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Review

Repetitive transcranial magnetic stimulation (rTMS) for obsessive–compulsive disorder (OCD): An exploratory meta-analysis of randomized and sham-controlled trials

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ABSTRACT

Objective: Randomized and sham-controlled trials (RCTs) on repetitive transcranial magnetic stimulation (rTMS) for treating obsessive–compulsive disorder (OCD) have yielded conflicting results that may be due to limited statistical power among individual studies. We pursued the present systematic review and meta-analysis to assess the efficacy of rTMS for OCD and to generate hypotheses for more robustly powered RCTs.

Method: We searched the literature for RCTs on rTMS for OCD from 1995 through December 2012 using MEDLINE, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, and SCOPUS. We then performed an exploratory random-effects meta-analysis with the main outcome measures as pre-post changes in Yale–Brown Obsessive Compulsive Scale (Y-BOCS) scores, response to treatment and overall dropout rates at study end.

Results: Data were obtained from 10 RCTs, totaling 282 subjects with OCD. The pooled Hedges' g for pre-post Y-BOCS scores was 0.59 ($z = 2.73$, $p = 0.006$), indicating a significant and medium-sized difference in outcome favoring active rTMS. Furthermore, response rates were 35% and 13% for patients receiving active and sham rTMS, respectively (OR = 3.4, $p = 0.002$). Sub-group analyses indicated that LF-rTMS and rTMS protocols targeting non-DLPFC regions (i.e., orbitofrontal cortex or supplementary motor area) seem to be the most promising for reducing OCD-related symptoms. No differences on baseline depression scores or dropout rates at study end were observed between active and sham rTMS groups, although OCD severity at baseline was higher in the active group.

Conclusions: Our exploratory analyses show that active rTMS seems to be efficacious for treating OCD. Moreover, LF-rTMS and protocols targeting the orbitofrontal cortex or the supplementary motor area seem to be the most promising. Nevertheless, future RCTs on rTMS for OCD should include larger sample sizes and be more homogeneous in terms of demographic/clinical variables as well as stimulation parameters and brain targets.

Obsessive–compulsive disorder (OCD) is a chronic and often severe neuropsychiatric disorder with a 12-month prevalence of 1.2% and lifetime prevalence of 2.3% (Ruscio et al., 2010). It is mainly characterized by obsessions (i.e., anxiety provoking, unwanted, persistent thoughts, impulses or images that are experienced as intrusive, inappropriate, and distressing) and compulsions (i.e., repetitive, time-consuming behaviors or mental acts often performed to neutralize the anxiety secondary to obsessions) (Heyman et al., 2006; Stein, 2002). OCD is usually associated with dramatic impairments in interpersonal and occupational functioning (Markarian et al., 2010; Steketee, 1997) and is one of the most disabling medical conditions with considerable direct and indirect economic and societal costs (DuPont et al., 1995).

Although the aetiology and pathophysiology of OCD remain unclear, growing evidence suggests that this illness is associated with dysfunctions in the orbitofronto-striato-pallido-thalamic circuitry including the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), medial prefrontal cortices, anterior cingulate gyrus, supplementary motor area (SMA), and basal ganglia (Del Casale et al., 2011; Fineberg et al., 2011; Milad and Rauch, 2012).

Current first-line treatment strategies for OCD include high doses of selective serotonin reuptake inhibitors (SSRIs; e.g., citalopram, paroxetine) or the tricyclic antidepressant clomipramine

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given over long periods of time and/or combined with cognitive-behavioral therapy (Koran et al., 2007; Stein et al., 2012). In patients with resistant OCD, the pharmacological treatment has been broadened to include serotonin–norepinephrine reuptake inhibitors, intravenous clomipramine or citalopram, and/or atypical antipsychotics (Abudy et al., 2011; Bandelow et al., 2008). However, even with such diverse therapeutic options, up to 60% of patients with OCD are either unable to tolerate medication side-effects or only partially improve following treatment, and are thereby left with persistent symptoms with lasting repercussions on their global functioning and well-being (Jenike, 2004; Pallanti and Quercioli, 2006; Simpson et al., 2006). Therefore, novel treatments for OCD are of considerable interest, one of which is repetitive transcranial magnetic stimulation (rTMS) (Blom et al., 2011; Jaafari et al., 2012; Pigot et al., 2008).

rTMS is a non-invasive neuromodulation technique that is able to modulate 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 either decrease or increase cortical excitability in relatively focal areas, with frequencies $\leq$1 Hz (low frequency rTMS or LF-rTMS) being usually inhibitory and higher frequencies ($\geq$5 Hz; high frequency rTMS or HF-rTMS) being usually excitatory (Rosa and Lisanby, 2012).

