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Review article

An updated meta-analysis: Short-term therapeutic effects of repeated transcranial magnetic stimulation in treating obsessive-compulsive disorder

Dong-Dong Zhou[a], Wo Wang[a], Gao-Mao Wang[a], Da-Qi Li[a], Li Kuang[a,b,*]

[a] Mental Health Center, University-Town Hospital of Chongqing Medical University, Chongqing, China
[b] Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

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ABSTRACT

Background: This study was conducted to evaluate the short-term therapeutic effects of using repeated transcranial magnetic stimulation (rTMS) to treat obsessive-compulsive disorder (OCD) and to examine potential influencing factors.

Method: We searched the PubMed, EMBASE, CENTRAL, Wanfang, CNKI, and Sinomed databases on September 18, 2016 and reviewed the references of previous meta-analyses. Sham-controlled, randomized clinical trials using rTMS to treat OCD were included. Hedge's g was calculated for the effect size. Subgroup analyses and univariate meta-regressions were conducted.

Results: Twenty studies with 791 patients were included. A large effect size (g=0.71; 95%CI, 0.55–0.87; P < 0.001) was found for the therapeutic effect. Targeting the supplementary motor area (SMA) (g=0.56; 95%CI, 0.12–1.01; P < 0.001), left dorsolateral prefrontal cortex (DLPFC) (g=0.47; 95%CI, 0.02–0.93; P=0.02), bilateral DLPFC (g=0.65; 95%CI, 0.38–0.92; P < 0.001) and right DLPFC (g=0.93; 95%CI, 0.70–1.15; P < 0.001), excluding the orbitofrontal cortex (OFC) (g=0.56; 95%CI, −0.05–1.18; P=0.07), showed significant improvements over sham treatments. Both low-frequency (g=0.73; 95%CI, 0.50–0.96; P < 0.001) and high-frequency (g=0.70; 95%CI, 0.51–0.89; P < 0.001) treatments were significantly better than sham treatments, with no significant differences between the effects of the two frequencies. The subgroup analyses indicated that patients who were non-treatment resistant, lacked concurrent major depressive disorder (MDD) and received threshold-intensity rTMS showed larger therapeutic effects than the corresponding subgroups. The subgroup analysis according to sham strategy showed that tilted coils yielded larger effects than sham coils. Meta-regression analyses revealed that none of the continuous variables were significantly associated with the therapeutic effects.

Limitations: Only short-term therapeutic effects were assessed in this study.

Conclusions: Based on this study, the short-term therapeutic effects of rTMS are superior to those of sham treatments. The site of stimulation, stimulation frequency and intensity and sham condition were identified as potential factors modulating short-term therapeutic effects. The findings of this study may inspire future research.

1. Introduction

Approximately 1–3% of the global population suffers from obsessive-compulsive disorder (OCD) (Horwath and Weissman, 2000). Pathological obsessions and compulsions can lead to significant distress and functional impairment. In addition, approximately 40–60% of OCD patients remain resistant to current first-line therapies (Pallanti and Quercioli, 2006).

Several randomized control trials using repeated transcranial magnetic stimulation (rTMS) to treat OCD have been published since 1997, but their results are inconclusive. The differences in results may be due to their use of different rTMS protocols or the inclusion of patients with different characteristics. Three meta-analyses evaluating the efficacy of rTMS for treating OCD have been conducted (Berlim et al., 2013; Ma and Shi, 2014; Trevizol et al., 2016). Berlim et al. (2013) included 10 RCTs with 282 subjects and identified a significant and medium effect size in favor of active rTMS (g=0.59), and the subgroup analyses in their study (which were only performed according to stimulation frequency and target) indicated that there was no significant difference in the high-frequency (HF) and dorsolateral

* Correspondence to: Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical University, 1 YouYi Rd, Yuzhong District, Chongqing 400016, China.
E-mail address: kuangli0308@163.com (L. Kuang).

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prefrontal cortex (DLPFC) subgroups. A second meta-analysis (Ma and Shi, 2014) was limited to SSRI-resistant OCD patients and included 9 RCTs with 290 subjects. It found that rTMS can be an effective addition to SSRI therapy and subgroup analyses were conducted only for the weeks of rTMS treatment. In the third meta-analysis (Trevizol et al., 2016), 15 studies (n=483) were included, and a medium effect size (g=0.45) was found. The meta-regression identified no significant variables. Recently, several RCTs using rTMS to treat OCD have been published (Elbeh et al., 2016; Hawken et al., 2016; Pelissolo et al., 2016; Seo et al., 2016). Thus, it is necessary to perform an updated meta-analysis to explore other important factors which may be associated with the efficacy of rTMS for treating OCD.

