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REVIEW ARTICLE

A Meta-Analysis of the Effectiveness of Different Cortical Targets Used in Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Obsessive-Compulsive Disorder (OCD)

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Abstract Randomised and sham-controlled trials (RCTs) of repetitive transcranial magnetic stimulation (rTMS) in the treatment of obsessive-compulsive disorder (OCD) have yielded conflicting results, which may be due to the variability in rTMS parameters used. We performed an updated systematic review and meta-analysis on the effectiveness of rTMS for the treatment of OCD and aimed to determine whether certain rTMS parameters, such as cortical target, may be associated with higher treatment effectiveness. After conducting a systematic literature review for RCTs on rTMS for OCD through to 1 December 2016 using MEDLINE, PubMed, Web of Science, PsycINFO, Google, and Google Scholar, we performed a random-effects meta-analysis with the outcome measure as pre-post changes in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores. To determine whether rTMS parameters may have influenced treatment effectiveness, studies were further analysed according to cortical target, stimulation frequency, and length of follow-up. Data were obtained from 18 RCTs on rTMS in the treatment of OCD. Overall, rTMS yielded a modest effect in reducing Y-BOCS scores with Hedge's g of 0.79 (95% CI = 0.43–1.15, $p < 0.001$). Stimulation of the supplementary motor area yielded the greatest reductions in Y-BOCS scores relative to other cortical targets. Subgroup analyses suggested that low frequency rTMS was more effective than high frequency rTMS. The effectiveness of rTMS was also greater at 12 weeks follow-up than at

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four weeks follow-up. Our meta-analysis implies that low frequency rTMS applied over the supplementary motor area may offer the greatest effectiveness in the treatment of OCD. The therapeutic effects of rTMS also appear to persist post-treatment and may offer beneficial long-term effectiveness. With our findings, it is suggested that future large-scale studies focus on the supplementary motor area and include follow-up periods of 12 weeks or more.

Keywords Repetitive transcranial magnetic stimulation · rTMS · Obsessive-compulsive disorder · OCD · Cortical target · Stimulation frequency · rTMS parameters · Long-term effectiveness · Treatment

Obsessive-compulsive disorder (OCD) is a chronic and debilitating psychiatric disorder with a lifetime prevalence of 2.3% [1]. It is mainly characterised by obsessions, which are persistent and intrusive thoughts, urges or images that an individual finds distressing, and compulsions, which are repetitive, time-consuming behaviours or mental acts usually performed to prevent or reduce distress [2]. OCD is severely incapacitating due to its intensity and continuous or deteriorative course [3], and is also associated with impaired social and occupational functioning, and reduced quality of life [4, 5].

Current first-line treatments for OCD include selective serotonin reuptake inhibitors (SSRIs) or cognitive-behavioural therapy (CBT) [6]. However, 40–60% of OCD patients fail to respond to medication, or are unable to tolerate medication side effects [7]. The majority of patients with OCD also remain symptomatic following CBT [8]. Treatment-resistant OCD patients are defined as those who undergo satisfactory trials of first-line treatments without showing an adequate response, usually defined by a reduction in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score ≥ 25% with respect to baseline [9]. Thus, novel strategies, such as repetitive transcranial magnetic stimulation (rTMS) should be considered for the efficacious treatment of resistant OCD [10–12].

rTMS is a non-invasive neuromodulation method where strong electrical currents are passed through a coil to induce repetitive magnetic field pulses in a localised area directly below the coil. The pulses have sufficient intensity to pass through the skull to superficial brain areas, where it depolarises cortical neurons [13]. Depending on the stimulation frequency, rTMS can either inhibit cortical activity at ≤1 Hz (low-frequency rTMS or LF-rTMS) or enhance cortical activity at ≥5 Hz (high-frequency rTMS or HF-rTMS) [14, 15].

Although the aetiology and pathophysiology of OCD are not completely understood, OCD has been associated with dysfunctions in the orbitofronto-striato-pallido-thalamic circuitry [16–18]. This includes the dorsolateral prefrontal cortex (DLPFC), anterior cingulate gyrus, supplementary motor area (SMA), orbitofrontal cortex (OFC), medial prefrontal cortices, and basal ganglia [16–18]. Neurophysiological studies reveal that the DLPFC, SMA and OFC are hyperactive in patients with OCD [18], and this hyperactivity has been associated with deficits in processing information and response control [19–22]. Abnormalities in the DLPFC have been linked to deficits in monitoring, working memory and higher-level planning in OCD [21, 23]. Hyperactivity in the SMA may explain deficient inhibitory control over behaviour in patients with OCD, as the SMA has extensive connections with subcortical striatal areas involved in response control [22]. The OFC is involved in emotional and motivational processing, and excessive activity in this region may relate to deficits in the inhibition of irrelevant information in OCD [19].

As rTMS can modulate cortical activity, it has been utilised in the treatment of OCD due to the neurophysiological abnormalities proposed to underlie the disorder. Initial studies applying rTMS over the DLPFC did not report superiority over placebo [11, 12]. Although significant improvements in OCD symptoms have been found following HF-rTMS applied over the DLPFC in open-label trials [24, 25], no significant differences between active and sham groups have been found in randomised controlled trials (RCTs) utilising LF-rTMS [26] or HF-rTMS [27]. The heterogeneity in protocols and conflicting results in the limited literature on rTMS in OCD have made it difficult to conclude whether rTMS is efficacious from individual studies, but meta-analyses have revealed that active rTMS is superior to sham rTMS in the treatment of OCD [28, 29].

Studies targeting the SMA or OFC have found significant improvements in OCD following rTMS [30–34]. A meta-analysis by Berlim et al. [28] suggested that the SMA and OFC are more appropriate rTMS targets than the DLPFC. This has been attributed to the restoration of cortical inhibition induced by LF-rTMS applied over the SMA and OFC, thus allowing patients with OCD to inhibit intrusive thoughts, impulses and repetitive motor responses [28]. In support of this, LF-rTMS applied over the SMA has been found to restore cortical inhibition in the motor cortex in patients with OCD, and is correlated with an improvement in OCD symptoms [35, 36]. While the SMA and OFC appear to be more promising targets, Berlim et al. [28]'s subgroup analysis included a small number of studies. In contrast to the positive findings in the majority of studies targeting the SMA with LF-rTMS [30, 32, 37], Pelissolo et al. [38] found that active LF-rTMS targeting the SMA was not superior to sham controls. A more recent meta-analysis by Trevizol et al. [29] also failed to find methodological predictors (including cortical targets) of rTMS responsiveness. The main characteristics of published meta-analyses on rTMS in OCD are summarised in Table 1. However, the number of RCTs focusing on the SMA [31, 38] and OFC [33] is increasing.

The long-term effectiveness of rTMS in the treatment of OCD must also be evaluated as rTMS is a labor-intensive and time-consuming technique [58]. The existing meta-analyses [28, 29] have only examined the efficacy of rTMS for OCD at the end of treatment, and it is unknown whether the therapeutic effects of rTMS are maintained after treatment ceases. For example, Ruffini et al. [34] found a loss of significance between active and sham groups 12 weeks post-rTMS targeted at the OFC. Meanwhile, Gomes et al. [30] found that the therapeutic effects were significantly larger and maintained in patients who received active rTMS targeted at the SMA compared to sham controls at 12 weeks post-rTMS.

This study aimed to perform a more extensive meta-analysis on the efficacy of rTMS in the treatment of OCD using a larger number of recently published RCTs to assess whether certain rTMS parameters, such as cortical target and stimulation frequency are more effective in improving OCD symptoms. The study also aimed to extend existing literature by evaluating the post-treatment effects of rTMS in the treatment of OCD.