Considering the extent of the putative neural network underlying OCD and the ability of rTMS to modulate brain activity, Greenberg and colleagues (Greenberg et al., 1997) introduced this neuromodulation technique as a potential therapeutic approach for OCD. They enrolled 12 patients with OCD and administered active HF-rTMS to the right and the left DLPFC (experimental condition) or to the mid-occipital cortex (control condition) for 20 min. Compulsions and depressive symptoms significantly decreased immediately after right and left DLPFC stimulation, and remained less intense for several hours, whereas obsessions were not affected; contrastingly, mid-occipital stimulation led to an increase in the severity of compulsions (Greenberg et al., 1997). Since this initial study, several open label and randomized and sham-controlled trials (RCTs) have investigated the clinical utility of rTMS targeting areas within the cortico-striatal network for OCD (Blom et al., 2011; Jaafari et al., 2012; Pigot et al., 2008).

However, it remains unclear as to whether rTMS is effective for OCD, because the available data from RCTs to date have produced conflicting results (Marazziti and Consoli, 2010). For example, LF-rTMS over the right DLPFC (Alonso et al., 2001) and HF-rTMS over the left DLPFC (Sachdev et al., 2007) have not been found to be superior to sham rTMS, whereas LF-rTMS applied over the SMA (Mantovani et al., 2010) or the left OFC (Ruffini et al., 2009) have been associated with significant improvements in OCD when compared to sham rTMS. A likely explanation for these discrepant findings is 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 of rTMS for OCD (Huf et al., 2011). In a previous attempt to conduct a meta-analysis on this subject, the authors were unable to report pooled effect size estimates due to the lack of data at that time (Martin et al., 2003). More recently, Slotema et al. (2010) have reported that active rTMS was not better than sham rTMS for reducing OCD symptoms (Hedges' $g = 0.15$; $p = 0.52$), although they only included 3 RCTs in their meta-analysis.

In the past few years, several additional RCTs have been published and this has motivated the present systematic review and exploratory meta-analysis on the efficacy and acceptability of rTMS for OCD.

1. Methodology of the literature review

1.1. Search strategy

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

- Screening the bibliography of the previous general reviews on rTMS for OCD (Blom et al., 2011; Jaafari et al., 2012; Pigot et al., 2008), of the meta-analysis by Slotema et al. (2010), and of all included RCTs;
- Searching MEDLINE, EMBASE, PsycINFO, the Cochrane Central Register of Controlled Trials (CENTRAL), and SCOPUS from January 1, 1995 until December 3, 2012;

The search procedures (including syntax, parameters, and results) are described in detail in the Supplemental Data.

1.2. 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; single- or double-blinded; 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); $\geq$5 subjects with OCD randomized per study arm.
- Sample Characteristics: Subjects aged 18–75 years with a diagnosis of primary OCD according to the Diagnostic and Statistical Manual of Mental Disorders IV (APA, 1994) or International Classification of Diseases (WHO, 1992) criteria.
- Treatment Characteristics: LF- ($\leq$1 Hz) or HF- ($\geq$5 Hz) rTMS given for $\geq$5 sessions either as monotherapy or as an augmentation strategy for OCD.
- Publication-Related: Articles written in English.

Studies were excluded if they:

- Started rTMS concomitantly with a new psychotropic medication (e.g., antidepressants, antipsychotics).
- Did not report pre- and post-rTMS Y-BOCS scores.

1.3. Data extraction

Data were recorded in a structured fashion as follows:

- Sample Characteristics – Mean age, gender, treatment strategy (i.e., augmentation or monotherapy), presence of treatment-resistant OCD.
- rTMS-Related – Stimulation frequency and intensity (including the total number of stimuli delivered), brain target(s), number of treatment sessions, type of sham.
- Primary Outcome Measure – Score changes (pre-post rTMS) on the Yale- Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989a, 1989b).
- Secondary Outcome Measure – Number of responders to treatment based on the RCTs' definition (i.e., $\geq$25–40% reduction in post-treatment Y-BOCS scores);
- Tertiary Outcome Measures – Score changes (pre-post rTMS) on the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959), and on the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) or Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979).

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- Acceptability of Treatment – Overall dropout rates for active and sham rTMS groups at study end.

1.4. 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 since we assumed that the true effect sizes 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). Score changes (pre- to post-rTMS) on the Y-BOCS, HAM-A, and HAM-D/MADRS were investigated with pooled Hedges' g effect sizes. As we could not retrieve the correlations between pre- and post-rTMS measures from the individual RCTs we followed the recommendation by Rosenthal (1993) and assumed a conservative estimation of $r = 0.7$. Response to treatment was assessed with Odds Ratios (OR) and the Number Needed to Treat (NNT). We considered an NNT $\leq$ 10 as clinically meaningful because such a treatment difference would be routinely encountered in day-to-day clinical practice (Citrome, 2011). Acceptability of treatment was assessed with ORs for differential dropout rates between active and sham rTMS groups (Borenstein et al., 2009; Grissom and Kim, 2012). Also, to rule out the presence of baseline differences in illness severity between active and sham rTMS groups, we computed pooled Hedges' g effect sizes for subjects' Y-BOCS and HAM-D/MADRS scores. As the included RCTs were heterogeneous concerning their stimulation targets and parameters, we carried out 2 exploratory analyses by subgrouping them into LF- and HF-rTMS protocols, and into DLPFC and non-DLPFC (i.e., OFC/SMA) stimulation targets.

