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REVIEW ARTICLE

A systematic review and meta-analysis on the efficacy and acceptability of bilateral repetitive transcranial magnetic stimulation (rTMS) for treating major depression

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Background. Bilateral repetitive magnetic stimulation (rTMS) is a promising novel therapeutic intervention for major depression (MD). However, clinical trials to date have reported conflicting evidence concerning its overall efficacy, which might have resulted from low statistical power. Thus, meta-analytical approaches could be useful in examining this issue by allowing the integration of findings from multiple studies and thus producing more accurate estimates of the treatment effect.

Method. We searched the literature for randomized, double-blind and sham-controlled trials (RCTs) on bilateral rTMS for treating MD from 1995 to July 2012 using EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, SCOPUS, and ProQuest Dissertations and Theses, and from October 2008 until May 2012 using Medline. The main outcome measures were response and remission rates. We used a random-effects model, odds ratios (ORs) and the number needed to treat.

Results. Data were obtained from seven RCTs, totaling 279 subjects with MD. After an average of 12.9 (S.D. = 2.7) sessions, 24.7% (40/162) and 6.8% (8/117) of subjects receiving active bilateral rTMS and sham rTMS were classified as responders [OR 4.3, 95% confidence interval (CI) 1.95–9.52, $p < 0.0001$]. Also, 19% (23/121) and 2.6% (2/77) of subjects were remitters following active bilateral rTMS and sham rTMS, respectively (OR 6.0, 95% CI 1.65–21.8, $p = 0.006$). No difference between baseline mean depression scores for the bilateral and sham rTMS groups was found, and the former was comparable with the latter in terms of drop-out rates at study end. Furthermore, we did not find significant differences efficacy- and acceptability-wise between active bilateral and unilateral rTMS at study end. Finally, heterogeneity between the included RCTs was not significant, and the risk of publication bias was found to be low.

Conclusions. Bilateral rTMS is a promising treatment for MD as it provides clinically meaningful benefits that are comparable with those of standard antidepressants and unilateral rTMS. Furthermore, bilateral rTMS seems to be an acceptable treatment for depressed subjects.

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

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a safe and non-invasive neuromodulation technique that is being intensively explored as a novel treatment for major neuropsychiatric disorders (Rosa & Lisanby, 2012). rTMS is capable of inducing electrical currents and depolarizing neurons in focal brain areas with the use of rapidly changing electromagnetic fields generated by a coil placed over the scalp (George & Post, 2011). When applied repetitively, these electrical currents can modulate cortical excitability, decreasing it or increasing it, depending on the parameters of stimulation (Fregni & Pascual-Leone, 2007). Accordingly, frequencies $\leqslant 1$ Hz [low-frequency (LF)-rTMS] are usually inhibitory, while higher frequencies [usually 5–20 Hz or high-frequency (HF)-rTMS] are usually excitatory (Fitzgerald *et al*. 2002; Marangell *et al*. 2007).

To date, several randomized controlled trials (RCTs) have shown the efficacy and safety of both HF-rTMS and LF-rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) and the right DLPFC, respectively, for treating major depression (MD) (Fitzgerald *et al*. 2003; O'Reardon *et al*. 2007; George

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et al. 2010). More recently, a third rTMS treatment protocol for MD has been described, namely bilateral stimulation (either simultaneously or sequentially) targeting both the left and the right DLPFC (Daskalakis *et al*. 2008). The use of this novel neuromodulation approach in MD is supported by several lines of neurobiological evidence. For example, neuroimaging studies have demonstrated that the underlying neural circuitry of MD probably involves dysregulation of cortical functioning, with lower and higher activity observed in the left and the right DLPFC, respectively (Fitzgerald *et al*. 2006*b*, 2008). Furthermore, neurophysiological studies have shown asymmetrical differences in cortical excitability in depressed subjects compared with healthy controls (Bajbouj *et al*. 2006; Salustri *et al*. 2007). This has led to the assertion that bilateral rTMS might be a more optimal neuromodulation treatment for MD compared with unilateral stimulation, as the combination of HF-rTMS and LF-rTMS could be therapeutically synergistic because both may act via reciprocal and potentially complementary mechanisms (Rotenberg, 2008).