Methods

Search Strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [59]. A systematic search of the databases MEDLINE (from 1946), PubMed (from 1946), Web of Science (from 1900), PsycINFO (from 1806), Google and

Table 1 Summary of published meta-analysis on the efficacy of rTMS in the treatment of OCD

Meta-analysis	Model	k	Subject diagnosis	Main Outcome Measure	Main finding	Included studies
Berlim et al. [39]	Random-Effects	10	OCD	Y-BOCS	Hedge's g = 0.59, 95% CI = 0.17–1.01	Alonso et al. [26]*; Prasko et al. [40]*; Sachdev et al. [27]*; Kang et al. [41]*; Ruffini et al. [34]*, Badawy et al. [42]*; Mantovani et al. [32]*; Sarkhel et al. [43]*; Mansur et al. [44]*, Gomes et al. [30]*
Ma and Shi [45]	Random-Effects	9	SSRI-resistant OCD	Y-BOCS	WMD = 3.89, 95% CI = 1.27–6.50	Alonso et al. [26]*; Prasko et al. [40]*, Kang et al. [41]*, Mantovani et al. [35]*, Mansur et al. [44]*, Gomes et al. [30]*, Zhang et al. [46]; Cheng et al. [47]; Ma [48]*
Trevizol et al. [29]	Random-Effects	15	OCD	Y-BOCS	WMD = 2.94, 95% CI = 1.26–4.60	Alonso et al. [26]*; Prasko et al. [40]*; Sachdev et al. [27]*; Kang et al. [41]*; Ruffini et al. [34]*; Badawy et al. [42]*; Mantovani et al. [32]*; Sarkhel et al. [43]*; Zhang et al. [46]; Mansur et al. [44]*; Gomes et al. [30]*; Cheng et al. [47]; Ma [48]*, Nauczyciel et al. [33]*; Haghighi et al. [49]*
Zhou et al. [50]	Random-Effects	20	OCD	Y-BOCS	Hedge's g = 0.71, 95% CI = 0.55–0.87	Alonso et al. [26]*; Sachdev et al. [27]*; Kang et al. [41]*; Ruffini et al. [34]*; Mantovani et al. [35]*; Tang et al. [51]; Zhang et al. [46]; Mansur et al. [44]*; Cheng et al. [47]; Ma [48]*, Nauczyciel et al. [33]*, Haghighi et al. [49]*; Han and Jiang [52]; Luo et al. [53]; Elbeh et al. [54]*; Hawken et al. [31]*; Jahangard et al. [55]*; Pelissolo et al. [38]*; Seo et al. [56]*; Zhang et al. [57]

SSRI selective serotonin reuptake inhibitor, *WMD* weighted mean difference

*Studies included in the current meta-analysis

Google Scholar through to 1 December 2016 was performed to identify relevant articles. The search used the terms 'obsessive compulsive disorder' or 'OCD' or 'obsessions' or 'compulsions' AND 'transcranial magnetic stimulation' or 'TMS'; these terms were searched as text word and as exploded medical subject headings where possible. The reference list of previous systematic reviews [10–12] and existing meta-analyses [28, 29, 45] on rTMS in OCD was examined for appropriate studies. No language restrictions were placed on either the search or study selection, however all searched papers were published in English. Unpublished studies were not searched.

Study Selection

Studies were included if they met the following inclusion criteria: (1) included subjects aged 18–75 years with a primary diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental disorders (DSM-IV) [60] or the Diagnostic and Statistical Manual of Mental disorders (DSM-IV-TR) [60] or the International Classification of Diseases [61]; (2) randomised, sham-controlled trials with either single- or double-blinding or parallel or cross-over design (with only data from the initial randomisation being used for the latter to avoid carryover effects); (3) greater than five subjects with OCD randomised per study arm; (4) LF- (≤1 Hz) or HF-rTMS (≥5 Hz) given for ≥5 sessions either as monotherapy or as an augmentation strategy for OCD (5) reported pre- and post-rTMS Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [62] scores and standard deviation (SD) to evaluate the severity of symptoms as the outcome. We excluded studies if they started rTMS concurrently with a new psychotropic medication or if they otherwise did not satisfy the inclusion criteria.

Data Extraction

The data extraction was performed using a standardised data extraction form, collecting information on sample characteristics (mean age, gender, number of cases and controls, monotherapy or augmentation, presence of treatment-resistant OCD), rTMS treatment characteristics (cortical target(s), stimulation frequency, intensity, treatment duration, number of treatment sessions, type of sham), and score changes (pre-post rTMS, pre-follow-up rTMS, duration of follow-up, SD) on the Y-BOCS. Authors were not contacted for missing data.

Statistical Analysis

All analyses were performed with Comprehensive Meta-analysis Version 3.0 (Biostat, Englewood, NJ, 2014), which uses an inverse-invariance method to weigh individual effect sizes. Hedge's g and 95% confidence intervals (CI) were calculated for the effectiveness of rTMS in the treatment of OCD using the primary outcome measure of reduction in Y-BOCS score from pre- to post-rTMS, and the reduction in Y-BOCS score from pre-rTMS to follow-up for analyses on the longer-term effects of rTMS in OCD. This was performed using a random-effects model [63]. We assessed heterogeneity with Cochran's Q statistic, with $p < 0.10$ indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity. I^2 values of 25%, 50% and 75% corresponded to low, moderate and high degrees of heterogeneity respectively [64]. We quantified publication bias using the Egger's regression model [65], with the effect of bias assessed using the fail-safe number method [66].

We conducted a mixed-effects analysis, and used a random-effects model to combine studies within each subgroup. A fixed-effect model was then used to combine subgroups and yield the overall effect. To assess whether OCD improvement was modified by cortical target, another subgroup analysis was performed by subgrouping the RCTs into right DLPFC (R-DLPFC), left DLPFC (L-DLPFC), bilateral DLPFC (B-DLPFC), OFC, and SMA. We also assessed whether rTMS effectiveness was dependent on stimulation frequency by subgrouping RCTs into LF- and HF-rTMS protocols. Additionally, we assessed whether LF- or HF-rTMS was more effective at the DLPFC by subgrouping RCTs with a DLPFC target by their stimulation frequency. As all existing RCTs targeting the SMA have been performed with LF-rTMS, the effectiveness of stimulation frequency targeting the SMA was not analysed.

We further assessed the duration of clinical improvements post-rTMS using RCTs reporting follow-up Y-BOCS scores. The effectiveness of rTMS post-treatment was evaluated by calculating the reduction from pre-rTMS to follow-up Y-BOCS scores. Two additional meta-analyses were performed using RCTs with short-term follow-up (≤ 4 weeks) and longer-term follow-up (12 weeks) periods.

Results

Eighteen RCTs were included in this meta-analysis [26, 27, 30–32, 34, 38, 40–44, 48, 49, 54–57]. Figure 1 shows the selection of studies from the 1140 potentially relevant studies identified from our original search. This resulted in 484 subjects with OCD, of whom 262 were randomised to active rTMS ($M = 33.63$ years, $SD = 5.32$) and 222 randomised to sham rTMS ($M = 33.78$ years, $SD = 5.17$). The mean number of rTMS sessions delivered was 14.63 ± 6.0. rTMS was used as an augmentation strategy for OCD in all RCTs and most enrolled subjects had some degree of treatment-resistance. Due to this, only data from the group receiving rTMS as augmentation was included from the Badawy et al. [42] study. A pooled effect size was calculated for the HF-rTMS and LF-rTMS groups in the Elbeh et al. [54] study to avoid including the same comparison sham group twice, as recommended by Borenstein et al. [67]. The main characteristics of the included RCTs are described in Table 2. In the case of multiple follow-up measurements [31, 44], the follow-up Y-BOCS score at the last follow-up period was used to calculate the improvement in OCD severity (as assessed using Y-BOCS score reductions) from pre-rTMS to follow-up in the subsequent meta-analyses. The duration of follow-up from which this data were taken for these analyses has been reported in Table 2.

Pre-Post OCD Symptoms

Data relating to Y-BOCS score changes were available from all 18 RCTs and was either reported in the articles or assessed by graphic evaluation. The change in Y-BOCS scores was calculated as the reduction in Y-BOCS scores from pre-rTMS to post-rTMS, and greater reduction indicated greater improvements in the severity of OCD symptoms. Overall, active rTMS was significantly superior to sham rTMS in reducing Y-BOCS scores ($g = 0.79$, 95% CI = 0.43–1.15, $p < 0.001$), as shown in Fig. 2. RCTs reporting pre-post Y-BOCS scores had moderate heterogeneity ($I^2 = 71.32$, $p < 0.001$). Visual inspection of the Forest Plot suggested that this was mainly caused by two studies [30, 31].