Before conducting this meta-analysis, we made several assumptions. OCD symptoms are correlated with hyperactivity in the cortico-striato-thalamo-cortical circuits (Anticevic et al., 2014; Milad and Rauch, 2012), and we assumed that the inhibitory effect of LF stimulation would be more effective than the excitatory effect of HF stimulation (Speer et al., 2009). The DLPFC, which is connected to the striatum, the anterior cingulate cortex, and the thalamus (Barbas, 2000; Paus et al., 2001; Petrides and Pandya, 1999), is the most common target for rTMS. Stimulating the DLPFC can also affect connected areas, some of which are associated with OCD symptoms. Therefore, we assumed that stimulating the DLPFC could result in effective treatment.

2. Methods

This meta-analysis adhered to the Cochrane Handbook 5.1.0 (Higgins and Green, 2013). It followed a predetermined but unpublished protocol and was not registered.

2.1. Search strategy

We searched the CENTRAL, EMBASE, PubMed, Wanfang, China National Knowledge Internet (CNKI) and Sinomed databases on September 18, 2016, and we also reviewed the references in previous meta-analyses (Berlim et al., 2013; Ma and Shi, 2014; Trevizol et al., 2016). The keywords used in the literature search were as follows: “magnetic stimulation” or “rTMS” or “transcranial magnetic” and “obsessive” or “compulsive” or “OCD”. Our inclusion criteria were as follows: a) Participants: subjects who were diagnosed with OCD; b) Intervention: rTMS was performed as the intervention, and studies using single TMS were excluded; c) Comparison: active rTMS was compared with sham rTMS; d) Outcome: the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was used to evaluate the severity of symptoms; e) studies with a randomized, single-blind or double-blind design; f) articles that provided the statistical parameters necessary to calculate Hedge's g or articles written by authors who were willing to provide these parameters upon request; and g) published articles that were written in English or Chinese. Studies examining deep rTMS, priming rTMS, or theta-burst rTMS were not included in this study.

2.2. Data extraction

Three investigators extracted the following variables from the studies: a) participant characteristics (i.e., percentage of female subjects, mean age, presence of concurrent major depressive disorder (MDD), presence of treatment resistance, baseline score on the Y-BOCS, duration of illness, and onset of illness); b) rTMS parameters (i.e., stimulation frequency, targets, number of sessions, total pulses, total pulses per session (TPPS), weeks of treatment, stimulation intensity, trains per session, inter-train interval, duration of single trains, and sham strategy); and c) sample size, all-cause dropouts, and mean and standard deviations (SDs) of the post-intervention Y-BOCS scores (the first assessment after treatment) in both groups.

2.3. Data processing

This meta-analysis was conducted in Comprehensive Meta-Analysis (CMA version 2), and a random-effects model was used. To explore potential influencing factors (e.g., the clinical characteristics of subjects and rTMS parameters), subgroup analyses were conducted for categorical variables and a meta-regression was conducted for continuous variables. Hedge's g was computed for the post-intervention Y-BOCS scores to determine the effect size of the study. According to the Cochrane Handbook 5.1.0, effect sizes that are < 0.4, 0.4–0.7 and > 0.7 indicate small, moderate and large effects, respectively. The risk difference (RD) was computed for all-cause dropouts to evaluate the acceptability of treatment. Heterogeneity was evaluated using I^2 statistics (Cooper et al., 2009). Egger's tests (Egger et al., 1997) were performed to evaluate publication bias.

2.4. Risk of bias assessment

According to the Cochrane Handbook 5.1.0 (Higgins and Green, 2013), the risk of bias was assessed for six domains. Because it is impossible to blind the rTMS operator, a low risk of performance bias implied blinding the participants. We excluded studies in which the selection bias was evaluated as high risk.

3. Results

The literature search is described in Fig. 1 and resulted in 24 eligible studies (Alonso et al., 2001; Badawy et al., 2010; Cheng et al., 2013; Elbeh et al., 2016; Gomes et al., 2012; Haghighi et al., 2015; Han and Jiang, 2015; Hawken et al., 2016; Jahangard et al., 2016; Kang et al., 2009; Luo et al., 2015; Ma et al., 2014; Mansur et al., 2011; Mantovani et al., 2010; Nauczyciel et al., 2014; Pelissolo et al., 2016; Prasko et al., 2006; Ruffini et al., 2009; Sachdev et al., 2007; Sarkhel et al., 2010; Seo et al., 2016; Tang et al., 2010; Zhang et al., 2010; Zhang, 2016). Elbeh et al. (2016) included two intervention arms, and both were included, along with a shared sham group. We followed the suggestion of the Cochrane Handbook 5.1.0 (Higgins and Green, 2013) and divided the sample size of the sham group into approximately equal groups. Haghighi et al. (2015), Jahangard et al. (2016) and Nauczyciel et al. (2014) used a cross-over design, and thus, data from only the first phase were included to prevent carry-over effects. The main characteristics (e.g., participant characteristics, rTMS parameters) of those eligible studies are described in Table 1, and additional characteristics are available in Supplementary Table 1.