However, the efficacy of bilateral rTMS for MD remains unclear, as RCTs to date have produced conflicting results. For example, Loo *et al*. (2003) and McDonald *et al*. (2006) have shown bilateral rTMS to be no better than sham rTMS for MD, whereas Fitzgerald *et al*. (2006*a*) and Blumberger *et al*. (2012) have reported that bilateral rTMS produced significantly higher rates of clinical improvement in depressed subjects when compared with sham rTMS. These discrepant findings are probably due to a lack of statistical power among some of the individual RCTs (Maxwell *et al*. 2008). Therefore, the use of meta-analytical approaches could produce more accurate estimates of the treatment effect by integrating the findings from multiple studies (Huf *et al*. 2011). Accordingly, we have carried out a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials (RCTs) on bilateral rTMS for MD with a focus on clinically meaningful outcomes, namely response and remission rates. Furthermore, we have assessed the acceptability of bilateral rTMS by comparing the differential drop-out rates between subjects receiving active or sham bilateral rTMS.

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 from 1 October 2008 until 20 July 2012 (as previous meta-analyses have screened this database up to late 2008: Slotema *et al*. 2010; Allan *et al*. 2011);
(3) Searching EMBASE, PsycINFO, the Cochrane Central Register of Controlled Trials (CENTRAL), SCOPUS and ProQuest Dissertations and Theses (PQDT) from 1 January 1995 until 20 July 2012.

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

Study selection

Candidate studies 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 cross-over design (with only data from the initial randomization being used for the latter to avoid carry-over effects); five or more subjects with MD randomized per study arm;
(2) Sample characteristics: subjects aged 188–75 years with a diagnosis of primary major depressive episode (unipolar or bipolar) according to the Diagnostic and Statistical Manual of Mental Disorders or the International Classification of Diseases criteria;
(3) Treatment characteristics: bilateral rTMS (administered sequentially or simultaneously) given for five or more sessions either as a monotherapy or as an augmentation strategy for MD;
(4) Publication-related: articles written in English.

Studies were excluded if they:

(1) enrolled subjects with 'narrow' diagnoses (e.g. postpartum depression) or secondary MD (e.g. vascular depression);
(2) started rTMS concomitantly with a new antidepressant;
(3) did not report rates of response to treatment and/or remission.

Data extraction

Data were recorded in a structured fashion as follows:

(1) Sample characteristics: mean age, gender, treatment strategy used (i.e. augmentation or monotherapy), presence of treatment-resistant MD;

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(2) rTMS-related: stimulation frequency and intensity (including the total number of stimuli delivered), number of treatment sessions, type of sham;
(3) Primary outcome measure: number of responders to treatment based on the RCT's 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 Montgomeryy–Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979)] at study end;
(4) Secondary outcome measure: number of remitters based on the RCT's primary efficacy measure (e.g. 17-item or 21-item HAMD scores $\leqslant 7$ or $\leqslant 8$, respectively, or MADRS scores $\leqslant 6$) at study end;
(5) Acceptability of treatment: overall drop-out rates of active and sham rTMS groups at study end.

Data synthesis and analyses

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 it was 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', were preferred over data from completers (Fergusson *et al*. 2002). The efficacy of bilateral rTMS for MD as well as its acceptability were investigated by odds ratios (ORs) and the number needed to treat (NNT) (Borenstein *et al*. 2009) for rates of response/remission and drop-outs. 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). Also, to rule out the presence of baseline differences in depressive symptoms between active and sham rTMS groups, we computed the pooled standardized mean difference (SMD) of subjects' baseline scores on the HAMD or the MADRS.

Heterogeneity was assessed using the Q statistics and I^2 (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 (Rothstein *et al*. 2005), Egger's regression intercept (Egger *et al*. 1997), and Duval and Tweedie's trim-and-fill procedure (random effects) (Duval & Tweedie, 2000) to test for the presence of publication bias (Borenstein *et al*. 2009; Cooper *et al*. 2009).