Egger's regression analysis showed that publication bias was present ($p = 0.004$), as shown in Fig. 3. The Fail-Safe N of missing studies that would render our result statistically non-

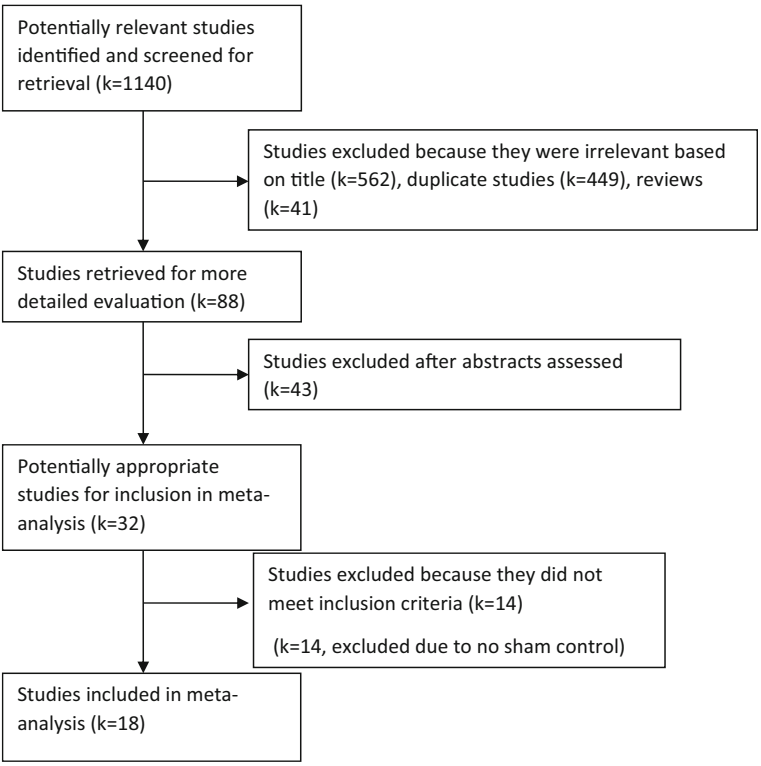

Fig. 1 The selection of studies included in the meta-analysis

significant was 16. However, it is highly improbable that 16 studies with non-significant or negative findings were missed or excluded in the current meta-analysis as a systematic search of multiple databases was performed. Furthermore, as no more than 25 studies have been published over the past 20 years, it is unlikely that 16 similar studies were unpublished. As the Funnel Plot was not symmetrical, the trim-and-fill procedure was performed and found no difference in point estimate (g = 0.66). Therefore, publication bias was not an issue in the current meta-analysis.

Cortical Target

As shown in Fig. 4, RCTs applying active rTMS over the B-DLPFC, R-DLPFC and the SMA yielded significant improvements in Y-BOCS scores over sham rTMS. Targeting the SMA produced the greatest effect size (g = 1.68, 95% CI = 0.07–3.29, $p = 0.041$), followed by the B-DLPFC (g = 1.18, 95% CI = 0.45–1.91, $p = 0.002$), and R-DLPFC (g = 0.58, 95% CI = 0.20–0.97, $p = .003$). Active rTMS was not significantly superior to sham rTMS in improving Y-BOCS scores in RCTs targeting the L-DLPFC (g = 0.24, 95% CI = −0.17 – 0.65, $p = 0.253$). RCTs targeting the OFC showed a trend towards improvement in Y-BOCS scores with active rTMS, but did not reach statistical significance (g = 0.60, 95% CI = −-0.02–1.22, $p = 0.059$).

Heterogeneity was not statistically significant among RCTs included in the subgroup analysis on cortical target (Q = 6.94, $p = 0.14$). However, it must be noted that our subgroup analysis included a small number of studies, and Cochran's Q has low power with few studies.

Table 2 Included randomised and sham-controlled trials on rTMS for OCD: Main characteristics

Study	Active rTMS			Sham rTMS				rTMS parameters						
	n	Age (yrs)	Female/ male (n)	n	Age (yrs)	Female/ male (n)	Strategy	Cortical target	Frequency (Hz)	Sessions	%RMT	Total pulses	Treatment duration (weeks)	Follow-up period (weeks)
Alonso et al. [26]	10	39.2	8/2	8	30.3	4/4	90°	R-DLPFC	1	18	110	21,600	6	N/A
Prasko et al. [40]	18	28.9	5/13	12	33.4	7/5	90°	L-DLPFC	1	10	110	18,000	5	2
Sachdev et al. [27]	10	29.5	3/7	8	35.8	5/3	Sham coil	L-DLPFC	10	10	110	15,000	2	N/A
Kang et al. [41]	10	28.6	2/8	10	26.2	1/9	45°	R-DLPFC + Pre-SMA	1	10	110	12,000	2	2
Ruffini et al. [34]	16	41.5	6/10	7	39.3	3/4	90°	L-OFC	1	15	80	9000	3	12
Badawy et al. [42]	20	27.7	8/12	20	28.9	13/7	Unspecified angle	L-DLPFC	20	15	?	12,000	3	N/A
Mantovani et al. [32]	9	39.7	4/5	9	39.4	3/6	Sham coil	Pre-SMA	1	20	100	24,000	4	N/A
Sarkhel et al. [43]	21	29.4	11/10	21	32.0	8/13	45 degrees	R-DLPFC	10	10	110	8000	2	2
Mansur et al. [44]	13	42.1	6/7	14	39.3	8/6	Sham coil	R-DLPFC	10	30	110	60,000	6	2
Gomes et al. [30]	12	35.5	8/4	10	37.5	5/5	Sham coil	Pre-SMA	1	10	100	12,000	2	12
Ma et al. [48]	25	27.1	8/17	21	29.9	8/13	Unplugged device	B-DLPFC	8–12	10	80	6480–8720	2	1
Nauczyciel et al. [33]	9	40	7/2	10	39	8/2	Sham coil	R-OFC	1	10	120	12,000	1	N/A
Haghighi et al. [49]	10	34.9	3/7	11	36.6	6/5	45–90°	B-DLPFC	20	20	100	7500	5	N/A
Elbeh et al. [54]	15	28.9	6/9	15	25.5	5/10	90°	R-DLPFC	10	10	100	20,000	2	12
	15	26.8	4/11	15	25.5	5/10	90°	R-DLPFC	1	10	100	20,000	2	12

Table 2 (continued)

Study	Active rTMS			Sham rTMS				rTMS parameters						
	n	Age (yrs)	Female/ male (n)	n	Age (yrs)	Female/ male (n)	Strategy	Cortical target	Frequency (Hz)	Sessions	%RMT	Total pulses	Treatment duration (weeks)	Follow-up period (weeks)
Elbeh et al. [54]														
Hawken et al. [31]	10	33	?	12	31	?	90°	SMA	1	25	110	?	6	N/A
Jahangard et al. [55]	5	32.4	1/4	5	33.8	2/3	45–90°	B-DLPFC	20	10	100	7500	2	N/A
Pelissolo et al. [38]	20	39.1	13/7	16	42.3	9/7	Sham coil	Pre-SMA	1	20	100	30,000	4	N/A
Seo et al. [57]	14	34.6	6/8	13	36.3	7/6	Sham coil	R-DLPFC	1	15	100	18,000	3	N/A

L left, *R* right, *B* bilateral, *DLPFC* dorsolateral prefrontal cortex, *OFC* orbitofrontal cortex, *SMA* supplementary motor area

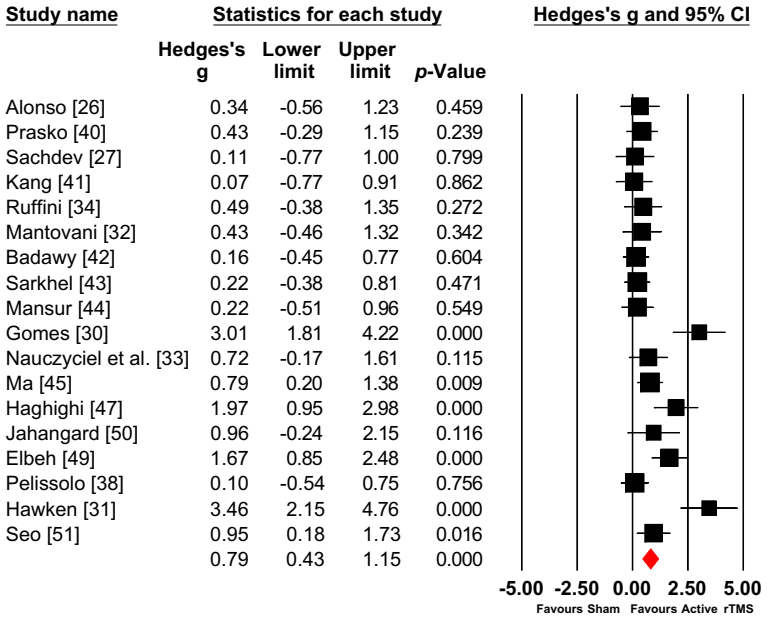

Fig. 2 Meta-analysis of Active vs. Sham rTMS for OCD: Pre-post Y-BOCS scores

Heterogeneity was low between RCTs targeting the L-DLPFC ($I^2 = 0$, $p = 0.81$) and OFC ($I^2 = 0$, $p = 0.72$). RCTs targeting the B-DLPFC had insignificant heterogeneity ($I^2 = 48.67$, $p = 0.14$), whereas those targeting the SMA were highly heterogeneous ($I^2 = 91.04$, $p < 0.001$). Visual inspection of the Forest Plot suggested that this was caused by two studies [30, 31]. Indeed, after removal of these studies from analyses, heterogeneity was no longer significant ($I^2 = 0$, $p = 0.56$) and active rTMS was not significantly superior to sham rTMS (g = 0.22, 95% CI = −0.31 – 0.74, $p = 0.419$). RCTs targeting the R-DLPFC ($I^2 = 57.19$, $p = 0.04$) were heterogenous, and appeared to be caused by two studies [54, 65].