The bias risk assessment is described in Supplementary Table 2. A high risk of bias in randomization was found in Badawy et al. (2010) and Sarkhel et al. (2010). The baseline Y-BOCS scores differed significantly between the intervention and control groups in Gomes et al. (2012) and Prasko et al. (2006), and this difference may have led to systematic differences between groups. These studies were therefore excluded from the quantitative synthesis. Only 6 studies (Gomes et al., 2012; Hawken et al., 2016; Mantovani et al., 2010; Pelissolo et al., 2016; Sachdev et al., 2007; Tang et al., 2010) excluded subjects who had received rTMS in the past, and only 3 studies (Kang et al., 2009; Mansur et al., 2011; Sachdev et al., 2007) assessed the effectiveness of the blinding procedures they used.

3.1. Meta-analysis of OCD symptoms

In this study, Hedge's g was 0.71 (95%CI, 0.55–0.87; $P < 0.001$), with low heterogeneity (I^2=10%) (Fig. 2), and Egger's regression was non-significant (P=0.58). In addition, the funnel plot was approximately symmetrical (Supplementary Fig 1).

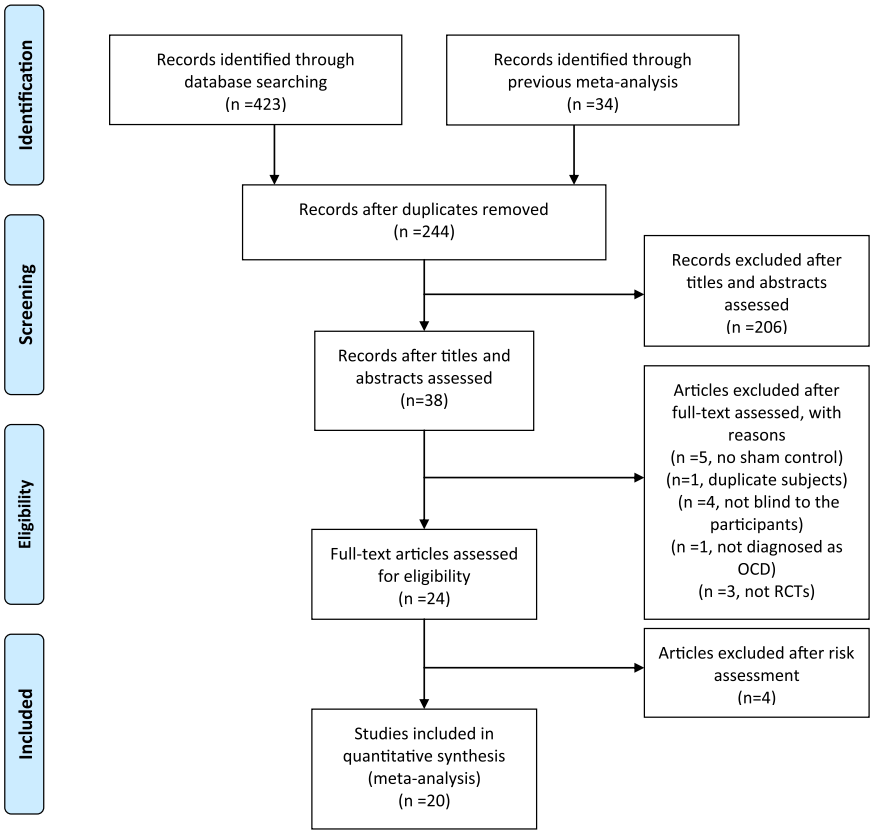

Fig. 1. Flowchart of the literature search.

3.2. Subgroup analysis

Treatments targeting the bilateral DLPFC (g=0.65; 95%CI, 0.38–0.92; P < 0.001), left DLPFC (g=0.47; 95%CI, 0.02–0.93; P=0.02), right DLPFC (g=0.93; 95%CI, 0.70–1.15; P < 0.001) and supplementary motor area (SMA) (g=0.56; 95%CI, 0.12–1.01; P < 0.001), excluding the orbitofrontal cortex (OFC) (g=0.56; 95%CI, −0.05–1.18; P=0.07), showed significant improvements over the effects of sham treatments (Fig. 3). Both LF and HF treatments were significantly better than sham treatments, with no significant differences identified between the effects of LF and HF stimulation (P=0.85) (Fig. 4). The subgroup analysis according to sham strategy showed that tilted coils yielded larger effects than sham coils (P=0.03) (Fig. 5). The subgroups of participants who were not treatment-resistant and who did not have MDD showed larger therapeutic effects than their corresponding subgroups (P=0.40, P=0.11, respectively) (Fig. 6 and Fig. 7). Applying 100% of the resting motor threshold (RMT) (indicating threshold intensity) led to larger therapeutic effects than the application of 80%, 110% and 120% RMTs (Fig. 8). All I^2 values for heterogeneity were lower than 30%.

3.3. Univariate meta-regressions

No significant variables were identified in the univariate meta-regressions (Supplementary Table 3).

3.4. Sensitivity analysis

One study moved analysis was conducted and showed that the effect size was not significantly changed. (Supplementary Fig 2).