Results

Literature search

Of the five RCTs on bilateral rTMS for MD included in the previous meta-analyses, four were selected for the present investigation (Loo *et al*. 2003; Fitzgerald *et al*. 2006*a*; Garcia-Toro *et al*. 2006; McDonald *et al*. 2006). Also, we retrieved three RCTs on bilateral rTMS for MD from Medline, PsycINFO, EMBASE, CENTRAL, SCOPUS and PQDT, and they were all included in this study (Pallanti *et al*. 2010; Blumberger *et al*. 2012; Fitzgerald *et al*. 2012). Please refer to the Supplementary material for a detailed description of the study selection procedures.

Included RCTs: main characteristics

Overall, seven RCTs were included in our meta-analysis, totaling 279 subjects with MD, of whom 162 were randomized to active bilateral rTMS [mean age = 49.3 (S.D. = 5.7) years, 56.2% females] and 117 were randomized to sham rTMS [mean age = 47.4 (S.D. = 3.3) years, 58.1% females]. The mean number of rTMS sessions delivered was 12.9 (S.D. = 2.7). Also, bilateral rTMS was used as an augmentation strategy for MD in almost all RCTs (six out of seven), and all included subjects had some degree of treatment-resistant depressive illness. The main characteristics of the included RCTs are described on Tables 1 and 2.

Response rates

Data relating to response rates were available from all seven RCTs. Overall, 40 (out of 162, 24.7%) and eight (out of 117, 6.8%) subjects receiving active bilateral rTMS or sham rTMS were classified as responders to treatment, respectively. The pooled OR was 4.3 [95% confidence interval (CI) 1.95–9.52, $z = 3.6$, $p < 0.0001$], indicating a significant difference in outcome favoring active bilateral rTMS (Fig. 1). The risk difference translated into a NNT of six (95% CI 3.9–10.2), meaning that about one in every six patients will present a response following bilateral rTMS.

Heterogeneity between RCTs did not exceed that expected by chance [degrees of freedom (df) = 6, $Q_6 = 1.77$, $p = 0.94$, $I^2 = 0$], implying that the variance among the effect sizes was no greater than expected by sampling error. Furthermore, the associated funnel plot was reasonably symmetrical (please refer to the Supplementary material). Publication bias was assessed more conservatively with Egger's regression intercept, which was -0.72 (df = 5, $t = 0.86$, two-tailed $p = 0.43$), suggesting a low risk of publication bias. In the Duval and Tweedie's trim-and-fill procedure, no RCT was trimmed and filled on the opposite side of zero, thus reinforcing the low risk of publication bias.

Remission rates

Data relating to remission rates were available from four RCTs. Overall, significantly more patients

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Table 1. *Included randomized, double-blind and sham-controlled trials on bilateral rTMS for major depression: demographic/clinical characteristics and rTMS parameters*

	Active rTMS					Sham rTMS								
				Mean depression score (S.D.)						Mean depression score (S.D.)				
Study	*n*	Mean age, years (S.D.)	Female/male, *n*	Pre	Post	*n*	Mean age, years (S.D.)	Female/male, *n*	Type	Pre	Post	Primary diagnosis	Treatment strategy	TRD[a]
Loo *et al*. (2003)	9	54.9 (18)	6/3	38.4 (6.3)[b]	N.A.	10	48.4 (10.88)	6/4	Inactive coils	33.1 (5.2)[b]	N.A.	15.8% with BD[c]; 84.2% with MDD[d]	Monotherapy (26.3%); augmentation (73.7%)	Yes[d]
Fitzgerald *et al*. (2006*a*)	25	46.8 (10.7)	15/10	34 (5.9)[b]	26.2 (10.2)[b]	25	43.7 (10.2)[b]	16/9	45°	34.1 (5.2)[b]	30.9 (8.2)[b]	16% with BD; 84% with MDD	Augmentation	Yes[e]
Garcia-Toro *et al*. (2006)	10	48.5 (13.28)	4/6	27.3 (5)[a]	20.1 (8.2)[a]	10	47.2 (11.8)	7/3	45°	25.1 (7.3)[a]	23.6 (7.8)[a]	All with MDD	Augmentation	Yes[e]
McDonald *et al*. (2006)	50	49[f]	27/23	N.A.	19.2[c]	12	54[f]	5/7	90°	N.A.	19.8[c]	13% with BD; 87% with MDD	Monotherapy	Yes[g]
Pallanti *et al*. (2010)	20	47.6 (12.33)	11/9	28.7 (6.0)[c]	N.A.	20	47.85 (9.1)	12/8	Sham coil	29 (3.5)[c]	N.A.	All with MDD	Augmentation	Yes[e]
Blumberger *et al*. (2012)	26	58 (12.5)	14/12	25.1 (3.8)[c]	15.3 (6.7)[c]	20	45.8 (13.3)	14/6	90°	25.2 (2.8)[c]	17.8 (4.5)[c]	All with MDD	Augmentation	Yes[e]
Fitzgerald *et al*. (2012)	22	40.45 (15.5)	14/8	24.3 (3.6)[c]	22.2 (6.0)[c]	20	44.9 (15.7)	8/12	45°	22.8 (2.1)[c]	22.6 (5)[c]	All with MDD	Augmentation	Yes[e]