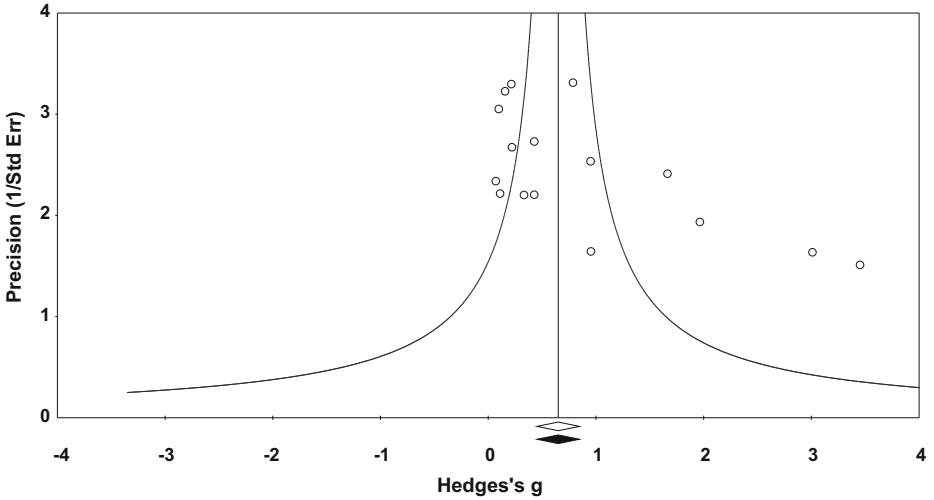

Fig. 3 Funnel plot of included RCTs reporting pre-post Y-BOCS scores indicating publication bias

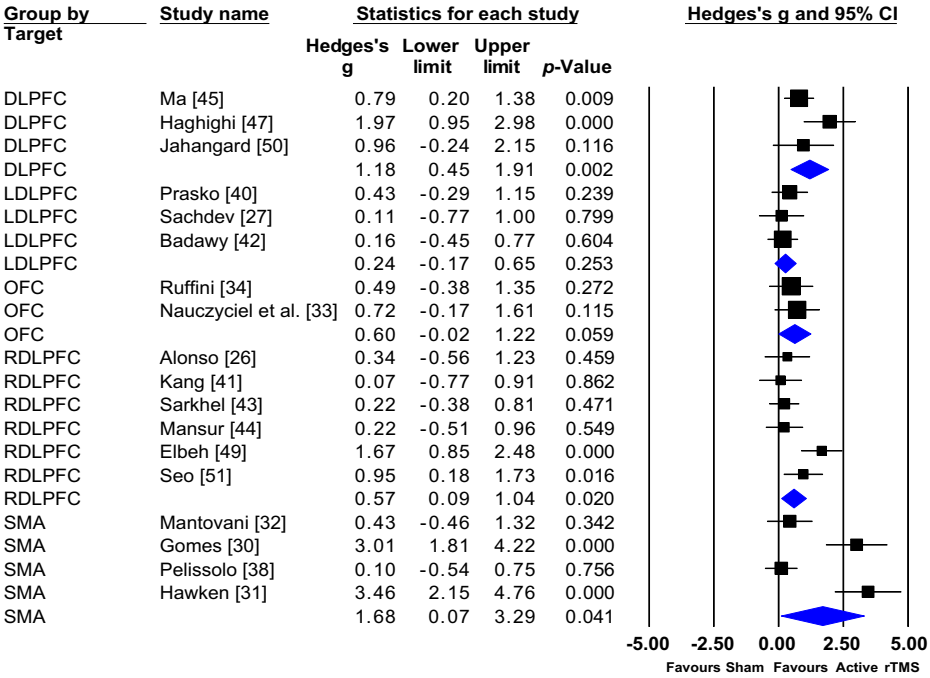

Fig. 4 Subgroup analysis of Active vs. Sham rTMS by specific cortical target: pre-post Y-BOCS scores. L: left; R: right; DLPFC: dorsolateral prefrontal cortex; OFC: orbitofrontal cortex; SMA: supplementary motor area

Stimulation Frequency

As shown in Fig. 5, statistically significant improvements in Y-BOCS scores were found in RCTs with LF-rTMS (g = 0.97, 95% CI = 0.42–1.51, $p = 0.001$) and HF-rTMS (g = 0.55, 95% CI = 0.13–0.97, $p = 0.01$). Heterogeneity was insignificant between RCTs with HF-rTMS protocols ($I^2 = 53.30$, $p = 0.05$). Heterogeneity was high between RCTs with LF-rTMS protocols ($I^2 = 77.35$, $p < 0.001$). Visual inspection of the Forest Plot suggested that this was caused by three studies [30, 31, 54]. Heterogeneity was no longer significant upon removal of these three studies ($I^2 = 0$, $p = 0.79$), but active LF-rTMS still offered greater improvements in OCD symptoms than sham rTMS (g = 0.42, 95% CI = 0.14–0.70, $p = 0.003$).

Post-rTMS Effects

Four Weeks or Less Data relating to Y-BOCS scores of four weeks or less post-rTMS were available from 6 RCTs. Active rTMS remained statistically significantly superior to sham rTMS in treating OCD within four weeks post-treatment (g = 0.81, 95% CI = 0.01–1.60, $p = 0.047$), as shown in Fig. 6. There was high heterogeneity among RCTs with follow-up periods of four weeks or less ($I^2 = 84.48$, $p < 0.001$). Visual inspection of the Forest Plot suggested that it was caused by one study [31] and heterogeneity was no longer significant upon removal of this study ($I^2 = 0$, $p = 0.88$).

Twelve Weeks Data relating to Y-BOCS scores at 12 weeks post-rTMS were available from three RCTs. Active rTMS remained statistically significantly superior to sham rTMS in

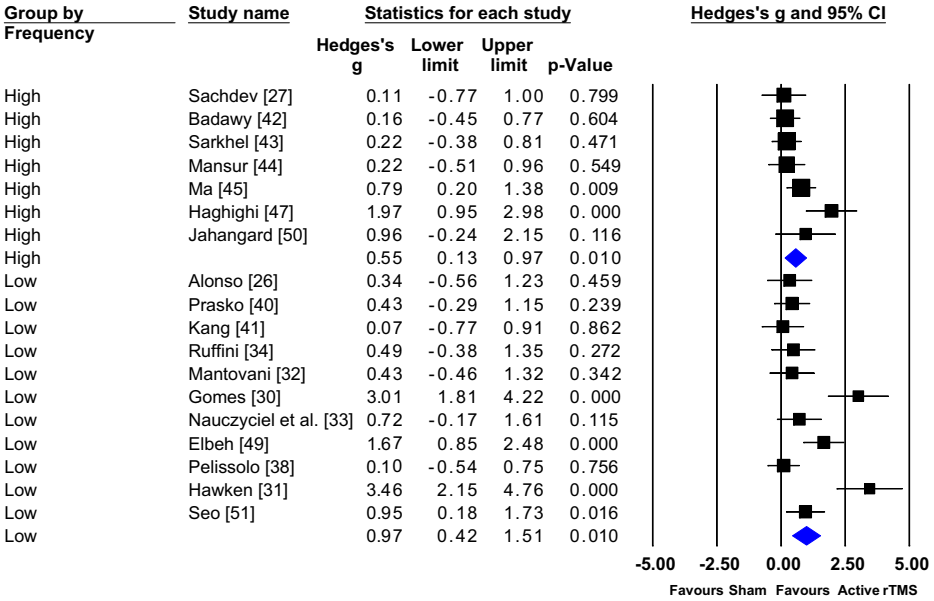

Fig. 5 Subgroup analysis of Active vs. Sham rTMS by stimulation frequency: HF-rTMS vs. LF-rTMS

treating OCD at 12 weeks post-treatment (g = 1.26, 95% CI = 0.12–2.39, $p = 0.030$), as shown in Fig. 7. There was high heterogeneity among RCTs with follow-up periods of 12 weeks ($I^2 = 79.27$, $p = 0.008$), and visual inspection of the Forest Plot suggested that this was caused by one study [30]. All results from subgroup analyses have been summarised in Table 3.

