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REVIEW

Clinically Meaningful Efficacy and Acceptability of Low-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) for Treating Primary Major Depression: A Meta-Analysis of Randomized, Double-Blind and Sham-Controlled Trials

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Clinical trials on low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) over the right dorsolateral prefrontal cortex have yielded conflicting evidence concerning its overall efficacy for treating major depression (MD). As this may have been the result of limited statistical power of individual trials, we have carried the present systematic review and meta-analysis to examine this issue. We searched the literature for English language randomized, double-blind and sham-controlled trials (RCTs) on LF-rTMS for treating MD from 1995 through July 2012 using EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, SCOPUS, and ProQuest Dissertations & Theses, and from October 2008 until July 2012 using MEDLINE. The main outcome measures were response and remission rates as well as overall dropout rates at study end. We used a random-effects model, odds ratios (ORs) and number needed to treat (NNT). Data were obtained from eight RCTs, totaling 263 subjects with MD. After an average of 12.6 ± 3.9 rTMS sessions, 38.2% (50/131) and 15.1% (20/132) of subjects receiving active LF-rTMS and sham rTMS were classified as responders (OR = 3.35; 95% CI = 1.4–8.02; $p = 0.007$). Also, 34.6% (35/101) and 9.7% (10/103) of subjects receiving active LF-rTMS and sham rTMS were classified as remitters (OR = 4.76; 95% CI = 2.13–10.64; $p < 0.0001$). The associated NNT for both response and remission rates was 5. Sensitivity analyses have shown that protocols delivering >1200 magnetic pulses in total as well as those offering rTMS as a monotherapy for MD were associated with higher rates of response to treatment. No differences on mean baseline depression scores and dropout rates for active and sham rTMS groups were found. Finally, the risk of publication bias was low. In conclusion, LF-rTMS is a promising treatment for MD, as it provides clinically meaningful benefits that are comparable to those of standard antidepressants and high-frequency rTMS. Furthermore, LF-rTMS seems to be an acceptable intervention for depressed subjects.

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INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique for modulating cortical and subcortical function with the use of rapidly changing electromagnetic fields generated by a coil placed over the scalp (George and Post, 2011). Depending on the parameters of stimulation, rTMS can modulate cortical excitability in relatively focal areas (Fregni and Pascual-Leone, 2007), with frequencies $\leqslant 1$ Hz (low-frequency rTMS or LF-rTMS) being usually inhibitory, and higher frequencies ($\geqslant 5$ Hz; high-frequency rTMS or HF-rTMS) being usually excitatory (Fitzgerald *et al*, 2002; Marangell *et al*, 2007).

rTMS is being increasingly investigated as a potential treatment for several neuropsychiatric disorders (George *et al*, 2009), and particularly for major depression (MD) (Daskalakis *et al*, 2008). The first evidence for its antidepressant effects was observed with a high-frequency protocol (20 Hz) applied to the left dorsolateral prefrontal cortex (DLPFC) (George *et al*, 1995), and to date several meta-analyses have confirmed the overall efficacy and safety of HF-rTMS for treating depressed subjects (Berlim *et al*,

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submitted-b; Slotema *et al*, 2010). As the latter can be uncomfortable at higher intensities (Janicak *et al*, 2008), and is also associated with an increased risk of adverse effects (Loo *et al*, 2008), LF-rTMS over the right DLPFC has been more recently proposed as an alternative therapeutic strategy for MD (Schlaepfer *et al*, 2003). Indeed, initial clinical trials showed that LF-rTMS has antidepressant properties (Klein *et al*, 1999). However, questions remain as to whether this neuromodulation technique has clinically relevant effects in MD as RCTs to date have produced conflicting results. For example, Hoppner *et al* (2003) and Kauffmann *et al* (2004) showed that LF-rTMS was not superior to sham rTMS, whereas Stern *et al* (2007) and Pallanti *et al* (2010) found that LF-rTMS was associated with significantly higher rates of clinical improvement when compared with sham rTMS. A likely reason for these discrepant findings might be the lack of statistical power among some of the individual RCTs (Maxwell *et al*, 2008). Therefore, the use of meta-analytical approaches could be helpful in examining this issue by allowing the integration of findings from multiple studies and the more accurate estimation of the treatment effects associated with LF-rTMS' (Huf *et al*, 2011).