rTMS, Repetitive transcranial magnetic stimulation; S.D., standard deviation; TRD, treatment-resistant depression; N.A., information not available; BD, bipolar depression; MDD, major depressive disorder; HAMD, Hamilton Depression Rating Scale.

[a] Montgomery–Asberg Depression Rating Scale.

[b] 21-item HAMD.

[c] 17-item HAMD.

[d] Failure to respond to ⩾1 antidepressants in the current major depressive episode.

[e] Failure to respond to ⩾2 antidepressants in the current major depressive episode.

[f] Median.

[g] Failure to respond to ⩾3 antidepressants in the current major depressive episode.

Table 2. *Included randomized, double-blind and sham-controlled trials on bilateral rTMS for major depression: rTMS parameters*

	Left DLPFC			Right DLPFC				
Study	Frequency, Hz	% rMT	Total pulses	Frequency, Hz	% rMT	Total pulses	Protocol	Sessions, *n*
Loo *et al*. (2003)	15	90	27 000	15	90	27 000	Simultaneous	15
Fitzgerald *et al*. (2006*a*)	10	100	7500	1	110	4200	Sequential	10
Garcia-Toro *et al*. (2006)	20	110	12 000	1	110	18 000	Sequential	10
McDonald *et al*. (2006)	10	110	10 000	1	110	6000	Sequential	10
Pallanti *et al*. (2010)	10	100	15 000	1	110	6300	Sequential	15
Blumberger *et al*. (2012)	10	100[a]	21750	1	100[a]	6975	Sequential	15
Fitzgerald *et al*. (2012)	10	120	22 500	1	120	13500	Sequential	15

rTMS, Repetitive transcranial magnetic stimulation; DLPFC, dorsolateral prefrontal cortex; rMt, resting motor threshold.
[a] 120% of the rMT in subjects older than 60 years old.

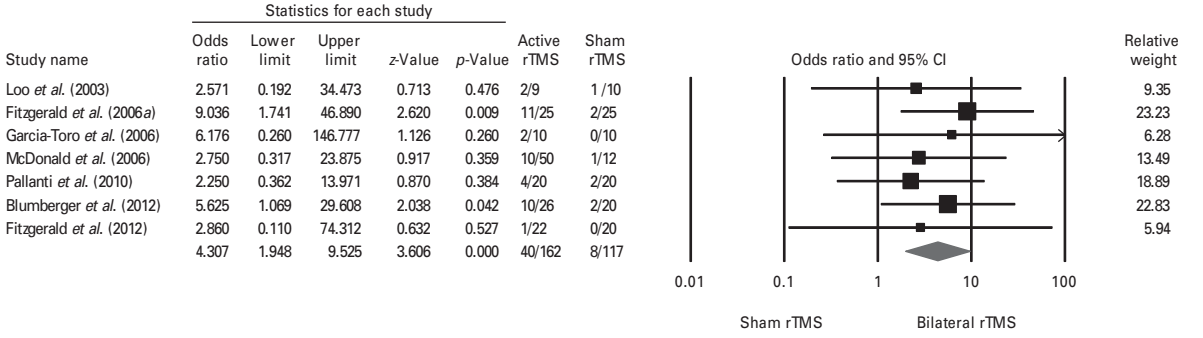

Fig. 1. Meta-analysis of bilateral repetitive transcranial magnetic stimulation (rTMS) *versus* sham rTMS for major depression: response rates. CI, Confidence interval.