Discussion

The current study is the first meta-analysis to assess whether the effectiveness of rTMS in improving OCD symptoms is moderated by its application over different cortical targets. Our findings reveal that rTMS applied over the SMA yields greater improvements in OCD severity than rTMS applied over the DLPFC or OFC, which has not been found in previous meta-

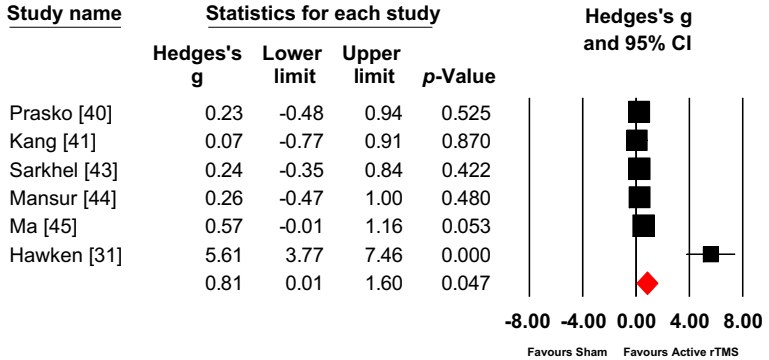

Fig. 6 Meta-analysis of Active vs. Sham rTMS for OCD: ≤ 4 weeks post-treatment

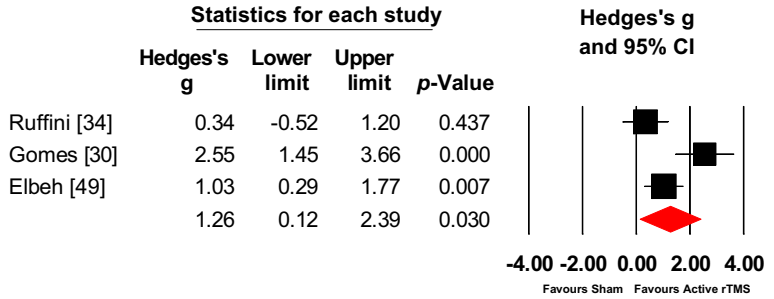

Fig. 7 Meta-analysis of Active vs. Sham rTMS for OCD: 12 weeks post-treatment

analyses. This may be attributed to the inclusion of two recent studies targeting the SMA with rTMS [31, 38]. Given that a large reduction in OCD severity following rTMS treatment was found in Hawken et al. [31], the inclusion of this study may have contributed to the significant advantage of a SMA target over other cortical targets, found in the current meta-analysis. While Berlim et al. [28] identified the SMA and OFC as more promising rTMS targets for treating OCD than the DLPFC, the current meta-analysis performed separate subgroup analyses for RCTs targeting the SMA and OFC, and revealed that targeting the SMA yielded significant improvements in OCD symptoms, whereas active rTMS targeting the OFC did not appear to be more effective than sham rTMS. Although studies targeting the OFC and SMA remain scarce, which limits our ability to draw conclusions, the current meta-analysis extends existing research by clarifying the differing effectiveness of rTMS in OCD when applied over different cortical regions.

The SMA appears to be the most effective cortical target in the treatment of OCD using rTMS, and this has been attributed to the normalisation of hyperactive orbitofronto-striatal circuits induced by LF-rTMS [32]. The SMA plays a central role in motor planning and response-inhibition [18, 21, 68], and has extensive connections to regions involved in cognitive and emotional processes [69, 70]. Studies suggest that hyperactivity in this area may be associated with deficient inhibitory control over repetitive behaviours that patients with OCD display [22, 71], thus making it an attractive target for the inhibitory effects of LF-rTMS. In support of this, motor-pathway excitability increases from baseline after LF-rTMS, demonstrating increased cortico-subcortical inhibition, and is associated with beneficial responses in patients with OCD [32]. Furthermore, cortical excitability studies have found that LF-rTMS

Table 3 Summarised subgroup analyses

Subgroups	k	Heterogeneity I^2(%)	P for I^2	Hedge's g (95% CI)	P for Hedge's g
Cortical target					
SMA	4	91.04	<0.001	1.68 (0.07–3.29)	0.041
B-DLPFC	3	48.67	0.14	1.18 (0.45–1.91)	0.002
R-DLPFC	6	57.19	0.04	0.58 (0.20–0.97)	0.003
L-DLPFC	3	0	0.81	0.24 (−0.17–0.65	0.253
OFC	2	0	0.72	0.60 (−0.02–1.22)	0.059
Frequency					
High	7	53.30	0.05	0.55 (0.13–0.97)	0.01
Low	11	77.35	<0.001	0.97 (0.42–1.51)	0.001
< 4 weeks post-treatment	6	84.48	<0.001	0.81 (0.01–1.60)	0.047
12 weeks post-treatment	3	79.27	0.008	1.26 (0.12–2.39)	0.030

applied over the pre-SMA increased inhibition in the primary motor cortex, which was correlated with effective clinical response in OCD symptoms [35]. Therefore, it appears that LF-rTMS targeted at the SMA may have assisted patients with OCD to inhibit repetitive motor responses and improve OCD symptoms by restoring cortical inhibition. Van den Heuvel [72] has also reported that different brain areas may be involved in OCD depending on the specific OCD symptom, e.g. harm/checking symptoms versus contamination/cleaning symptoms. Hence, future studies should also attempt to examine the relationship between treatment response after stimulation of different anatomical areas and specific OCD symptoms.

LF-rTMS has also been used to normalise hyperactivity in the OFC as it is associated with deficient control over intrusive thoughts, impulses, or urges present in OCD [11]. However, the OFC is located deep beneath the scalp and is difficult to stimulate with conventional rTMS devices [33, 34]. Our findings indicate that rTMS applied over the OFC was not significantly more effective than sham rTMS, however it must be noted that this subgroup only consisted of two RCTs, and the effectiveness of the OFC as a cortical target for rTMS cannot be concluded.

Alternatively, the use of LF-rTMS in all RCTs with a SMA target may have accounted for the higher effectiveness associated with the SMA. This is because LF-rTMS has been found to be more effective than HF-rTMS in both previous meta-analyses [28] and in our subgroup analysis on frequency in the current meta-analysis. It could be argued that the use of both excitatory HF-rTMS and inhibitory LF-rTMS in RCTs targeting the DLPFC may have attenuated its potential effectiveness as a cortical target. However, upon inspection of the subgroup analyses comparing HF- to LF-rTMS targeted at the DLPFC, LF-rTMS targeted at the SMA appeared to be more effective than LF-rTMS targeting the DLPFC. Therefore, the effectiveness associated with the SMA appears better explained by cortical target rather than frequency.

Our findings indicate that rTMS targeted at the DLPFC offered greater improvements in OCD symptoms than sham rTMS, in contrast to Berlim et al. [28]'s findings of a non-significant difference between active and sham rTMS applied over the DLPFC, regardless of frequency. This could be explained by the inclusion of a greater number of RCTs in the current meta-analysis. The recent meta-analysis by Zhou et al. [50] also found significant improvements of active rTMS applied over the DLPFC in comparison to sham treatments, supporting the findings of the current meta-analysis.

Nevertheless, rTMS applied over the DLPFC was less effective in improving OCD symptoms than rTMS applied over the SMA. It has been suggested that rTMS applied over the DLPFC induces improvements in comorbid anxiety and depression rather than specific OCD symptoms [12, 27, 32]. Most of the RCTs included in our meta-analysis had patients with comorbid anxiety and depression [30, 32, 33, 38, 41, 43, 44, 57], and rTMS applied over the DLPFC may have produced improvements in OCD symptoms that were secondary to improvements in depression and anxiety. For example, meta-analyses of rTMS applied over the DLPFC in patients with depression have reported a significant reduction in depression scores after active rTMS compared to sham [39, 73, 74]. A case study also found that patients who responded to rTMS treatment (> 25% reduction in Y-BOCS scores) did not have comorbid psychiatric disorders [75]. The current study may have found significant but less effective reductions in OCD severity following active rTMS applied over the DLPFC relative to the SMA, due to potential non-specific improvements in depression and anxiety associated with a DLPFC target.

Alternatively, studies have reported greatest improvements in depressive symptoms when HF-rTMS was applied over the DLPFC [73, 74], whereas the current meta-analysis found the

greatest improvement in OCD symptoms following LF-rTMS applied over the SMA. Improvement in OCD symptoms may be independent of improvements in comorbid depression due to the differences in rTMS protocols. The current meta-analysis did not assess whether improvements in comorbid depression or anxiety were linked to specific rTMS frequencies and cortical targets used in the alleviation of OCD symptoms, and cannot conclude whether improvements in OCD are independent or secondary to the potential antidepressant or anxiolytic effects of rTMS. However, comorbidity is common in patients with OCD [76] and findings from the current meta-analysis therefore offer ecological validity in assessing whether rTMS offers clinical utility, especially in the treatment of resistant OCD.

Moreover, the current meta-analysis is the first to assess whether improvements in OCD symptoms persist post-rTMS. Our findings revealed that active rTMS was superior to sham rTMS in improving OCD symptoms at four weeks or less and at 12 weeks post-treatment. Although the instability of this finding within four weeks post-treatment is evident in the 95% confidence interval, rTMS appears to offer beneficial medium and longer-term effectiveness – the therapeutic effects of active rTMS were maintained post-treatment.