Recently, Schutter (2010) has conducted the first meta-analysis on LF-rTMS for MD and found that this neuromodulation technique was significantly more effective than sham rTMS in reducing post-treatment scores on standard depression scales (ie, *Hedges'g* = 0.63; 95% CI = 0.03–1.24). However, the clinical magnitude of these reported changes in depressive symptomatology is difficult to interpret, especially in light of current recommendations on the assessment of treatment efficacy in MD that advocate the use of more clinically relevant outcomes such as response and remission rates (Rush *et al*, 2006a). Furthermore, the study by Schutter (2010) lacked information regarding some of its key methodological aspects (eg, search syntaxes and outputs, reasons for excluding studies), and this poses a limitation to its replicability.

Therefore, to summarize the best available evidence on the use of LF-rTMS for treating MD (taking into consideration the limitations of the previous meta-analysis), we have carried out a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Furthermore, we assessed overall treatment acceptability based on the differential dropout rates among subjects receiving active or sham rTMS.

METHODOLOGY OF THE LITERATURE REVIEW

Search Strategy

We identified articles for inclusion in this meta-analysis by

- Screening the bibliography of the previous meta-analyses on rTMS for MD (Allan *et al*, 2011; Burt *et al*, 2002; Couturier, 2005; Gross *et al*, 2007; Herrmann and Ebmeier, 2006; Kozel and George, 2002; Lam *et al*, 2008; Martin *et al*, 2002; Martin *et al*, 2003; McNamara *et al*, 2001; Schutter, 2009; Slotema *et al*, 2010), of the only meta-analysis on LF-rTMS for MD published to date (Schutter, 2010), as well as of all included RCTs;
- Searching MEDLINE from 1 October 2008 until 22 July 2012 [as previous meta-analyses have screened this database up to late 2008 (Allan *et al*, 2011; Slotema *et al*, 2010)];
- Searching 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 and Green, 2008):

Study Validity. Random allocation; double-blind (ie, patients and clinical raters blinded to treatment conditions); sham-controlled (ie, 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;

Sample characteristics. Subjects aged 18–75 years with a diagnosis of primary major depressive episode (unipolar or bipolar) according to the Diagnostic and Statistical Manual of Mental Disorders (APA, 1994) or the International Classification of Diseases (WHO, 1992) criteria;

Treatment characteristics. LF-rTMS (ie, $\leqslant 1$ Hz) given for $\geqslant 10$ sessions either as a monotherapy or as an augmentation strategy for MD;

Publication-related. Articles written in English.

Studies were excluded if they:

- Enrolled subjects with 'narrow' diagnoses (eg, postpartum depression) or secondary MD (eg, vascular depression);
- Started rTMS at the same time as a new antidepressant;
- Did not report rates of response to treatment and/or remission.

In cases where potentially eligible studies were missing key data for our meta-analysis, their corresponding authors were contacted twice by E-mail at a 2-week interval (please refer to the Supplementary Material for additional information).

Data Extraction

Data were recorded in a structured fashion as follows:

Sample characteristics. Mean age, sex, treatment strategy used (ie, augmentation or monotherapy), primary diagnosis, presence of treatment-resistant MD;

rTMS-related. Stimulation frequency and intensity (including the total number of stimuli delivered), number of treatment sessions, type of sham;

Primary outcome measure. Number of responders (Rush *et al*, 2006a) 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 [HAM-D] (Hamilton, 1960) or on the Montgomery–Asberg Depression Rating Scale [MADRS] (Montgomery and Asberg, 1979)) at study end;

Secondary outcome measure. Number of remitters (Rush *et al*, 2006a) based on the RCTs' primary efficacy measure (eg, 17- or 21-item HAM-D scores $\leqslant$7 or $\leqslant$8, respectively, or MADRS scores $\leqslant$6) at study end;

Acceptability of treatment. Overall dropout 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, Englewood, NJ, USA), and IBM SPSS Version 20 (IBM Corporation, Chicago, IL, USA).