Heterogeneity was assessed using the Q statistic and I^2 index (Cooper et al., 2009). Values of $p < 0.1$ for the former and >35% for the latter were deemed as indicative of between-study heterogeneity (Borenstein et al., 2009). We further used Funnel Plots, Egger's Regression Intercept (Egger et al., 1997), the Fail Safe Number (Rosenthal, 1979), and the 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).

2. Results

2.1. Literature search

We retrieved 59 references (after discarding duplicates) from MEDLINE, PsycINFO, EMBASE, CENTRAL and SCOPUS. Of these, 10 met the eligibility criteria (Alonso et al., 2001; Badawy et al., 2010; Gomes et al., 2012; Kang et al., 2009; Mansur et al., 2011; Mantovani et al., 2010; Prasko et al., 2006; Ruffini et al., 2009; Sachdev et al., 2007; Sarkhel et al., 2010). Please refer to the Supplementary Material for a detailed description of the study selection procedure.

2.2. Included RCTs: main characteristics

Overall, 10 RCTs were included in this meta-analysis. This resulted in 282 subjects with OCD, of whom 161 were randomized to active rTMS (mean age = 34.1 ± 6.1 years; 44% females), and 121 were randomized to sham rTMS (mean age = 34.2 ± 4.8 years; 48% females). The mean number of rTMS sessions delivered was 14.8 ± 6.5. rTMS was used as an augmentation strategy for OCD in all RCTs and most enrolled subjects had some degree of treatment-resistance. The main characteristics of the included RCTs are described in Table 1.

2.3. Pre-post OCD symptoms

Data relating to Y-BOCS score changes were available from all 10 RCTs. Overall, the pooled Hedges' g was 0.59 (95% CI = 0.17 to 1.01, $z = 2.73$, $p = 0.006$), indicating a significant and medium-sized difference in outcome favoring active rTMS (Fig. 1).

The Fail-Safe N of missing studies that would make this result statistically non-significant (i.e., $p > 0.05$) was 29, the associated Funnel Plot was reasonably symmetrical (please refer to the Supplementary Material), Egger's regression intercept was 6.12 (d.f. = 7, $t = 3.1$, two-tailed $p = 0.018$), and no study was trimmed in the Duval and Tweedie's Trim & Fill procedure.

RCTs reporting on pre-post Y-BOCS scores were heterogeneous ($Q = 25.7$, d.f. = 9, $p = 0.002$, $I^2 = 65\%$). Visual inspection of the Forest Plot suggested that this was caused by one trial (Gomes et al., 2012). Heterogeneity was no longer statistically significant after the removal of this study in a sensitivity analysis ($Q = 3.1$, d.f. = 8, $p = 0.93$, $I^2 = 0\%$), but the results were unaltered in terms of a statistically significant between-group difference (Hedges' $g = 0.4$, 95% CI = 0.15 to 0.64, $z = 3.19$, $p = 0.001$).

2.4. Response to treatment

Data relating to response rates were available from 8 RCTs. Respectively, 35% (42/120) and 13% (11/87) of subjects receiving active or sham rTMS were classified as responders. The pooled OR was 3.39 (95% CI = 1.54 to 7.48, $z = 3.03$, $p = 0.002$), indicating a significant difference in outcome favoring active rTMS (Fig. 2). The risk difference translated into an NNT of 5, meaning that 1 in every 5 patients will respond following active rTMS treatment for OCD (Citrome, 2011).

Heterogeneity between RCTs was not statistically significant ($Q = 4.7$, df = 7, $p = 0.69$, $I^2 = 0\%$). The Fail-Safe N was 12, the associated Funnel Plot was reasonably symmetrical (please refer to the Supplementary Material), Egger's regression intercept was 0.48 (df = 6, $t = 0.2$, two-tailed $p = 0.85$), and no clinical trial was trimmed in the Duval and Tweedie's Trim & Fill procedure.

2.5. Pre-post overall anxiety symptoms

Data relating to HAM-A score changes were available from 8 RCTs. Overall, the pooled Hedges' g was 0.31 (95% CI = 0.04 to 0.59, $z = 2.27$, $p = 0.023$), indicating a significant but small-sized difference in outcome favoring active rTMS (Fig. 3).