Our findings further imply that active rTMS was more effective at improving OCD symptoms at 12 weeks post-treatment compared to four weeks or less post-treatment. It is possible that the therapeutic effects of rTMS are gradual and take several weeks to become established. This delay in clinical response may be explained by the gradual restoration of cortical inhibition post-rTMS, as emerging evidence suggests that rTMS interacts with the normal processes of brain plasticity to induce structural remodelling of neuronal networks [77]. However, due to the few studies included in the analysis of efficacy of rTMS at 12 weeks follow-up, the current findings should be interpreted with caution.

Nevertheless, OCD improvements appeared to be greater at the 12-week timepoint, which resembles the timepoint required for improvements induced by pharmacological interventions for OCD to become apparent. Recommended pharmacotherapy trials for SSRIs and clomipramine last 12 weeks [78, 79], and it is well-established that the benefits of clomipramine and various SSRIs have been found to increase slowly and gradually over several weeks, with the greatest effectiveness seen at 12 weeks [80, 81]. The gradual improvements associated with SSRIs for OCD have been attributed to the slow reversal of structural brain abnormalities [82], and the beneficial effects of rTMS may similarly require sufficient time for these neuronal changes to occur. rTMS may induce long-term changes in the effectiveness of synapses between cortical neurons in a manner that resembles long-term depression and long-term potentiation [77]. However, the long-term effects of rTMS are poorly understood, and further investigation into its mechanism of action is required.

It is also possible that our finding of greater effectiveness at 12 weeks can be accounted by other factors. For example, patients assessed at follow-up may have received other treatments post-rTMS which could have contributed to delayed improvement in OCD symptoms. Alternatively, pharmacotherapy may have begun to become effective after 12 weeks in patients with OCD in the RCTs with follow-ups, therefore inflating effectiveness at a later timepoint. However, most enrolled patients had chronic and resistant OCD, and had failed at least one adequate trial of pharmacotherapy for OCD. Therefore, this is unlikely to account for our findings of greater rTMS effectiveness at a later follow-up period of 12 weeks. The high heterogeneity in RCTs with follow-up periods of four weeks or less, and 12 weeks must also be noted. This was most likely due to a lack of consistency in the length of follow-up in the included RCTs, especially as we grouped RCTs with follow-up periods ranging from one to four weeks in our four weeks or less post-rTMS meta-analysis. Despite this, our findings

indicate that future RCTs should include follow-up at 12 weeks post-rTMS, and aim to perform follow-up periods past 12 weeks to further elucidate the full effect of rTMS in the treatment of OCD.

Taken together, our findings indicate that active rTMS is significantly superior to sham rTMS in the treatment of OCD, in line with findings from existing meta-analyses [28, 29]. Our subgroup analyses further reveal that both active LF- and HF-rTMS were more effective than sham rTMS. Despite this, LF-rTMS was more effective at improving OCD symptoms than HF-rTMS, which may be attributed to the inhibitory effects of LF-rTMS on the hyperactive orbitofronto-striatal circuits associated with deficient control over irrelevant information and responses in OCD [19, 21–23].

However, the current findings should be interpreted in light of the limitations of the included RCTs. Many of the RCTs were heterogeneous in terms of clinical variables and stimulation parameters. Furthermore, many of the enrolled patients had resistant OCD, which limits our ability to draw definitive conclusions about the effectiveness of rTMS in the treatment of OCD with other characteristics, such as early illness course or drug-naivety. As many of the patients were also maintained on pharmacological treatments throughout rTMS trials, it is possible that there exists a synergistic effect between rTMS and these medications. It is suggested that future studies perform rTMS trials on drug-naïve patients with OCD. Presently however, rTMS is being mainly considered as a treatment for resistant OCD, rather than a first-line treatment as it is a time-consuming and labour-intensive technique [58].

The large improvements in OCD symptoms associated with active rTMS applied over the SMA should be interpreted cautiously as inspection of the 95% CI reveals the instability of these improvements. In our subgroup analysis on cortical target, there was significantly high heterogeneity among RCTs targeting the SMA. This was mainly caused by two trials [30, 31], and removal of these trials revealed negligible benefits of active rTMS over the SMA. Gomes et al. [30] reported that their sample consisted of patients with fewer years of disease – therefore being less chronic – and with shorter duration of the current OCD episode, which may explain the higher treatment effectiveness found in their study relative to other studies. Meanwhile, Hawken et al. [31] performed the largest number of rTMS sessions, which may have accounted for their findings of higher rTMS effectiveness.

The current meta-analysis did not examine rTMS response rates or dropout rates, which is a limitation which must be considered when evaluating rTMS as a possible therapeutic option for patients with resistant OCD. Berlim et al. [28] found that 35% and 13% of subjects receiving active or sham rTMS respectively, were classified as responders. Regarding acceptability of rTMS treatment, drop-out rates have not been reported to differ between active and sham rTMS in multiple studies.

The quality of available sham rTMS conditions has also been under dispute [28]. Zhou et al. [50] recently reported a larger effect size in clinical trials utilising a tilted-coil placebo compared to those with sham coils. Thus, sham coils may produce larger placebo effects than tilted coils as sham coils can produce auditory and somatic sensations similar to that of an active coil [83].

Finally, the objective measure of publication bias suggested that there was a significant possibility of a publication bias. However, we performed a comprehensive and systematic search of existing literature, with extensive inclusion criteria to isolate high-quality trials. Furthermore, the trim-and-fill procedure confirmed the beneficial effect of active rTMS over sham rTMS in the treatment of OCD, thus rendering the severity of possible publication bias negligible.

Although the clinical utility of rTMS in the treatment of OCD requires further investigation as to the most optimal stimulation parameters, the current meta-analysis indicates that LF-rTMS applied over the SMA may offer the greatest improvement in OCD symptoms. Furthermore, the therapeutic effects of rTMS appear to be persist post-rTMS, thus offering promising long-term effectiveness. With this, it is suggested that future large-scale studies focus on the SMA as a cortical target for rTMS in the treatment of OCD and include follow-up periods of 12 weeks or more to further elucidate the full effect of rTMS for OCD.

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Compliance with Ethical Standards

Conflict of Interests The Authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants performed by any of the authors.

References

1. Ruscio A, Stein D, Chiu W, Kessler R. The epidemiology of obsessive-compulsive disorder in the national comorbidity survey replication. Mol Psychiatry. 2010;15(1):53–63.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. Washington, D.C: American Psychiatric Association; 2013.
3. Skoog G, Skoog I. A 40-year follow-up of patients with obsessive-compulsive disorder. Arch Gen Psychiatry. 1999;56(2):121–7.
4. DuPont RL, Rice D, Shiraki S, Rowland C. Economic costs of obsessive-compulsive disorder. Med Interface. 1995;8(4):102–9.
5. Fullana MA, Mataix-Cols D, Caspi A, Harrington H, Grisham JR, Moffitt TE, et al. Obsessions and compulsions in the community: prevalence, interference, help-seeking, developmental stability, and co-occurring psychiatric conditions. Am J Psychiatr. 2009;166(3):329–36.
6. Stein DJ, Koen N, Fineberg N, Fontenelle LF, Matsunaga H, Osser D, et al. A 2012 evidence-based algorithm for the pharmacotherapy for obsessive-compulsive disorder. Curr Psychiatry Rep. 2012;14(3):211–9. https://doi.org/10.1007/s11920-012-0268-9.
7. Pallanti S, Hollander E, Bienstock C, Koran L, Leckman J, Marazziti D, et al. Treatment non-response in OCD: methodological issues and operational definitions. Int J Neuropsychopharmacol. 2002;5(2):181–91.
8. Abramowitz JS, Franklin ME, Foa EB. Empirical status of cognitive-behavioral therapy for obsessive-compulsive disorder: a meta-analytic review. Rom J Cogn Behav Psychother. 2002;2(2):89–104.
9. Rauch SL, Jenike MA. Management of treatment resistant obsessive-compulsive disorder: concepts and strategies. In: Hollander E, Zohar J, Marazziti D, Olivier B, editors. Obsessive compulsive disorder. Chicester: Wiley; 1994. p. 227–44.
10. Blom RM, Figee M, Vulink N, Denys D. Update on repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: different targets. Curr Psychiatry Rep. 2011;13(4):289–94.
11. Saba G, Moukheiber A, Pelissolo A. Transcranial cortical stimulation in the treatment of obsessive-compulsive disorders: efficacy studies. Curr Psychiatry Rep. 2015;17(5):1–8.
12. Jaafari N, Rachid F, Rotge JY, Polosan M, El-Hage W, Belin D, et al. Safety and efficacy of repetitive transcranial magnetic stimulation in the treatment of obsessive-compulsive disorder: a review. World J Biol Psychiatry. 2012;13(3):164–77.
13. Husain F, Nandipati G, Braun A, Cohen L, Tagamets M, Horwitz B. Simulating transcranial magnetic stimulation during PET with a large-scale neural network model of the prefrontal cortex and the visual system. NeuroImage. 2002;15(1):58–73.