3.5. Meta-analysis of all-cause dropouts

The risk difference of all-cause dropouts between active and sham groups was −0.02 (95%CI, −0.05-0.02; P=0.38; I^2=0%) (Fig. 9).

4. Discussion

In this updated meta-analysis, we included 20 randomized clinical trials with the largest sample size (n=791) to date. Our study indicated that applying HF stimulation and targeting the DLPFC both showed significant results, which is different from the result of Berlim et al. (2013). Compared with the previous meta-analysis, we explored additional categorical and continuous variables that could influence the short-term effects of rTMS on OCD patients.

Targeting the left, right and bilateral DLPFC showed significant improvements compared with the effects of sham treatments. Targeting the right DLPFC resulted in the highest effect size (g=0.93), followed by targeting the bilateral DLPFC (g=0.65) and the left DLPFC (g=0.47). The left and right DLPFC may have different roles, with the right side potentially playing a more dominant role during OCD treatment. This finding is in accordance with previous studies. OCD treatments primarily lead to right-hemisphere changes (Kang et al., 2003; Rauch et al., 2006; Saxena et al., 2002). Another study showed that the right resting motor threshold (RMT) was lower than that of the left and that this hemispheric asymmetry was normalized by increasing the right RMT after rTMS treatment (Mantovani et al., 2013). For non-DLPFC targets, only two studies targeting the orbitofrontal cortex (OFC) (Nauczyciel et al., 2014; Ruffini et al., 2009) and three targeting the supplementary motor area (SMA) (Hawken et al., 2016; Mantovani et al., 2010; Pelissolo et al., 2016) were included, and future investigations are needed to clarify the efficacy of targeting non-DLPFC areas.

Our results indicate that HF rTMS results in significant improvements compared to the effects of sham treatments, and no significant

Table 1
Main characteristics of the included studies.

Study name	Sample size (total)	Mean age (all paticipants)	Female% (all paticipants)	Presence of MDD[a]	Presence of resistant	Frequency	Sham strategy	RMT%	Targets	Weeks	The first assessment after rTMS (weeks)	ITT?
Alonso et al. (2001)	18	35.2	0.67	Without	Resistant	LF	Tilted coil	110	R-DLPFC	6	10	No
Sachdev et al. (2007)	18	32.3	0.44	Without	Resistant	HF	Sham coil	NA	L-DLPFC	2	2	No
Kang et al. (2009)	20	27.4	0.15	With	Resistant	LF	Tilted coil	110/100	R-DLPFC +SMA	2	2	No
Ruffini et al. (2009)	23	40.8	0.39	Without	Resistant	LF	Tilted coil	80	OFC	3	3	No
Mantovani et al. (2010)	18	39.5	0.39	With	Resistant	LF	Sham coil	100	SMA	4	4	Yes[b]
Tang et al. (2010)	53	31.7	0.49	NA	Resistant	HF	NA	100	R-DLPFC	6	6	Yes[c]
Zhang et al. (2010)	65	29.9	0.43	NA	Resistant	HF	Tilted coil	100	R-DLPFC	6	6	No
Mansur et al. (2011)	27	40.65	0.52	With	Resistant	HF	Sham coil	110	R-DLPFC	6	6	No
Cheng et al. (2013)	44	26.5	0.48	Without	Non-resistant	HF	Tilted coil	100	B-DLPFC	8	8	No
Ma et al. (2014)	46	28.37	0.35	Without	Resistant	HF	Sham coil	80	B-DLPFC	2	2	No
Nauczyciel et al. (2014)	19	39.53	0.79	With	Resistant	LF	Sham coil	120	OFC	1	1	No
Haghighi et al. (2015)	21	35.8	0.57	Without	Resistant	HF	Tilted coil	100	B-DLPFC	2	2	No
Han and Jiang (2015)	95	36.9	0.36	Without	Non-resistant	LF	Tilted coil	80	R-DLPFC	12	12	No
Luo et al. (2015)	56	31.3	0.5	NA	Resistant	HF	Tilted coil	80	L-DLPFC	6	6	No
Elbeh et al. (2016)a	22	26.15	0.53	Without	Resistant	LF	Tilted coil	100	R-DLPFC	2	2	No
Elbeh et al. (2016)b	23	27.2	0.37	Without	Resistant	HF	Tilted coil	100	R-DLPFC	2	2	No
Hawken et al. (2016)	22	33.6	0.5	Without	Resistant	LF	Tilted coil	110	SMA	6	6	Yes[c]
Jahangard et al. (2016)	10	33.1	0.7	Without	Resistant	HF	Tilted coil	100	B-DLPFC	2	2	No
Pelissolo et al. (2016)	36	40.5	0.6	With	Resistant	LF	Sham coil	100	SMA	4	4	Yes[d]
Seo et al. (2016)	27	35.4	0.48	With	Resistant	LF	Sham coil	100	R-DLPFC	3	3	No
Zhang et al., 2016	92	31.3	0.5	Without	Resistant	HF	NA	80	B-DLPFC	8	8	No

Abbreviations: MDD, major depressive disorder; NA, not available. R-DLPFC, right dorsolateral prefrontal cortex; L-DLPFC, left dorsolateral prefrontal cortex; B-DLPFC, bilateral dorsolateral prefrontal cortex; SMA, supplementary motor area; OFC, orbitofrontal cortex; RMT, resting motor threshold; LF, low frequecy; HF, high frequency; ITT, intent to treat. Note: a With means any % of patients and Without means all patients; b Worst case scenario analysis; c Last observation carried forward; d Modified intent-to-treat, defined as all randomized subjects who received at least 1 stimulation were included in the analysis, missing data was replaced with the mean variation in the sham group, whereas the patient in the active group was considered a failure.