Heterogeneity between RCTs was not statistically significant ($Q = 2.6$, d.f. = 7, $p = 0.92$, $I^2 = 0\%$). The Fail-Safe N was 3, the associated Funnel Plot was reasonably symmetrical (please refer to the Supplementary Material), Egger's regression intercept was 0.38 (d.f. = 5, $t = 0.21$, two-tailed $p = 0.84$), and no clinical trial was trimmed in the Duval and Tweedie's Trim & Fill procedure.

2.6. Pre-post depressive symptoms

Data relating to HAM-D/MADRS score changes were available from 7 RCTs. Overall, the pooled Hedges' g was 0.31 (95% CI = 0.01 to 0.61, $z = 2.03$, $p = 0.04$), indicating a significant but small-sized difference in outcome favoring active rTMS (Fig. 4).

Heterogeneity between RCTs was not statistically significant ($Q = 1.4$, d.f. = 6, $p = 0.97$, $I^2 = 0\%$). The Fail-Safe N was 1, the associated Funnel Plot was reasonably symmetrical (please refer to the Supplementary Material), Egger's regression intercept was 1.24 (d.f. = 5, $t = 1.18$, two-tailed $p = 0.29$), and no clinical trial was trimmed in the Duval and Tweedie's Trim & Fill procedure.

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Table 1
Included randomized and sham-controlled trials on rTMS for OCD: Main characteristics.

Study	Active rTMS			Sham rTMS				rTMS Parameters			Psychiatric comorbidity	Treatment strategy	Resistant OCD?
	n	Age ± SD (yrs)	Female/ male (*n*)	*n*	Age ± SD (yrs)	Female/ male (*n*)	Strategy	Brain target	Frequency (Hz)/sessions	% rMT[a]/total pulses			
Alonso et al., 2001	10	39.2 ± 13.0	8/2	8	30.3 ± 9.5	4/4	90°	R-DLPFC	1/18	110/21,600	None	Mixed[a]	Yes[b]
Prasko et al., 2006	20	28.4 ± 7.4	5/15	14	33.6 ± 8.4	8/6	N/A	L-DLPFC	1/10	110/?	None	Augmentation	Yes[c]
Sachdev et al., 2007	10	29.5 ± 9.9	3/7	8	35.8 ± 8.2	5/3	Sham coil	L-DLPFC	10/10	15,000	None	Mixed[d]	Yes[e]
Kang et al., 2009	10	28.6 ± 12.7	2/8	10	26.2 ± 10.5	1/9	45°	R-DLPFC + Pre-SMA	1/10	110/12,000	35% ($n = 7$) with MDD	Augmentation	Yes[f]
Ruffini et al., 2009	16	41.5 ± 9.06	6/10	7	39.3 ± 9.55	3/4	90°	L-OFC	1/15	80/9000	None	Augmentation	Yes[e]
Badawy et al., 2010	40	26.9 ± 6.7	18/22	20	28.9 ± 5.7	13/7	Unspecified angle	L-DLPFC	20/15	?/12,000	Unknown	Mixed	Yes
Mantovani et al., 2010	9	39.7 ± 8.6	4/5	9	39.4 ± 10.2	3/6	Sham coil	Pre-SMA	1/20	100/24,000	55.5% ($n = 10$) with MDD	Mixed[g]	Yes[h]
Sarkhel et al., 2010 [i]	21	29.4 ± 6.5	11/10	21	31.9 ± 7.8	8/13	45°	R-DLPFC	10/10	110/8000	Mild depressive symptoms[j]	Augmentation	N/A
Mansur et al., 2011	13	42.1 ± 11.9	6/7	14	39.3 ± 13.9	8/6	Sham coil[k]	R-DLPFC	10/30	110/60,000	Multiple[l]	Augmentation	Yes[m]
Gomes et al., 2012	12	35.5 ± 7.5	8/4	10	37.5 ± 6	5/5	Sham coil	Pre-SMA	1/10	100/12,000	77.3% ($n = 17$) with MDD	Augmentation	Yes[g]

L-OFC = Left orbitofrontal cortex; MDD = Major depressive disorder; N/A = Not available; rMT = Resting motor threshold; R-DLPFC = Right dorsolateral prefrontal cortex; L-DLPFC = Left dorsolateral prefrontal cortex; SMA = Supplementary motor area.