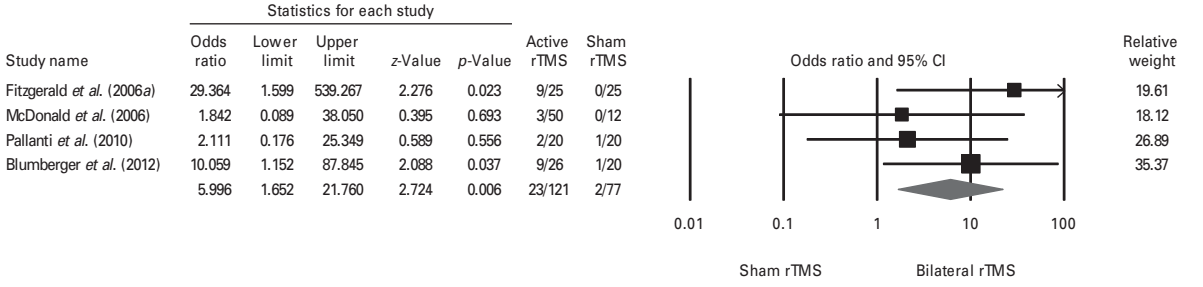

Fig. 2. Meta-analysis of bilateral repetitive transcranial magnetic stimulation (rTMS) *versus* sham rTMS for major depression: remission rates. CI, Confidence interval.

receiving active bilateral rTMS were remitters as compared with those receiving sham rTMS [19% (23/121) *v*. 2.6% (2/77), respectively]. The pooled OR was 6 (95% CI 1.65–21.8, $z=2.72$, $p=0.006$) (Fig. 2). The risk difference translated into a NNT of 7 (95% CI 4.1–11.7).

Heterogeneity between RCTs did not exceed that expected by chance (df = 3, $Q_3=2.62$, $p=0.45$, $I^2=0$). The associated funnel plot was reasonably symmetrical (please refer to the Supplementary material), and Egger's regression intercept was −0.68 (df = 2, $t=0.16$, two-tailed $p=0.89$), suggesting a low risk of publication bias. In the Duval and Tweedie's trim-and-fill procedure, no RCT was trimmed and filled on the opposite side of zero, thus reinforcing the low risk of publication bias.

Bilateral rTMS versus *unilateral rTMS: response and remission rates*

Data relating to response and remission rates following active bilateral and unilateral rTMS were available

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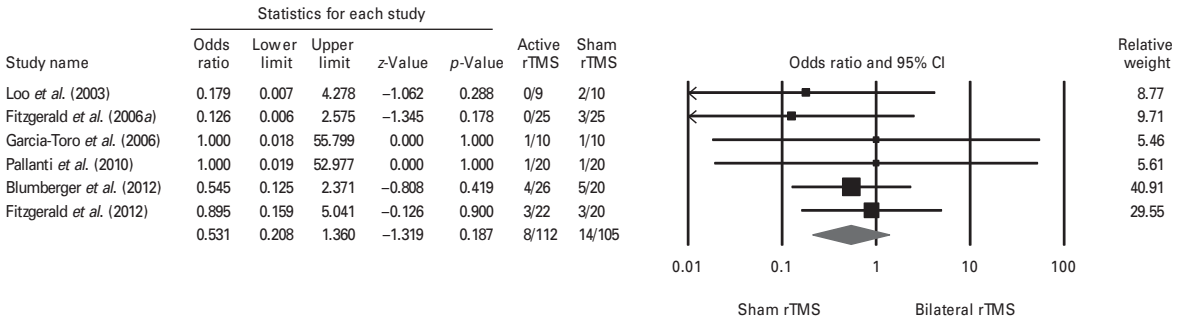

Fig. 3. Meta-analysis of bilateral repetitive transcranial magnetic stimulation (rTMS) *versus* sham rTMS for major depression: drop-out rates. CI, Confidence interval.

from three and two RCTs, respectively. Overall, there was no significant difference between these two neuromodulation approaches in terms of both response (OR 2.39, 95% CI 0.24–24.04, $z=0.74$, $p=0.46$) and remission rates (OR 1.6, 95% CI 0.04–63.72, $z=0.25$, $p=0.8$). For the associated forest plots, please refer to the Supplementary material.