14. Pascual-Leone A, Keenan J, Freund S, Stinchfield Z, Tormos J, Parker A, et al. Repetitive transcranial magnetic stimulation trials in depression. Eur Neuropsychopharmacol. 1998;8:S123–S4.
15. Speer AM, Kimbrell TA, Wassermann EM, Repella JD, Willis MW, Herscovitch P, et al. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. Biol Psychiatry. 2000;48(12):1133–41.
16. Fineberg N, Chamberlain S, Hollander E, Boulougouris V, Robbins T. Translational approaches to obsessive-compulsive disorder: from animal models to clinical treatment. Br J Pharmacol. 2011;164(4):1044–61.
17. Milad MR, Rauch SL. Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. Trends Cogn Sci. 2012;16(1):43–51.
18. Del Casale A, Kotzalidis G, Rapinesi C, Serata D, Ambrosi E, Simonetti A, et al. Functional neuroimaging in obsessive-compulsive disorder. Neuropsychobiology. 2011;64(2):61–85.
19. Chamberlain SR, Menzies L, Hampshire A, Suckling J, Fineberg NA, del Campo N, et al. Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives. Science. 2008;321(5887):421–2.
20. Nakao T, Nakagawa A, Yoshiura T, Nakatani E, Nabeyama M, Yoshizato C, et al. Brain activation of patients with obsessive-compulsive disorder during neuropsychological and symptom provocation tasks before and after symptom improvement: a functional magnetic resonance imaging study. Biol Psychiatry. 2005;57(8):901–10. https://doi.org/10.1016/j.biopsych.2004.12.039.
21. van den Heuvel OA, Veltman DJ, Groenewegen HJ, Cath DC, van Balkom AJ, van Hartskamp J, et al. Frontal-striatal dysfunction during planning in obsessive-compulsive disorder. Arch Gen Psychiatry. 2005;62(3):301–9.
22. Yücel M, Harrison BJ, Wood SJ, Fornito A, Wellard RM, Pujol J, et al. Functional and biochemical alterations of the medial frontal cortex in obsessive-compulsive disorder. Arch Gen Psychiatry. 2007;64(8):946–55.
23. Nakao T, Nakagawa A, Nakatani E, Nabeyama M, Sanematsu H, Yoshiura T, et al. Working memory dysfunction in obsessive–compulsive disorder: a neuropsychological and functional MRI study. J Psychiatr Res. 2009;43(8):784–91.
24. Greenberg BD, George MS, Martin JD, Benjamin J, Schlaepfer TE, Altemus M, et al. Effect of prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a preliminary study. Am J Psychiatr. 1997;154(6):867–9.
25. Sachdev PS, McBride R, Loo CK, Mitchell PB, Malhi GS, Croker VM. Right versus left prefrontal transcranial magnetic stimulation for obsessive-compulsive disorder: a preliminary investigation. J Clin Psychiatry. 2001;62(12):981–4.
26. Alonso P, Pujol J, Cardoner N, Benlloch L, Deus J, Menchon JM, et al. Right prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a double-blind, placebo-controlled study. Am J Psychiatry. 2001;158(7):1143–5.
27. Sachdev PS, Loo CK, Mitchell PB, TF MF, Malhi GS. Repetitive transcranial magnetic stimulation for the treatment of obsessive compulsive disorder: a double-blind controlled investigation. Psychol Med. 2007;37(11):1645–9.
28. Berlim MT, Neufeld NH, Van den Eynde F. Repetitive transcranial magnetic stimulation (rTMS) for obsessive-compulsive disorder (OCD): an exploratory meta-analysis of randomized and sham-controlled trials. J Psychiatr Res. 2013;47(8):999–1006. https://doi.org/10.1016/j.jpsychires.2013.03.022.
29. Trevizol AP, Shiozawa P, Cook IA, Sato IA, Kaku CB, Guimaraes FB, et al. Transcranial magnetic stimulation for obsessive-compulsive disorder: an updated systematic review and meta-analysis. J ECT. 2016;32(4):262–6. https://doi.org/10.1097/yct.0000000000000335.
30. Gomes PO, Rosa MA, Allam N, de Souza ER, Brasil-Neto J. A randomized double-blind trial of repetitive transcranial magnetic stimulation in obsessive -compulsive disorder with three months follow-up. J ECT. 2012;28(2):149.
31. Hawken ER, Dilkov D, Kaludiev E, Simek S, Zhang F, Milev R. Transcranial magnetic stimulation of the supplementary motor area in the treatment of obsessive-compulsive disorder: a multi-site study. Int J Mol Sci. 2016;17(3):420. https://doi.org/10.3390/ijms17030420.
32. Mantovani A, Simpson HB, Fallon BA, Rossi S, Lisanby SH. Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder. Int J Neuropsychopharmacol. 2010;13(2):217–27.
33. Nauczyciel C, Le Jeune F, Naudet F, Douabin S, Esquevin A, Verin M, et al. Repetitive transcranial magnetic stimulation over the orbitofrontal cortex for obsessive-compulsive disorder: a double-blind, crossover study. Transcult Psychiatry. 2014;4:e436.
34. Ruffini C, Locatelli M, Lucca A, Benedetti F, Insacco C, Smeraldi E. Augmentation effect of repetitive transcranial magnetic stimulation over the orbitofrontal cortex in drug-resistant obsessive-compulsive

disorder patients: a controlled investigation. Prim Care Companion J Clin Psychiatry. 2009;11(5):226–30. https://doi.org/10.4088/PCC.08m00663.
35. Mantovani A, Rossi S, Bassi BD, Simpson HB, Fallon BA, Lisanby SH. Modulation of motor cortex excitability in obsessive-compulsive disorder: an exploratory study on the relations of neurophysiology measures with clinical outcome. Psychiatry Res. 2013;210(3):1026–32.
36. Russo M, Naro A, Mastroeni C, Morgante F, Terranova C, Muscatello MR, et al. Obsessive-compulsive disorder: a "sensory-motor" problem? Int J Psychophysiol Off J Int Org Psychophysiol. 2014;92(2):74–8. https://doi.org/10.1016/j.ijpsycho.2014.02.007.
37. Kumar N, Chadda RK. Augmentation effect of repetitive transcranial magnetic stimulation over the supplementary motor cortex in treatment refractory patients with obsessive compulsive disorder. Indian J Psychiatry. 2011;53(4):340–2. https://doi.org/10.4103/0019-5545.91909.
38. Pelissolo A, Harika-Germaneau G, Rachid F, Gaudeau-Bosma C, Tanguy ML, BenAdhira R, et al. Repetitive transcranial magnetic stimulation to supplementary motor area in refractory obsessive-compulsive disorder treatment: a sham-controlled trial. Int J Neuropsychopharmacol. 2016;19(8) https://doi.org/10.1093/ijnp/pyw025.
39. Berlim MT, Van den Eynde F, Daskalakis ZJ. 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. Neuropsychopharmacology. 2013;38(4):543–51.
40. Prasko J, Paskova B, Zalesky R, Novak T, Kopecek M, Bares M, et al. The effect of repetitive transcranial magnetic stimulation (rTMS) on symptoms in obsessive compulsive disorder. A randomized, double blind, sham controlled study. Neuroendocrinol Lett. 2006;27(3):327–32.
41. Kang JI, Kim CH, Namkoong K, Lee CI, Kim SJ. A randomized controlled study of sequentially applied repetitive transcranial magnetic stimulation in obsessive-compulsive disorder. J Clin Psychiatry. 2009;70(12):1645–51.
42. Badawy AA, El Sawy H, El Hay MA. Efficacy of repetitive transcranial magnetic stimulation in the management of obsessive compulsive disorder. Egyptian Journal of Neurology, Psychiatry and Neurosurgery. 2010;47:393–7.
43. Sarkhel S, Sinha VK, Praharaj SK. Adjunctive high-frequency right prefrontal repetitive transcranial magnetic stimulation (rTMS) was not effective in obsessive-compulsive disorder but improved secondary depression. J Anxiety Disord. 2010;24(5):535–9.
44. Mansur CG, Myczkowki ML, Cabral SD, Sartorelli MDB, Bellini BB, Dias AM, et al. Placebo effect after prefrontal magnetic stimulation in the treatment of resistant obsessive-compulsive disorder: a randomized controlled trial. Int J Neuropsychopharmacol. 2011;14(10):1389–97. https://doi.org/10.1017/s1461145711000575.
45. Ma Z-R, Shi L-J. Repetitive transcranial magnetic stimulation (rTMS) augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant obsessive-compulsive disorder (OCD): a meta-analysis of randomized controlled trials. Int J Clin Exp Med. 2014;7(12):4897.
46. Zhang XZ, Gu Y, Zhao EQ, Li YZ. Research on treating refractory obsessive compulsive disorder with combination of sitaplam and repetitive transcranial magnetic stimulation. Chin J Health Psychol. 2010;18:778–80.
47. Cheng J, Li H, Shi YZ. The efficacy of repetitive transcranial magnetic stimulation on obsessive compulsive disorder. Journal of International Psychiatry. 2013;40:148–51.
48. Ma X, Huang Y, Liao L, Jin Y. A randomized double-blinded sham-controlled trial of alpha electroencephalogram-guided transcranial magnetic stimulation for obsessive-compulsive disorder. Chin Med J. 2014;127(4):601–6.
49. Haghighi M, Shayganfard M, Jahangard L, Ahmadpanah M, Bajoghli H, Pirdehghan A, et al. Repetitive transcranial magnetic stimulation (rTMS) improves symptoms and reduces clinical illness in patients suffering from OCD: results from a single-blind, randomized clinical trial with sham cross-over condition. J Psychiatr Res. 2015;68:238–44.
50. Zhou D-D, Wang W, Wang G-M, Li D-Q, Kuang L. An updated meta-analysis: short-term therapeutic effects of repeated transcranial magnetic stimulation in treating obsessive-compulsive disorder. J Affect Disord. 2017;215:187–96. https://doi.org/10.1016/j.jad.2017.03.033.
51. Tang LY, Chu FC, Li YD, Xu ZP. Treating refractory obsessive compulsive disorder with combination of paroxetine and repetitive transcranial magnetic stimulation: a double-blind sham controlled study. Chinese Journal of Behavioral Medical and Brain Science. 2010;19(7):604–6.
52. Han CF, Jiang DF. Effect of slow frequency repetitive Transcranial Magnetic Stimulation (rTMS) combined with fluvoxamine on obsessivecompulsive disorder in maintenance stage. J Psychiatry. 2015;28:446–48.