[a] 27.7% ($n = 5$) of subjects were un-medicated.
[b] 72.2% ($n = 13$) of subjects had resistant OCD (i.e., unsuccessful pharmacological treatment including combined clomipramine + fluvoxamine therapy).
[c] Non-response after a 8-week trial of a selective serotonin reuptake inhibitor (SSRI).
[d] 72.2% ($n = 13$) of subjects were currently on medication.
[e] Failure of ≥2 adequate trials of anti-obsessional drugs and cognitive behavior therapy (CBT).
[f] Failure of ≥2 adequate trials of SSRIs and CBT.
[g] 72.2% ($n = 13$) of subjects were currently on medication.
[h] Residual OCD symptoms despite an adequate trial of an SSRI and CBT (for at least 12 and 8 weeks, respectively).
[i] Single-blind (i.e., raters were aware of treatment allocation).
[j] Mean baseline score on the 17-item HAM-D of 12.3 ± 2.4.
[k] Deactivated magnetic coil.
[l] 85.2% ($n = 23$) of subjects with unipolar depression, 11.1% ($n = 3$) with bipolar disorder, 26% ($n = 7$) with other anxiety disorders, 7.5% ($n = 2$) with alcohol abuse, and 18.5% ($n = 5$) with motor tics.
[m] Patients scoring ≤ 30% on the Yale-Brown Obsessive–Compulsive Scale after ≥ 3 complete courses of SSRIs (including clomipramine) and 20 h of CBT.

2.7. Acceptability of rTMS treatment

Overall, no differences on dropout rates at study end were observed between active and sham rTMS groups (6.3% [9/143] vs. 5.6% [6/108], respectively; OR = 1.27; $z = 0.43$, $p = 0.67$) (Fig. 5).

2.8. Baseline illness severity

No baseline difference on mean depression scores was found between active and sham rTMS groups (Hedges' $g = 0.093$, 95% CI = −0.19 to 0.37, $z = 0.65$, $p = 0.52$), thus minimizing depression severity as a confounding factor. However, pre-rTMS Y-BOCS scores were significantly higher in the active rTMS group, compared to the sham rTMS group (Hedges' $g = 0.33$, 95% CI = 0.07 to 0.60, $z = 2.44$, $p = 0.02$). Please refer to the Supplementary Material for the Forest Plots.

2.9. Subgroup analyses

RCTs on LF-rTMS yielded statistically significant improvements in Y-BOCS scores (Hedges' $g = 0.8$, $z = 2.64$, $p = 0.008$) and only a trend toward improvements in HAM-D/MADRS scores

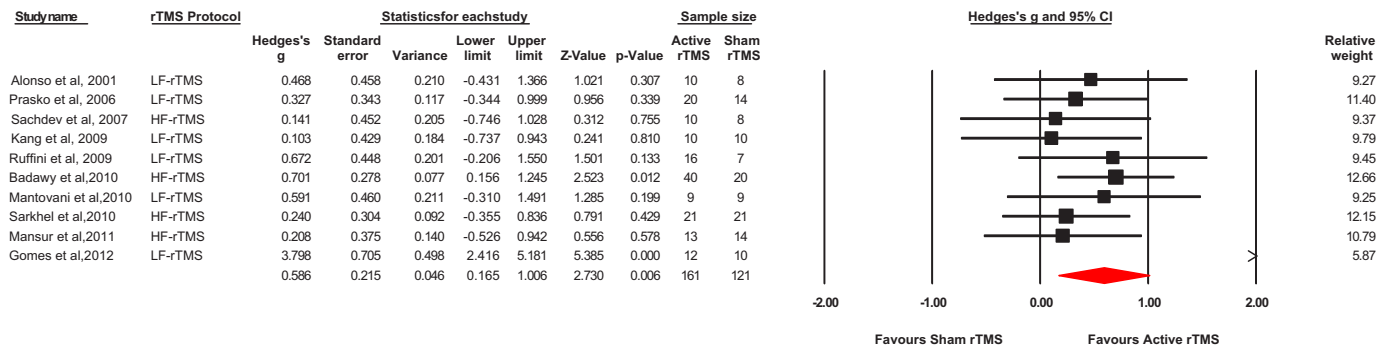

Fig. 1. Meta-analysis of Active vs. Sham rTMS for OCD: Pre-post Y-BOCS scores.

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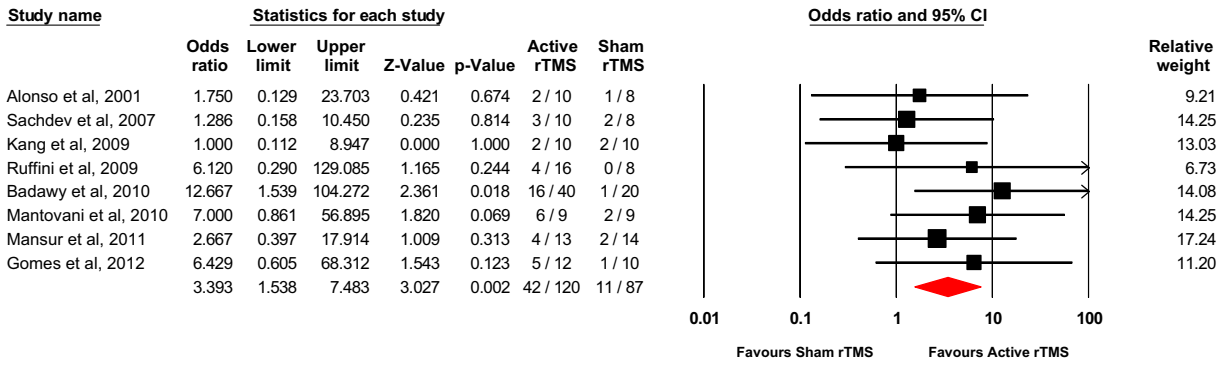