We used a random-effects model because it was assumed that the true treatment effects had likely 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 LF-rTMS for MD as well as its acceptability were investigated by odds ratios (ORs) (Deeks, 2002) and the number needed to treat (NNT) for rates of response/remission and dropouts (Borenstein *et al*, 2009). 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 HAM-D or the MADRS. Moreover, we conducted sensitivity analyses to determine the potential impact of the following variables on the effect size estimates for response and remission: total number of sessions (ie, 10 *vs* $>$10) or pulses ($\leqslant$1200 *vs* $>$1200), percentage of the resting motor threshold ($\leqslant$100 *vs* $>$100%), primary diagnosis (ie, samples with unipolar depression only *vs* samples with mixed unipolar/bipolar depression) and treatment strategy (ie, rTMS as augmentation *vs* monotherapy).

Heterogeneity was assessed using the Q statistics and I^2 (Cooper *et al*, 2009). Values of $p<0.1$ 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 and Tweedie's Trim & Fill procedure (Duval and Tweedie, 2000) to test for the presence of publication bias (Borenstein *et al*, 2009; Cooper *et al*, 2009).

RESULTS

Literature Search

Of the 10 RCTs on LF-rTMS for MD included in the previous meta-analyses, sixwere selected for the present

Table 1 Included Randomized, Double-Blind and Sham-Controlled trials on LF-rTMS for MDD: Main Characteristics

Study	LF-rTMS			Sham rTMS			rTMS parameters				Primary diagnosis	Treatment strategy	TRD[b]
	n	Age ± SD (years)	Female/male (*n*)	*n*	Age ± SD (years)	Female/male (*n*)	Type	Frequency (Hz)	% rMT[a]	Sessions (*n*)	Total pulses		
Klein *et al*, 1999	35	60.5 ± 15.1	28/7	32	58.9 ± 18.3	22/10	90°	1	110	10	1200	19.5% with BD[c]; 80.5% with MDD[d]	Augmentation	Yes[e]
Fitzgerald *et al*, 2003	20	45.55 ± 11.49	7/13	20	49.15 ± 14.24	11/9	45°	1	100	10	3000	12.5% with BD; 87.5% with MDD	Augmentation	Yes[e]
Hoppner *et al*, 2003	10	52 ± 11.67	8/2	10	56.44 ± 13.22	7/3	90°	1	110	10	1200	5% with BD; 95% with MDD	Augmentation	N/A
Kauffmann *et al*, 2004	7	N/A	N/A	5	N/A	N/A	45°	1	110	10	1200	All with MDD	Augmentation	Yes[e]
Januel *et al*, 2006	11	38.64 ± 11.16	9/2	16	37.19 ± 11.67	12/4	Sham coil	1	90	16	1920	All with MDD	Monotherapy	Yes[f]
Stern *et al*, 2007	10	52.8 ± 9.5	7/3	15	53.3 ± 9	9/6	90°	1	110	10	16000	All with MDD	Monotherapy	Yes[g]
Pallanti *et al*, 2010	20	51.2 ± 12.53	12/8	20	47.85 ± 9.12	12/8	Sham coil	1	110	15	6300	All with MDD	Augmentation	Yes[e]
Aguirre *et al*, 2011	19	45.05 ± 14.96	11/8	15	50.4 ± 11.02	12/3	90°	1	110	20	24000	All with MDD	Augmentation	Yes[g]

[a]Percentage of the resting motor threshold.
[b]Treatment-resistant depression.
[c]Bipolar depression.
[d]Major depressive disorder.
[e]Failure to respond to $\geqslant$2 antidepressants in the current major depressive episode (MDE).
[f]Failure to respond to $\geqslant$2 medical treatments.
[g]Failure to respond to $\geqslant$1 antidepressant in the current or previous MDE.