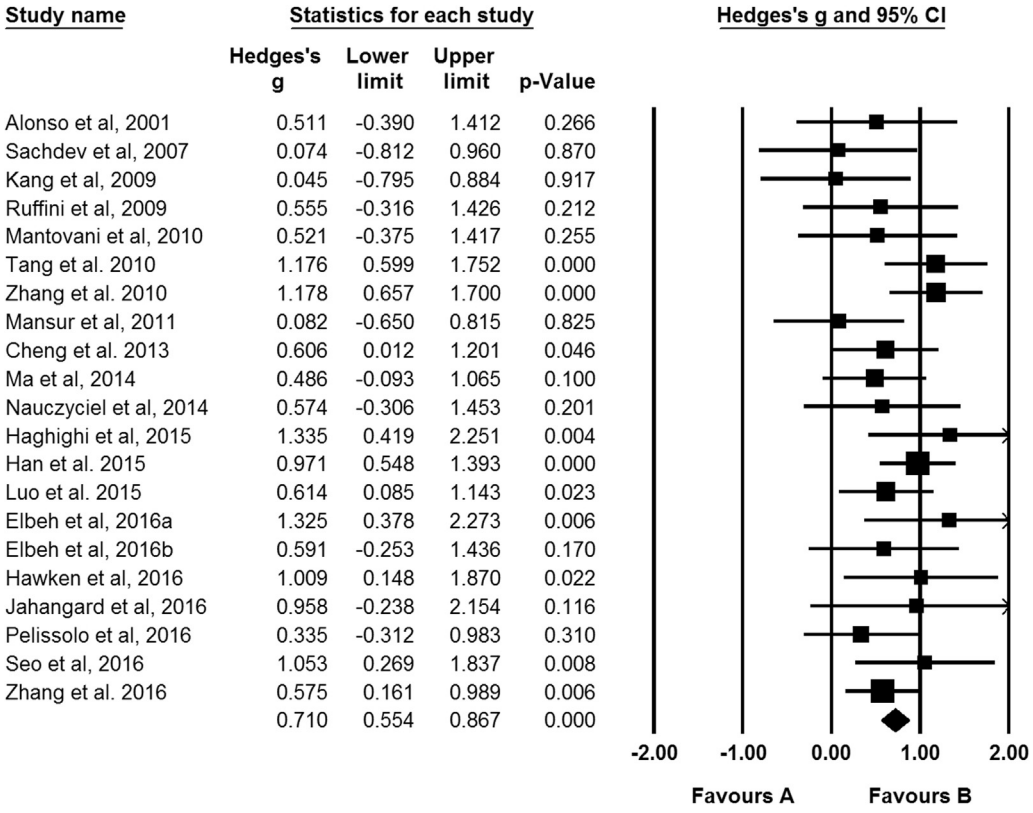

Fig. 2. Overall forest plot of the meta-analysis for therapeutic effects.