Fig. 2. Meta-analysis of Active vs. Sham rTMS for OCD: Response rates.

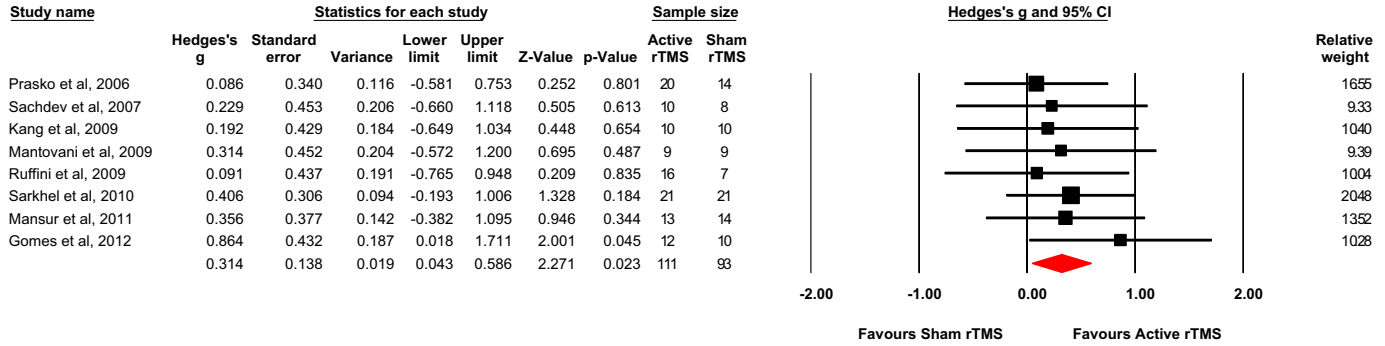

Fig. 3. Meta-analysis of Active vs. Sham rTMS for OCD: Pre-post HAM-A scores.

(Hedges' $g = 0.41$, $z = 1.82$, $p = 0.07$), but no changes in HAM-A (Hedges' $g = 0.29$, $z = 1.55$, $p = 0.12$). In contrast, RCTs on HF-rTMS did not result in significant overall improvements in Y-BOCS (Hedges' $g = 0.34$, $z = 1.01$, $p = 0.31$), HAM-A (Hedges' $g = 0.35$, $z = 1.68$, $p = 0.09$), or HAM-D/MADRS scores (Hedges' $g = 0.23$, $z = 1.08$, $p = 0.28$). In terms of the site of stimulation, RCTs focusing on the DLPFC failed to show improvements in Y-BOCS (Hedges' $g = 0.36$, $z = 1.42$, $p = 0.16$), HAM-A (Hedges' $g = 0.28$, $z = 1.56$, $p = 0.12$), or depression scores (Hedges' $g = 0.22$, $z = 1.15$, $p = 0.25$). In contrast, RCTs focusing on the OFC or the SMA yielded significant improvements in Y-BOCS scores (Hedges' $g = 1.37$, $z = 3.28$, $p = 0.001$) and a trend toward improvements in depression scores (Hedges' $g = 0.48$, $z = 1.87$, $p = 0.06$), but failed to improve HAM-A scores (Hedges' $g = 0.43$, $z = 1.69$, $p = 0.09$). Please refer to the Supplementary Material for the associated Forest Plots.

3. Discussion

This is the first meta-analysis assessing the efficacy and acceptability of rTMS for OCD. Our findings show that active rTMS significantly reduced overall OCD-related anxiety and depressive symptomatology following a mean of 14 sessions. Furthermore, active and sham rTMS groups did not differ in terms of depression scores at baseline or dropout rates at study end, although baseline Y-BOCS scores for the active rTMS group were significantly higher. Thus, active rTMS efficacy for OCD might have been even more pronounced if baseline Y-BOCS scores had been similar between the two groups.