investigation (Fitzgerald *et al*, 2003; Hoppner *et al*, 2003; Januel *et al*, 2006; Kauffmann *et al*, 2004; Klein *et al*, 1999; Stern *et al*, 2007). Also, we retrieved four RCTs on LF-rTMS for MD from MEDLINE, PsycINFO, EMBASE, CENTRAL, SCOPUS, and PQDT. Of these, only two RCTs met the eligibility criteria (Aguirre *et al*, 2011; Pallanti *et al*, 2010), as the remaining only applied LF-rTMS over the left DLPFC (Speer *et al*, 2009; Speer *et al*, 2000). Please refer to the Supplementary Material for a detailed description of the study selection procedure.

Included RCTs: Main Characteristics

Overall, eight RCTs were included in our meta-analysis, totaling 263 subjects with MD, of whom 131 were randomized to active LF-rTMS (mean age = 49.39 ± 7 years; 65.6% females), and 132 were randomized to sham rTMS (mean age = 50.46 ± 7.07 years; 66.4% females). The mean number of rTMS sessions delivered was 12.6 ± 3.9. Also, LF-rTMS was used as an augmentation strategy for MD in most RCTs (6 out of 8), and most subjects had some degree of treatment-resistant depressive illness. The main characteristics of the included RCTs are described in Table 1.

Response Rates

Data relating to response rates were available from all eight RCTs. Overall, 50 (out of 131; 38.2%) and 20 (out of 132; 15.1%) subjects receiving active LF-rTMS or sham rTMS were classified as responders to treatment, respectively. The pooled OR was 3.35 (95% CI = 1.34–8.02; $z = 2.71$; $p = 0.007$), indicating a significant difference in outcome favoring active LF-rTMS (Figure 1). The risk difference translated into a NNT of 5 (95% CI = 3–7.9), meaning that about one in every five patients will present with a response following LF-rTMS.

Heterogeneity between RCTs did not exceed that expected by chance (df = 7; $Q_7 = 10.99$, $p = 0.14$; $I^2 = 34.18$), implying that the variance among the effect sizes was no greater than expected by sampling error. The Fail-Safe N for response rates was 19, indicating that at least 19 unpublished or missing null-findings would be needed to render the clinical effect of active LF-rTMS statistically non-significant (ie, $p \geqslant 0.05$). Additionally, the associated Funnel Plot was reasonably symmetrical (Figure 2). Publication bias was assessed more conservatively with Egger's regression intercept, which was 0.95 (df = 6; $t = 0.73$; two-tailed $p = 0.49$), suggesting a low risk of publication bias. Also, no RCT was trimmed in the Duval and Tweedie's Trim & Fill procedure, thus reinforcing the low risk of publication bias.

Remission Rates

Data relating to remission rates were available from six RCTs. Overall, significantly more patients receiving active LF-rTMS were classified as remitters as compared with those receiving sham rTMS (34.6% (35/101) *vs* 9.7% (10/103), respectively). The pooled OR was 4.76 (95% CI = 2.13–10.64; $z = 3.8$; $p < 0.0001$) (Figure 3). The risk difference translated into a NNT of five (95% CI = 2.8–7.1).

Heterogeneity between RCTs did not exceed that expected by chance (df = 5; $Q_4 = 3.89$, $p = 0.56$; $I^2 = 0$). The associated Funnel Plot was reasonably symmetrical (Figure 4), the Fail-Safe N for remission rates was 15, and Egger's regression intercept was 0.33 (df = 4; $t = 0.33$; two-tailed $p = 0.76$), also suggesting a low risk of publication bias. Moreover, no RCT was trimmed in the Duval and Tweedie's Trim & Fill procedure, thus reinforcing the low risk of publication bias.

Acceptability of LF-rTMS Treatment

Overall, no differences on dropout rates were observed between active LF-rTMS and sham rTMS (5.3% (7/132) *vs* 11.28% (15/133), respectively; OR = 0.53; $z = -1.23$, $p = 0.22$) (Figure 5).