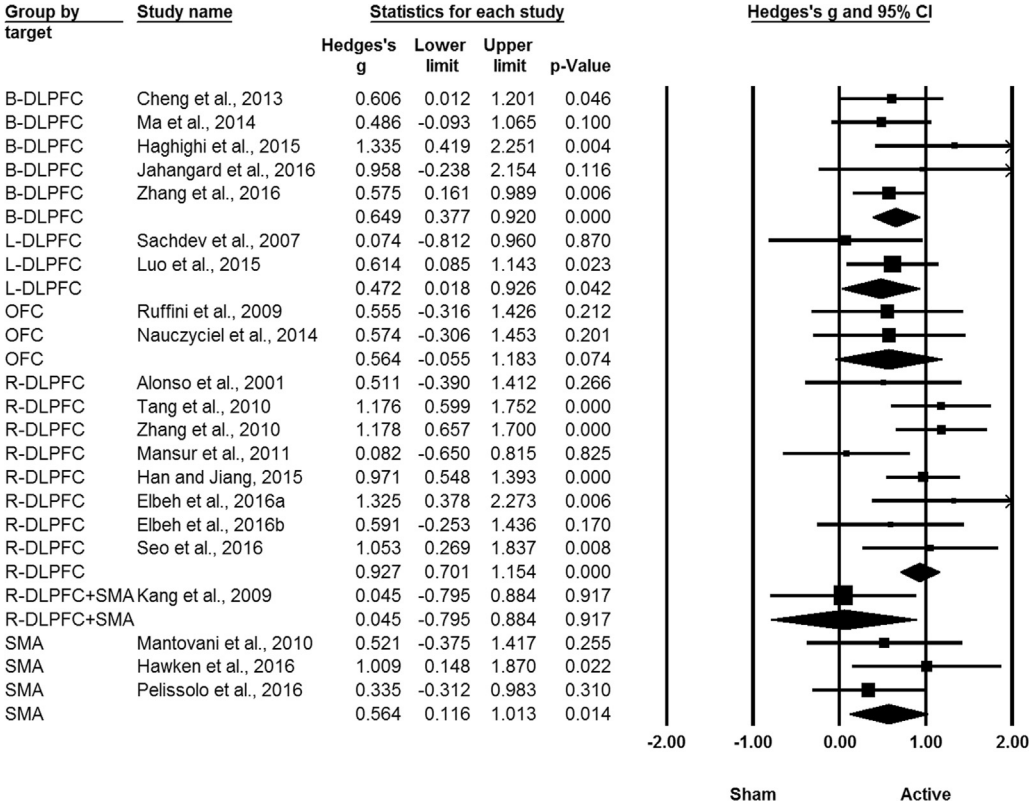

Fig. 3. Forest plot of subgroup analysis by targets. Abbreviations: R-DLPFC, right dorsolateral prefrontal cortex; L-DLPFC, left dorsolateral prefrontal cortex; B-DLPFC, bilateral dorsolateral prefrontal cortex; SMA, supplementary motor area; OFC, orbitofrontal cortex.

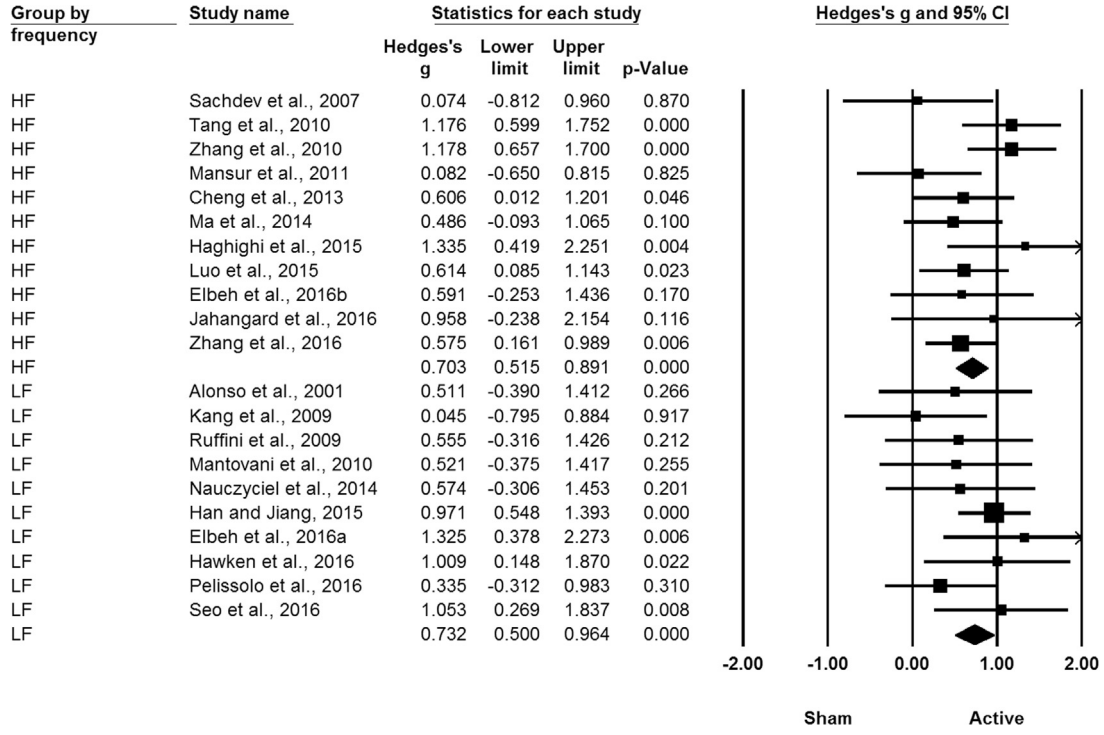

Fig. 4. Forest plot of subgroup analysis by stimulation frequency. Abbreviations: LF, low frequency; HF, high frequency.

differences between LF and HF stimulation were identified. A reasonable explanation for this finding is that both hyperactivity and hypoactivity are found in the affected brain areas of OCD patients (Busatto et al., 2000; Gu et al., 2008; Murayama et al., 2013; Nakao et al., 2005a, 2005b; Nakatani et al., 2003). Another potential explanation is that HF rTMS may have inhibitory effects (Houdayer et al., 2008). It has been demonstrated that LF stimulation has excitatory effects and HF stimulation has inhibitory effects (Eldaief et al., 2011; Hamada et al., 2012; Maeda et al., 2000). The underlying neurobiological changes caused by rTMS that occur when treating OCD patients may be complex and might not be explained simply as a result of inhibiting hyperactivity or increasing hypoactivity. A recent HF rTMS study showed that symptom improvement was associated with reductions in fronto-striatal hyperconnectivity (Dunlop et al., 2016). More neuroimaging studies investigating the application of rTMS for treating OCD are urgently needed to identify the mechanisms underlying these results.