Bilateral rTMS versus *sham rTMS: baseline depression severity*

No differences on mean baseline depression scores for active *versus* sham rTMS groups were found (SMD = 0.18, $z=1.3$, $p=0.2$), thus ruling out illness severity at baseline as a confounding factor. For the associated forest plot, please refer to the Supplementary material.

Acceptability of bilateral rTMS treatment

Data relating to drop-out rates from bilateral rTMS *versus* sham rTMS and active unilateral rTMS were available from six and three RCTs, respectively. Overall, no difference was observed between bilateral rTMS and sham rTMS groups [7.15% (8/112) *v.* 13.4% (14/105), respectively; OR 0.53, $z=-1.32$, $p=0.19$] (Fig. 3), and bilateral rTMS and active unilateral rTMS groups [11.8% (8/68) *v.* 5.9% (4/68), respectively; OR 1.8, $z=0.87$, $p=0.38$]. For the associated forest plot, please refer to the Supplementary material.

Sensitivity analysis

We reanalysed the effect size estimate for response rates after excluding the study by Loo *et al.* (2003), as they delivered bilateral HF-rTMS (instead of HF-rTMS to the left DLPFC and LF-rTMS to the right DLPFC). Our results show that its exclusion did not significantly affect the initial effect size estimates for the whole sample (adjusted OR 4.54, $z=3.6$, $p<0.0001$). For the associated forest plot, please refer to the Supplementary material.

Discussion

This is the first meta-analysis to assess the efficacy of bilateral rTMS for MD. Our results show that this neuromodulation technique is significantly more effective than sham rTMS in achieving response and remission (with pooled ORs of 4.3 and 6, and NNTs of 6 and 7, respectively). Indeed, 24.7% and 19% of depressed subjects receiving bilateral rTMS were responders and remitters following a mean of 13 sessions, respectively, compared with only 6.8% and 2.6% of those receiving sham rTMS. Furthermore, we found no significant between-group differences in drop-out rates or baseline depressive symptomatology. Also, we found no significant difference between active bilateral and unilateral rTMS in terms of efficacy and acceptability, although this finding should be interpreted with caution owing to the limited number of RCTs included in that analysis. Thus, bilateral rTMS seems to be an effective treatment for MD as it is associated with clinically meaningful improvements and is overall well tolerated.

This notion is further strengthened by the fact that the observed effect sizes and drop-out rates for bilateral rTMS are comparable with those reported for several commercially available antidepressants as well as for unilateral rTMS. For example, a recent meta-analysis of 122 trials on antidepressants for MDD 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 3.3 (95% CI 1.66–6.6). Moreover, we have recently shown that the ORs for response and remission after unilateral HF-rTMS in MD were 3 (M. T. Berlim *et al.* unpubished observations). Furthermore, our findings are comparable with those observed in the large and representative Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Rush *et al.* 2006). More specifically, in the latter, remission rates after lithium carbonate or triiodothyronine augmentation of a second unsuccessful

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antidepressant course were 20.4% (Nierenberg *et al*. 2006). In the current meta-analysis, remission rates following HF-rTMS in depressed individuals who had usually not responded to $\geqslant 2$ antidepressant trials were 19%. Such similar results reinforce the notion that the efficacy of bilateral rTMS is at least comparable with that of second- or third-line pharmacological strategies for MD.

The combination of HF-rTMS and LF-rTMS could potentially enhance treatment response in MD in a number of ways. For example, it is possible that some patients have left-side treatment-responsive MD and some have right-side treatment-responsive MD (Rossini *et al*. 2010). Therefore, it is conceivable that offering both treatments to all patients can maximize the likelihood of clinical improvement in any individual patient. Alternatively, the two rTMS protocols may have synergistic therapeutic effects by reversing both the hypo-function in the left DLPFC and the hyper-function in the right DLPFC. Interestingly, this hypothesis has been recently supported by multimodal neuroimaging data suggesting a relationship between the targeting of the underlying hyper- or hypo-metabolism in the DLPFC and overall treatment efficacy (Kimbrell *et al*. 1999; Kito *et al*. 2011; Martinot *et al*. 2011).