Our exploratory subgroup analyses further indicated that HF-rTMS protocols and rTMS applied over the DLPFC did not appear to be more effective than sham rTMS. On the contrary, LF-rTMS protocols and rTMS targeted at non-DLPFC regions (i.e., SMA or

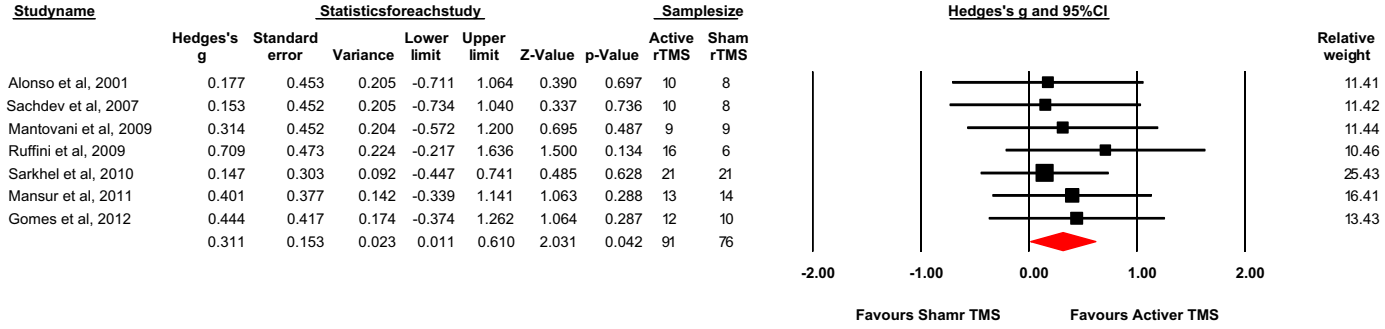

Fig. 4. Meta-analysis of Active vs. Sham rTMS for OCD: Pre-post HAM-D/MADRS scores.

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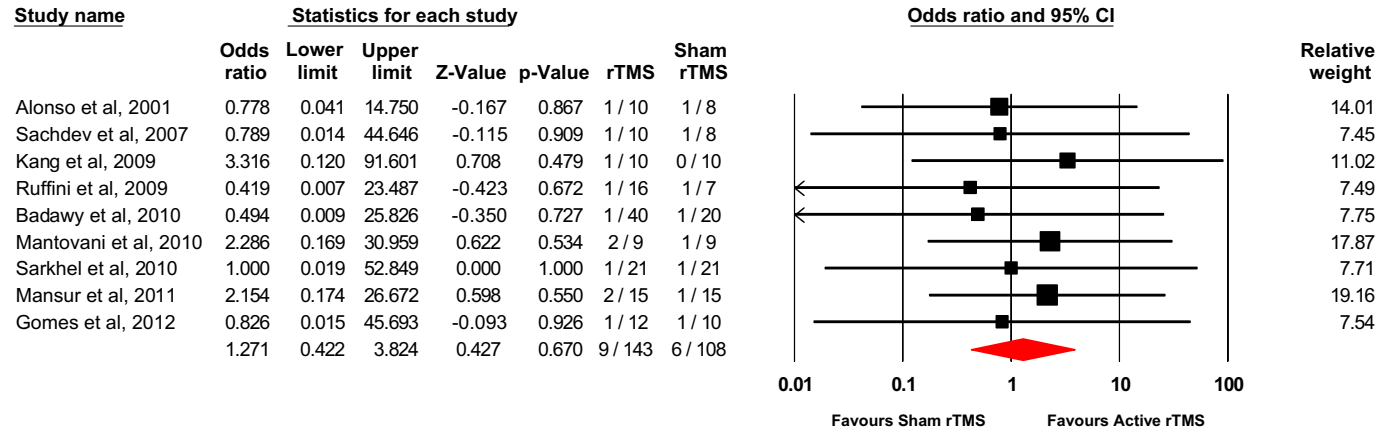

Fig. 5. Meta-analysis of Active vs. Sham rTMS for OCD: Dropout rates.

OFC), seem to be the most promising for treating OCD-related symptoms. This could be explained, at least in part, by the inhibitory effects of LF-rTMS on hyperactive orbitofronto-striatal circuits that seem to underlie deficient inhibition of irrelevant information and response control in OCD (Chamberlain et al., 2005; Menzies et al., 2008; van den Heuvel et al., 2005; Yucel et al., 2007). In other words, LF-rTMS-induced normalization of OFC/SMA activity could have enhanced the ability of patients with OCD to inhibit intrusive thoughts, impulses, images and repetitive motor responses (Mantovani et al., 2010; Ruffini et al., 2009).