Stimulation intensity, as measured by the percentage of the RMT, was also found to influence the efficacy of rTMS in treating OCD patients. A threshold intensity of 100% RMT was found to be more

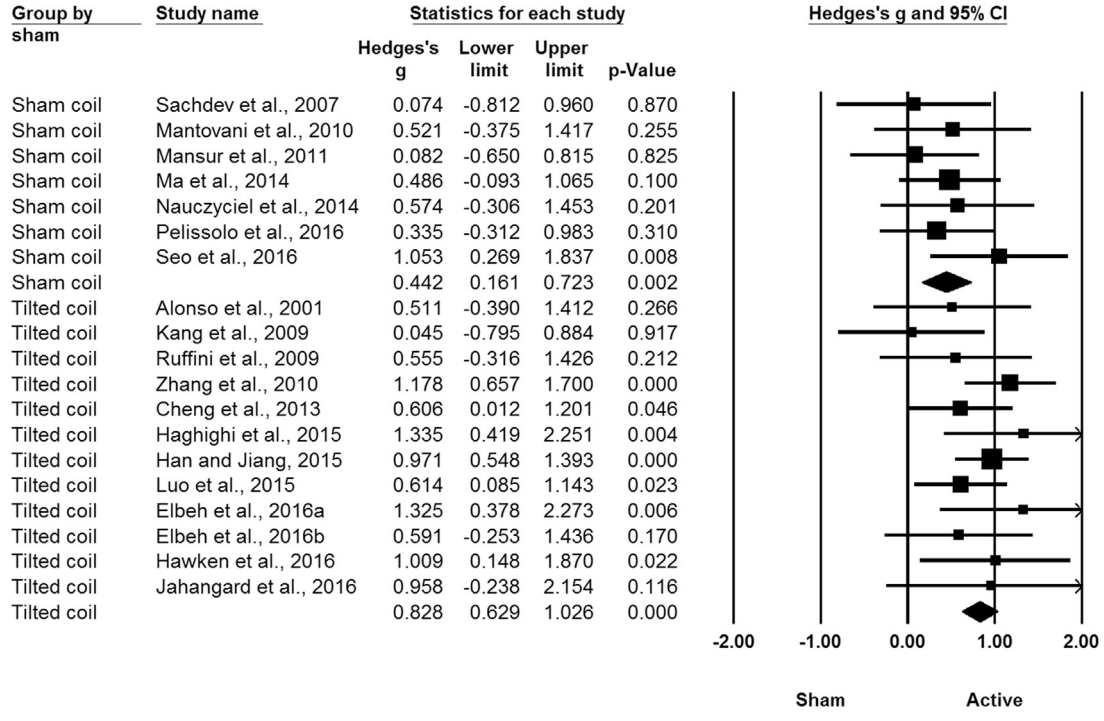

Fig. 5. Forest plot of subgroup analysis by sham strategy.