53. Luo XF, Huang MI, Ye XJ. Controlled clinical study of sertraline alone or combined repetitive transcranial magnetic stimulation in patients with refractory obsessive-compulsive disorder. J Clin Psychiatry. 2015;25: 238–240.
54. Elbeh KA, Elserogy YM, Khalifa HE, Ahmed MA, Hafez MH, Khedr EM. Repetitive transcranial magnetic stimulation in the treatment of obsessive-compulsive disorders: double blind randomized clinical trial. Psychiatry Res. 2016;238:264–9. https://doi.org/10.1016/j.psychres.2016.02.031.
55. Jahangard L, Haghighi M, Shyayganfard M, Ahmadpanah M, Bahmani DS, Bajoghli H, et al. Repetitive transcranial magnetic stimulation improved symptoms of obsessive-compulsive disorder, but also cognitive performance: results from a randomized clinical trial with a cross-over design and sham condition. Neuropsychobiology. 2016;73(4):224–32. https://doi.org/10.1159/000446287.
56. Seo HJ, Jung YE, Lim HK, Um YH, Lee CU, Chae JH. Adjunctive low-frequency repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex in patients with treatment-resistant obsessive-compulsive disorder: a randomized controlled trial. Clinical Psychopharmacology and Neuroscience. 2016;14(2):153–60. https://doi.org/10.9758/cpn.2016.14.2.153.
57. Zhang ZM. A control study of sertraline plus rTMS in the treatment of refractory OCD. J Clin Psychosom Dis. 2016;22:41–3.
58. Wassermann EM, Zimmermann T. Transcranial magnetic brain stimulation: therapeutic promises and scientific gaps. Pharmacol Ther. 2012;133(1):98–107. https://doi.org/10.1016/j.pharmthera.2011.09.003.
59. Moher D, Liberati A, Tetzlaff J, Altman DG. Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
60. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000.
61. Organization WH. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. Geneva: World Health Organization. 1993. Report No.: 9789241544559;9241544554; Contract No.: Report.
62. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. The Yale-Brown obsessive compulsive scale: I. Development, use, and reliability. Arch Gen Psychiatry. 1989;46(11):1006–11.
63. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88.
64. Higgins J, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses [journal article as teaching resource, deposited by John Flynn]. Br Med J. 2003;327:557–60.
65. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–34.
66. Orwin RG. A fail-safe N for effect size in meta-analysis. J Educ Stat. 1983;8(2):157–9.
67. Borenstein M, Hedges LV, Higgins J, Rothstein HR. Multiple comparisons within a study. Introduction to meta-analysis. Chichester: John Wiley & Sons, Ltd.; 2009. p. 239–42.
68. de Wit SJ, de Vries FE, van der Werf YD, Cath DC, Heslenfeld DJ, Veltman EM, et al. Presupplementary motor area hyperactivity during response inhibition: a candidate endophenotype of obsessive-compulsive disorder. Am J Psychiatr. 2012;169(10):1100–8.
69. Oliveri M, Babiloni C, Filippi M, Caltagirone C, Babiloni F, Cicinelli P, et al. Influence of the supplementary motor area on primary motor cortex excitability during movements triggered by neutral or emotionally unpleasant visual cues. Exp Brain Res. 2003;149(2):214–21.
70. Picard N, Strick PL. Imaging the premotor areas. Curr Opin Neurobiol. 2001;11(6):663–72.
71. Rossi S, Bartalini S, Ulivelli M, Mantovani A, Di Muro A, Goracci A, et al. Hypofunctioning of sensory gating mechanisms in patients with obsessive-compulsive disorder. Biol Psychiatry. 2005;57(1):16–20.
72. van den Heuvel OA, Remijnse PL, Mataix-cols D, Vrenken H, Groenewegen HJ, HBM U, et al. The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. Brain. 2009;132(Pt 4):853–68.
73. Kedzior KK, Azorina V, Reitz SK. More female patients and fewer stimuli per session are associated with the short-term antidepressant properties of repetitive transcranial magnetic stimulation (rTMS): a meta-analysis of 54 sham-controlled studies published between 1997–2013. Neuropsychiatr Dis Treat. 2014;10: 727–56.
74. Berlim M, Van den Eynde F, Tovar-Perdomo S, Daskalakis Z. 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. Psychol Med. 2014;44(02):225–39.
75. Hegde A, Ravi M, Subhasini VS, Arumugham SS, Thirthalli J, Reddy YCJ. Repetitive transcranial magnetic stimulation over presupplementary motor area may not be helpful in treatment-refractory obsessive-compulsive disorder. A Case Series Journal of ECT. 2016;32(2):139–42. https://doi.org/10.1097/yct.0000000000000291.

76. Angst J, Gamma A, Endrass J, Goodwin R, Ajdacic V, Eich D, et al. Obsessive-compulsive severity spectrum in the community: prevalence, comorbidity, and course. Eur Arch Psychiatry Clin Neurosci. 2004;254(3):156–64.
77. Ridding MC, Rothwell JC. Is there a future for therapeutic use of transcranial magnetic stimulation? Nat Rev Neurosci. 2007;8(7):559–67.
78. Stein DJ, Carey PD, Lochner C, Seedat S, Fineberg N, Andersen EW. Escitalopram in obsessive-compulsive disorder: response of symptom dimensions to pharmacotherapy. CNS Spectr. 2008;13(6): 492–8.
79. Rasmussen S, Hackett E, DuBoff E, Greist J, Halaris A, Koran L, et al. A 2-year study of sertraline in the treatment of obsessive-compulsive disorder. Int Clin Psychopharmacol. 1997;12(6):309–16.
80. Clomipramine Collaborative Study Group. Clomipramine in the treatment of patients with obsessive-compulsive disorder. Arch Gen Psychiatry. 1991;48(8):730.
81. Montgomery S, Kasper S, Stein D, Hedegaard KB, Lemming O. Citalopram 20 mg, 40 mg and 60 mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder. Int Clin Psychopharmacol. 2001;16(2):75–86.
82. Tang W, Zhu Q, Gong X, Zhu C, Wang Y, Chen S. Cortico-striato-thalamo-cortical circuit abnormalities in obsessive-compulsive disorder: a voxel-based morphometric and fMRI study of the whole brain. Behav Brain Res. 2016;313:17–22. https://doi.org/10.1016/j.bbr.2016.07.004.
83. Lefaucheur J-P, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol. 2014;125(11):2150–206.
84. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV. Washington, DC: American Psychiatric Association; 1994.

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