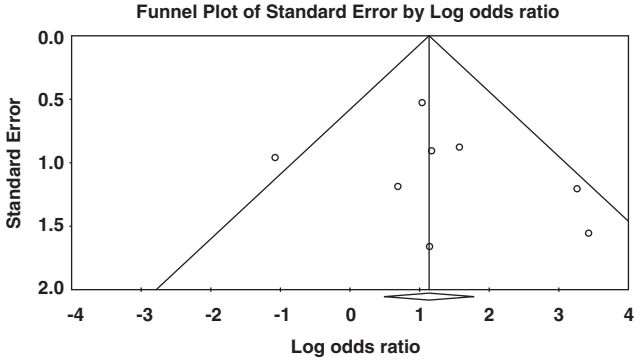

Figure 2 Meta-analysis of LF-rTMS *vs* Sham rTMS for major depression: funnel plot for studies reporting.

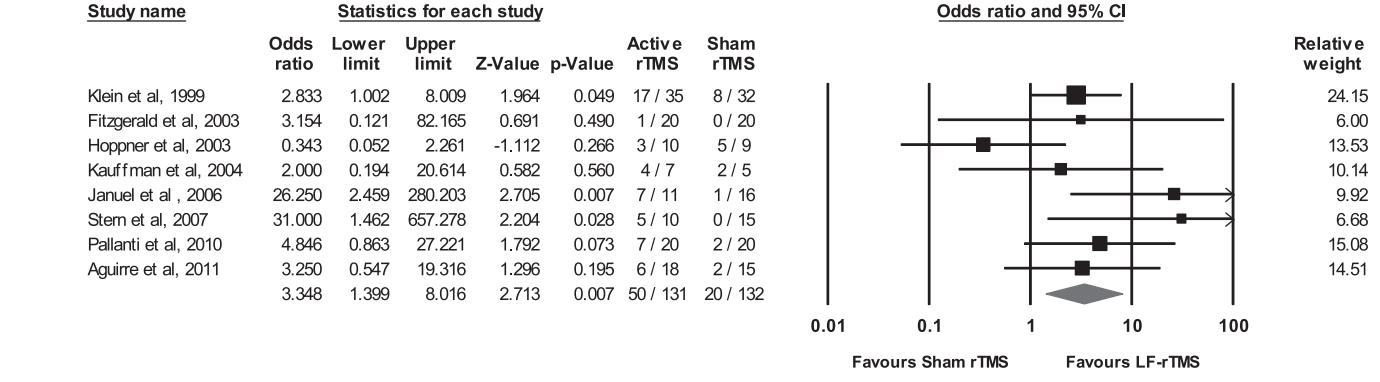

Figure 1 Meta-analysis of LF-rTMS *vs* Sham rTMSfor major depression: response rates.

LF-rTMS vs Sham rTMS: Baseline Depression Severity

No differences on mean baseline depression scores between active and sham rTMS groups were found (SMD = 0.1; $z = 0.69$, $p = 0.49$), thus ruling out illness severity at baseline as a confounding factor. For the associated Forrest Plot please refer to the Supplementary Material.

Sensitivity Analyses

LF-rTMS protocols delivering >1200 magnetic pulses in total were associated with a statistical trend towards higher rates of response to treatment (OR = 6.9; 95% CI = 2.39–19.92) when compared with protocols delivering ⩽1200 pulses in total (OR = 1.6; 95% CI = 0.59–4.39) ($Q = 3.82$; df = 1; $p = 0.051$). However, the total number of sessions and the percentage of the resting motor threshold were not associated with a differential efficacy of LF-rTMS. Additionally, we found no differences in terms of response and remission rates between the RCTs including subjects with unipolar MD only and those including mixed samples of subjects with unipolar and bipolar MD. Finally, response (but not remission) rates were significantly higher for RCTs using LF-rTMS as a monotherapy (OR = 27.94; 95% CI = 4.3–181.53) *vs* as an augmentation strategy (OR = 2.32; 95% CI = 1.17–4.6) for MD ($Q = 5.99$; df = 1; $p = 0.014$). For the associated Forrest Plots please refer to the Supplementary Material.