Nevertheless, as the therapeutic use of bilateral rTMS involves several variables, it is possible that the optimum protocol is yet to be determined. Accordingly, future studies should investigate new ways of improving the antidepressant effects of bilateral rTMS, such as the identification of more clinically relevant stimulation parameters (e.g. different frequencies, intensities, number of sessions, brain targets), as well as the use of baseline electrophysiological and/or neuroimaging evaluations to better predict which patients might benefit from bilateral rTMS (Arns *et al*. 2012). Furthermore, there is a need for larger RCTs comparing active bilateral and unilateral rTMS protocols in MD in order to better determine their differential efficacy and tolerability.

Limitations

First, the included RCTs enrolled a relatively small number of depressed subjects. Second, the quality of the available sham rTMS conditions is still unresolved (Rosa & Lisanby, 2012), and the use of coil tilting and/or first-generation sham coils is clearly not optimal (Rossi *et al*. 2009; George & Aston-Jones, 2010). Also, included RCTs differed in terms of their chosen sham configuration (i.e. unilateral *versus* bilateral sham rTMS). Third, the most commonly used strategy for locating the DLPFC (i.e. the '5 cm method') has been recently criticized for its inaccuracy (Rossi *et al*. 2009; Rosa & Lisanby, 2012), and future studies might benefit from neuronavigation approaches (Schonfeldt-Lecuona *et al*. 2010). Fourth, we have only examined the efficacy of bilateral rTMS at study end, and thus cannot estimate the stability of its medium- to long-term antidepressant effects and/or its cost-effectiveness. This is especially relevant considering the labor-intensive and time-consuming nature of rTMS (Wassermann & Zimmermann, 2012). Fifth, owing to the relatively small number of trials, we were unable to assess whether bilateral rTMS is differentially effective in unipolar and bipolar depression or when it is used as an augmentation strategy or as a monotherapy for MD. Sixth, the overall dose of rTMS treatment provided in most included RCTs, especially with left-sided HF-rTMS, was relatively low compared with more recent studies in MD (e.g. O'Reardon *et al*. 2007; George *et al*. 2010). 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 tackled by the comprehensive systematic review of the literature and the use of stringent inclusion criteria, and by the objective examination of both publication bias and study heterogeneity. In particular, the lack of significant heterogeneity among the included RCTs shows that our results are reliable overall, and we found the risk of publication bias to be low.

Conclusion

The current meta-analysis, which included 279 depressed subjects, shows that bilateral rTMS is a promising new treatment for MD that seems to be at least as effective and acceptable as standard antidepressants and unilateral rTMS. Considering that most trials to date have included patients with categorically defined treatment-resistant depression (Berlim & Turecki, 2007), bilateral rTMS could be seen as a potential second- or third-line treatment for MD. Furthermore, its clinical utility as a therapeutic alternative to depressed patients who did not improve following unilateral rTMS treatment should be further explored (as, for example, previous studies have shown that left-sided HF-rTMS can be effective in non-responders to right-sided LF-rTMS and vice-versa; Fitzgerald *et al*. 2009; Speer *et al*. 2009).

In summary, bilateral rTMS is a welcome addition to the therapeutic armamentarium for MD owing to its overall efficacy, favorable side-effects profile and lack of drug interactions. Nevertheless, major tasks for future research include the investigation of whether patients with distinct subtypes of MD preferentially respond to this neuromodulation technique, whether

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its beneficial effects are maintained over time and how it compares with other rTMS protocols. Also, the search for optimal stimulation parameters for bilateral rTMS as well as the investigation of its neurobiological underpinnings should be the focus of further studies.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291712002802.

Declaration of Interest

Z.J.D. received external funding through Neuronetics and Brainsway Inc., Aspect Medical and a travel allowance through Pfizer and Merck. Z.J.D. has also received speaker funding through Sepracor Inc. and served on the advisory board for Hoffmann-La Roche Ltd.

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