Overall, the efficacy of active rTMS for OCD seems to be comparable to that of alternative augmentation strategies. For example, a recent meta-analysis on resistant OCD (Dold et al., 2012) has shown that the augmentation of SSRIs with antipsychotics for 4–16 weeks resulted in a Standardized Mean Difference in pre-post Y-BOCS scores of 0.54 (95% CI = 0.15 to 0.93; $n = 392$). Moreover, 28% of participants receiving SSRIs + antipsychotics and 13% receiving SSRIs + placebo were classified as responders (Relative Risk = 2.10, 95% CI = 1.16 to 3.80; NNT = 6; $n = 394$); our estimates, when converted to the same effect sizes, are Standardized Mean Difference = 0.6 (95% CI = 0.17–1.4) and Relative Risk = 2.37 (95% CI = 1.28–4.39). This suggests that rTMS is probably as effective as other second- or third-line pharmacological strategies for OCD without the long-term metabolic adverse effects.

Ridding and Rothwell (2007) have cogently outlined the many factors related to the therapeutic use of rTMS. Yet the optimum protocol for OCD has not been determined. Therefore, future studies should investigate new ways of enhancing the effects of rTMS on OCD, such as the identification of more clinically-relevant stimulation parameters (e.g., preconditioning paradigms/priming, different waveforms, frequencies and/or number and duration of sessions) (Fitzgerald et al., 2008; George and Aston-Jones, 2010; Peterchev et al., 2011), as well as the use of baseline electrophysiological and neuroimaging evaluations to better predict which patients might benefit from treatment (Arns et al., 2012; Seghier et al., 2010). Novel developments in the field of neuromodulation, such as the H coil (Levkovitz et al., 2010), might also enhance the efficacy of rTMS by allowing the direct stimulation of deeper brain structures, while theta burst stimulation might produce more consistent and enduring after-effects (Huang et al., 2005; Wu et al., 2010).

3.1. Limitations

First, the included RCTs had relatively small samples and were heterogeneous in terms of demographic/clinical variables and stimulation parameters. Moreover, most enrolled patients had chronic and resistant OCD, and the overall results might have been different if alternative inclusion criteria were used (e.g., early illness course or drug-naivety). 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 may not be optimal (George and Aston-Jones, 2010; Rossi et al., 2009). In addition, we could not assess the integrity of blinding in the included RCTs owing to the absence of information in this regard. However, we have recently shown that a similar percentage of depressed subjects receiving active and sham rTMS were able to correctly guess their treatment allocation at study end (i.e., 52% vs. 59%, respectively; Risk Difference = −0.04, $z = -0.51$, $p = 0.61$) (Berlim et al., 2013). Third, the most commonly used strategies for locating brain targets (e.g., the "5 cm method" and the 10–20 EEG System) have been recently criticized for their inaccuracy (Rosa and Lisanby, 2012) and future studies might benefit from the use of neuronavigation approaches (Schonfeldt-Lecuona et al., 2010). Fourth, we have only examined the efficacy of rTMS for OCD at study end and thus could not estimate the stability of its medium- to long-term effects nor its cost-effectiveness. This is especially relevant given the labor-intensive and time-consuming nature of rTMS (Wassermann and Zimmermann, 2012). Fifth, we decided not to conduct meta-regression analyses or statistically compare groups in the subgroup analyses owing to the small number of included RCTs (Thompson and Higgins, 2002); the subgroup analyses, in particular, should be seen as exploratory in nature and thus far from conclusive. Sixth, although the included RCTs varied somewhat in terms of their treatment protocols, we found significant between-study heterogeneity (as assessed by the Q statistics and the I^2 index) in only one of the analyses (i.e., pre-post Y-BOCS score changes). Finally, meta-analyses have often been 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 and systematic review of the literature, the use of stringent inclusion criteria, and the objective examination of publication bias. The lack of significant overall heterogeneity among the included RCTs and our ability to discern the likely source of heterogeneity for pre-post Y-BOCS results shows that our findings are reliable (Ioannidis, 2008).

4. Conclusion

In contrast with rTMS trials for major depression, in which a small number of brain regions were investigated while demographic/clinical and/or stimulation parameters were manipulated (Daskalakis et al., 2008), the lack of such repeated studies for

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OCD and their overall heterogeneity limit our ability to conclusively synthesize the literature. We therefore cannot draw definitive conclusions about the clinical utility of rTMS for OCD. With this said, LF-rTMS (particularly targeting the SMA or the OFC) seems to be the most promising approach in terms of potential efficacy. Clearly, larger-scale and sufficiently powered RCTs including more homogeneous patient populations (e.g., in terms of concomitant pharmacotherapy and comorbidity with major depression), more robust stimulation protocols (e.g., in terms of intensity and duration) and longer-term follow-up periods (e.g., >3 months) are needed to better understand the therapeutic role of rTMS for OCD.

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Contributors

None.

Conflicts of interest

Dr. Berlim has received a researcher-initiated grant from Brainsway Inc. Dr Van den Eynde and Mr Nicholas Neufeld report no potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2013.03.022.

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