DISCUSSION

This is the first meta-analysis assessing the efficacy of LF-rTMS to the right DLPFC for MD in terms of response and remission rates. Our results show that this neuromodulation technique is significantly more effective than sham rTMS in producing clinically relevant outcomes (with pooled ORs of 3.35 and 4.76 for response and remission, respectively, and a NNT of 5 for both). Indeed, ~3–4 out of 10 depressed subjects receiving LF-rTMS were responders and remitters following a mean of ~13 sessions, respectively, compared with only about 1 out of 10 of those receiving sham rTMS. Furthermore, we did not find significant differences on dropout rates as well as on baseline depressive symptomatology between active and sham rTMS groups.

This notion is further strengthened by the fact that the observed treatment effect sizes for LF-rTMS are comparable to those reported for several commercially available antidepressants as well as for HF-rTMS. For example, a recent meta-analysis of 122 trials on antidepressants for MD 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 and Baldessarini, 2012); our estimate, when converted to rate ratio, is 2.14 (95% CI = 1.02–4.47). Moreover, we have recently shown that the ORs for response and remission after HF-rTMS in MD were ~3 (Berlim *et al*, submitted-a). Furthermore, our findings are comparable to those observed in the large and representative Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Rush *et al*, 2006b). More specifically, in the latter, remission rates after lithium carbonate or triiodothyronine augmentation of a second unsuccessful antidepressant course were 20.4% (Nierenberg *et al*, 2006). In the current meta-analysis, remission rates following LF-rTMS in depressed individuals who had usually not responded to ⩾2 antidepressant trials were 34.6%. Such results reinforce the notion that the efficacy of LF-TMS is at least comparable to that of second- or third-line pharmacological strategies for MD. Nevertheless, routine clinical use of rTMS is still limited by its relatively high cost and low availability as well as the lack of clear predictors of treatment response and of data on its medium- to long-term efficacy (George and Post, 2011; Wassermann and Zimmermann, 2012).

As the therapeutic use of LF-rTMS involves several variables, it is possible that the optimum protocol (eg, parameters and duration of stimulation) is yet to be determined. Of relevance, subgroup analyses have shown that the delivery of >1200 magnetic pulses in total and the

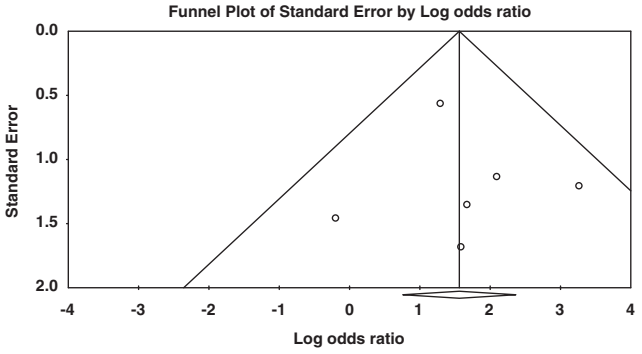

Figure 4 Meta-analysis of LF-rTMS *vs* Sham rTMS for major depression: funnel plot for studies reporting.

