielded encouraging results. Also, an interesting avenue for potentially enhancing the overall efficacy of HF-rTMS for MD is the targeting of alternative brain regions (e.g. dorsomedial, ventrolateral and ventromedial prefrontal cortices; Downar & Daskalakis, 2012). However, the clinical utility of this strategy has not yet been established in the literature.

Limitations

First, the quality of the available sham/control rTMS conditions is still unresolved (Rosa & Lisanby, 2012). The majority of the included RCTs have used active stimulation with the magnetic coil tilted at angles of 45° to 90° from the scalp. Even though the magnetic

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field intensity in this sham method is oriented away from the target, it has been demonstrated that it can still affect brain functioning (George & Aston-Jones, 2010). Furthermore, first-generation sham coils have been shown to only partially mimic the experience of real rTMS (Rossi *et al.* 2009), and this might have resulted in ineffective blinding. However, we have recently shown that a similar percentage of subjects receiving HF- and sham rTMS (52% *v.* 59%, respectively; risk difference=–0.04, z=–0.51, p=0.61) were able to correctly guess their treatment allocation at study end (Berlim *et al.* 2013). Second, the ideal strategy for targeting the DLPFC is still debatable (Rosa & Lisanby, 2012). Most RCTs in MD to date have used the so-called '5 cm rule', which involves the localization of the motor cortical site for optimal stimulation of the *abductor pollicis brevis* muscle, and then a measurement 5 cm anteriorly along the scalp surface to identify the DLPFC (George & Aston-Jones, 2010). However, a number of recent studies have shown this method to be probably suboptimal (Fitzgerald *et al.* 2009; Herbsman *et al.* 2009; Rusjan *et al.* 2010) and, thus, the use of neuronavigation, which involves the localization of the scalp position associated with the DLPFC based on structural magnetic resonance imaging scans from individual subjects, may be useful for future RCTs (Ruohonen & Karhu, 2010; Schonfeldt-Lecuona *et al.* 2010). Third, although the interaction between professionals administering rTMS and patients was kept to a minimum, the fact that the former were not blind to treatment allocation may have influenced treatment outcome (Rosa & Lisanby, 2012). Fourth, we only examined the efficacy of HF-rTMS immediately after study end, and thus cannot estimate the stability of its medium- to long-term antidepressant effects. This is especially relevant considering the labor-intensive and time-consuming nature of rTMS (Wassermann & Zimmermann, 2012). Although data remain limited in this regard, a recent 6-month follow-up study with over 90 depressed subjects has shown that the therapeutic benefits of HF-rTMS are durable, and that it can be also used for precluding impending relapse (Janicak *et al.* 2010). Additionally, Mogg *et al.* (2008) have reported that the clinical improvements associated with HF-rTMS were maintained overall at a 4-month follow-up. Fifth, because we did not have access to individual patient data, we could not compare the efficacy of HF-rTMS in patients at different stages of the treatment of MD. Sixth, one could argue that our main results were principally derived from two large multicenter trials (O'Reardon *et al.* 2007; George *et al.* 2010) (as the remaining RCTs were numerous but had relatively small samples). However, the random-effects model (DerSimonian & Kacker, 2007) employed in this meta-analysis assigned a relative weight of <35% to those two large trials. Finally, meta-analyses have been often criticized for combining heterogeneous studies, for the potential of publication bias, and for the inclusion of poor-quality trials (Borenstein *et al.* 2009). In the present study, however, these concerns were addressed by the use of stringent inclusion criteria, and by the objective examination of both publication bias and heterogeneity. In particular, the lack of significant heterogeneity among the included RCTs shows that our results are reliable overall. Also, the estimated fail-safe *N*s for response and remission rates after HF-rTMS were 321 and 67, respectively, and we believe that it is unlikely that such a large number of unpublished RCTs with null effects have been either missed by our literature search or never published.

Practical suggestions for future RCTs

We propose the following practical suggestions for future RCTs on rTMS for MD: (1) investigators should systematically and thoroughly report relevant MD-related variables (e.g. number of lifetime depressive episodes, current episode duration, current and past use of antidepressants and/or of other somatic or psychotherapeutic treatments, current suicidality), as well as response and remission rates according to current recommendations on efficacy assessment in MD (Rush *et al.* 2006); (2) trials should include other clinically relevant treatment outcomes encompassing constructs that go beyond the estimation of depressive symptoms (e.g. quality of life, social functioning) (Berlim & Fleck, 2003); (3) the use of novel sham rTMS techniques, such as focal electrical stimulation of the scalp (Borckardt *et al.* 2008), should be probably favored over coil angulation and first-generation sham coils; (4) studies should include longer follow-up periods (e.g. >6–12 months) in order to establish the medium- to long-term cost-effectiveness of HF-rTMS; and (f) the use of novel stimulation protocols [e.g. theta burst stimulation (Chistyakov *et al.* 2010), accelerated rTMS (Holtzheimer *et al.* 2010)] and techniques (e.g. deep transcranial magnetic stimulation; Levkovitz *et al.* 2010) should be carefully evaluated.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291713000512.

Declaration of Interest

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