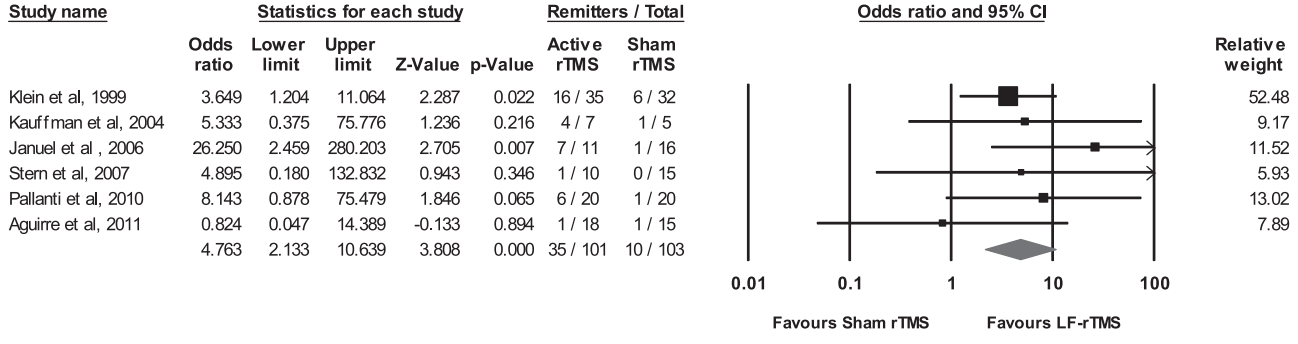

Figure 3 Meta-analysis of LF-rTMS *vs* Sham rTMS for major depression: remission rates.

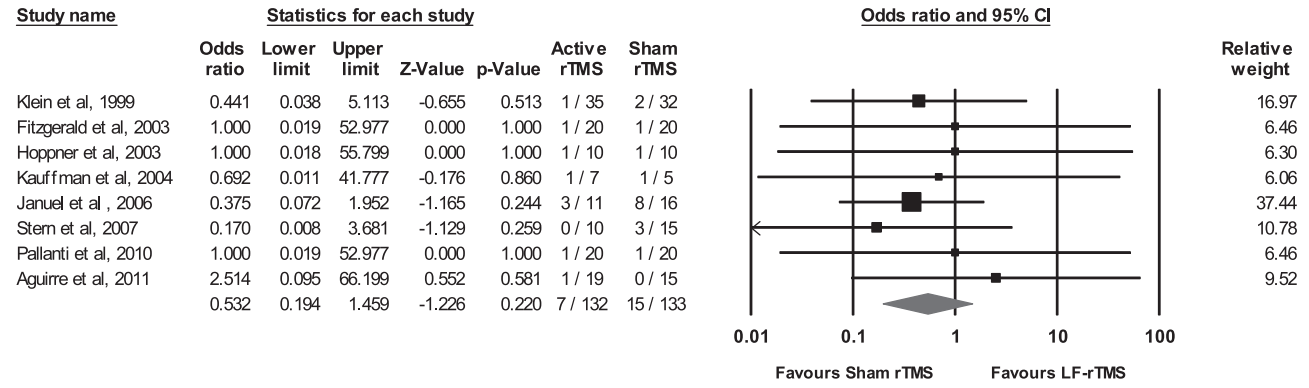

Figure 5 Meta-analysis of LF-rTMS *vs* Sham rTMS for major depression: dropout rates.

use of rTMS as a monotherapy for MD might be associated with higher rates of response to treatment. Nevertheless, future studies should investigate new ways of enhancing the antidepressant effects of LF-rTMS, such as the identification of more clinically relevant stimulation parameters/protocols (eg, preconditioning paradigms/priming, different rTMS waveforms, frequencies, intensities, number of sessions, brain targets) (Fitzgerald *et al*, 2008; George and Aston-Jones, 2010; Peterchev *et al*, 2011), as well as the use of baseline electrophysiological and/or neuroimaging evaluations to better predict which patients might benefit from LF-rTMS (Arns *et al*, 2012). Furthermore, novel developments in the field of neuromodulation, such as the H-coil (Levkovitz *et al*, 2010), might enhance the efficacy of LF-rTMS by allowing the direct stimulation of deeper brain structures.

Limitations

First, although the included RCTs enrolled a relatively small number of depressed subjects, the statistical power to test the summary effects in this meta-analysis was substantially higher than that of any of the primary studies (Borenstein *et al*, 2009). Second, the quality of the available sham rTMS conditions is still unresolved (Rosa and Lisanby, 2012), and the use of coil tilting and/or first generation sham coils is clearly not optimal (George and Aston-Jones, 2010; Rossi *et al*, 2009). In addition, we could not assess the integrity of blinding owing to the absence of this information from all but one of the included RCTs (Fitzgerald *et al*, 2003) which reported that 42% ($n=40$) and 60% ($n=20$) of subjects in the active and sham rTMS groups, respectively, were able to correctly guess their treatment allocation before disclosure (at $p>0.05$). Furthermore, we have recently conducted a meta-analysis on the integrity of blinding in high-frequency rTMS trials in MD and have showed that after an average of 13 rTMS sessions, 52 and 59% of subjects receiving active and sham rTMS ($n=396$), respectively, were able to correctly guess their treatment allocation ($p=0.58$) (Berlim *et al*, submitted-b). Third, the most commonly used strategy for locating the DLPFC (ie, the '5-cm method') has been recently criticized for its inaccuracy (Bradfield *et al*, 2012; Fitzgerald *et al*, 2009a; Fitzgerald *et al*, 2009b; Herbsman *et al*, 2009; Rusjan *et al*, 2010), and future studies might benefit from neuronavigation approaches (Ruohonen and Karhu, 2010; Schonfeldt-Lecuona *et al*, 2010). Fourth, we have only examined the efficacy of LF-rTMS at study end, and thus could not estimate the stability of its medium- to long-term antidepressant effects and/or its cost-effectiveness. This was mainly due to the absence of follow-up evaluations on all but two of the included RCTs (Aguirre *et al*, 2011; Stern *et al*, 2007). Briefly, Stern *et al* (2007) reported that the rates of response and remission 2 weeks post-treatment increased from 10–33.3% (ie, from 1–3 subjects) and from 50–60% (ie, from 5–6 subjects) for the LF-rTMS group, respectively, and were maintained at 0% for the sham rTMS group. Also, Aguirre *et al* (2011) have shown that the rates of response and remission 4 weeks post-treatment increased from 33.3–38.9% (ie, from 6–7 subjects) and from 5.5–16.7% (ie, from 1–3 subjects) for the LF-rTMS group, respectively, and were maintained at the same initial level for the sham rTMS group. Encouragingly, a recent 6-month follow-up study with over 90 depressed subjects has shown that the therapeutic benefits of high-frequency rTMS are durable, and that it can be used for precluding impending relapse (Janicak *et al*, 2010). Nevertheless, it is clear that future RCTs on rTMS should include longer follow-up periods (eg, >6–12 months), especially considering the labor-intensive and time-consuming nature of rTMS (Wassermann and Zimmermann, 2012). Finally, meta-analyses have been often criticized 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 comprehensive systematic review of the literature and the use of stringent inclusion criteria, and by the objective examination of 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 Ns for the primary outcome measures varied between 19 and 15, and we believe that it is unlikely that such a relatively large number of unpublished RCTs with null effects have been either missed by our literature search or were conducted but never published.

CONCLUSION

The current meta-analysis, which included 263 depressed subjects, provided no evidence that standard antidepressants or HF-rTMS are superior to LF-rTMS applied to the right DLPFC in the treatment of MD.

Overall, LF-rTMS has a few advantages. For example, it is associated with a significantly lower risk of seizure induction and may even have anti-epileptic properties (Fregni *et al*, 2006). Therefore, LF-rTMS would be preferred in subjects with risk factors for seizure or with substantial medical comorbidity. Furthermore, LF-rTMS is usually better tolerated than HF-rTMS (which produces a greater degree of local scalp discomfort during stimulation) (Loo *et al*, 2008), and could thus be potentially offered to a larger number of patients.

Nevertheless, major tasks for future research include the investigation of whether patients with distinct subtypes of MD (eg, bipolar *vs* unipolar) preferentially respond to this neuromodulation technique, whether its beneficial effects are maintained over time and, especially, how it compares with other rTMS protocols (particularly HF-rTMS). Also, further studies should focus on the search for optimal stimulation parameters as well as on the investigation of the neurobiological underpinnings of the effect of LF-rTMS.

DISCLOSURE

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