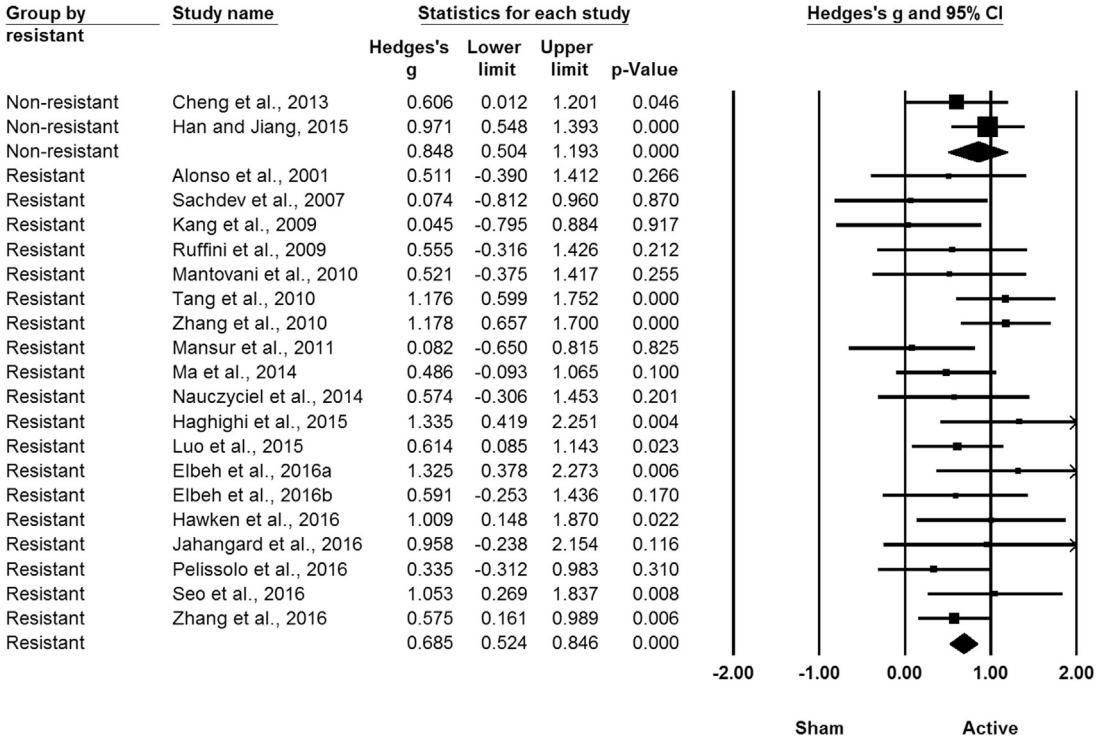

Fig. 6. Forest plot of subgroup analysis by the presence of treatment resistance.

effective than other stimulation intensities. OCD patients exhibit a significant reduction in their cortical silent period (CSP), RMT, and short-interval cortical inhibition (SICI), whereas intracortical facilitation (ICF) is significantly enhanced (Khedr et al., 2016; Radhu et al., 2013); that is to say, OCD patients have deficient inhibition and enhanced facilitation of cortical excitability. A recent review showed that a stimulation intensity of 80% of the RMT decreased ICF and increased RMT and that a stimulation intensity of 100% of the RMT increased SICI and CSP, whereas suprathreshold intensities produced inconsistent changes in RMT, CSP, and SICI and increased ICF (Nordmann et al., 2015). Threshold and subthreshold stimulation intensities may have more inhibitory effects than suprathreshold stimulation intensities, and this greater inhibition may explain why threshold and subthreshold stimulation intensities were found to be more effective. Another explanation could be that higher stimulation intensities extend the action of rTMS (Lefaucheur et al., 2014), affecting areas with opposing actions, or that the effects of treatment can only be obtained by stimulating specific and restricted areas. These

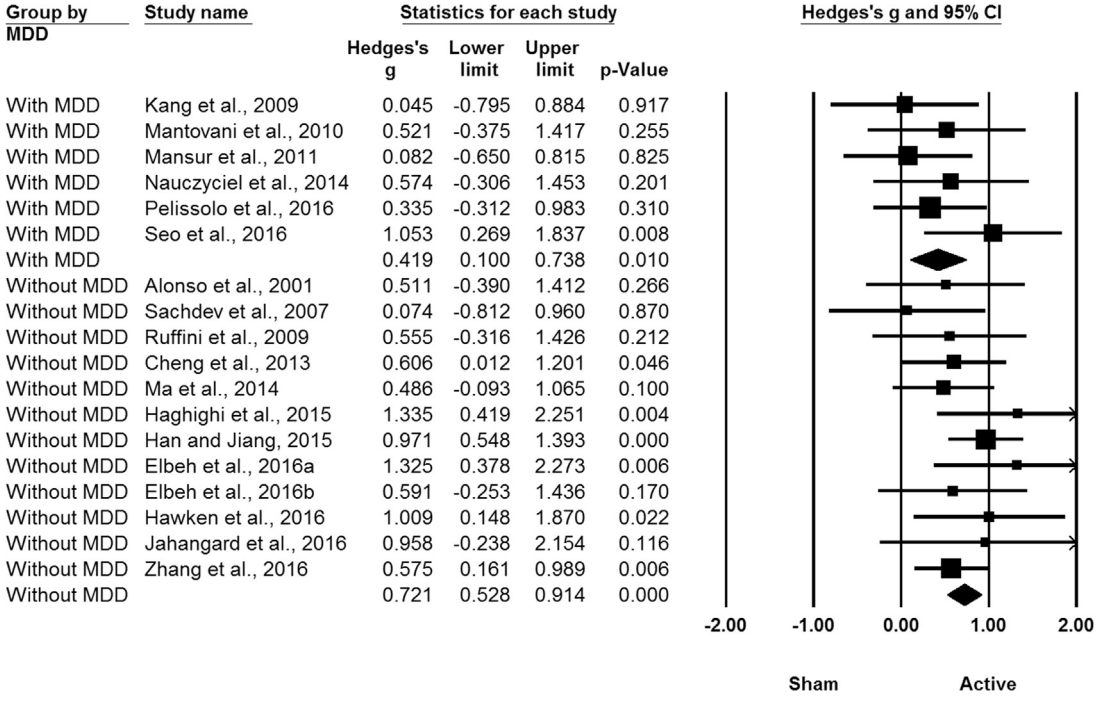

Fig. 7. Forest plot of subgroup analysis by the presence of MDD. Abbreviations: MDD, major depressive disorder.

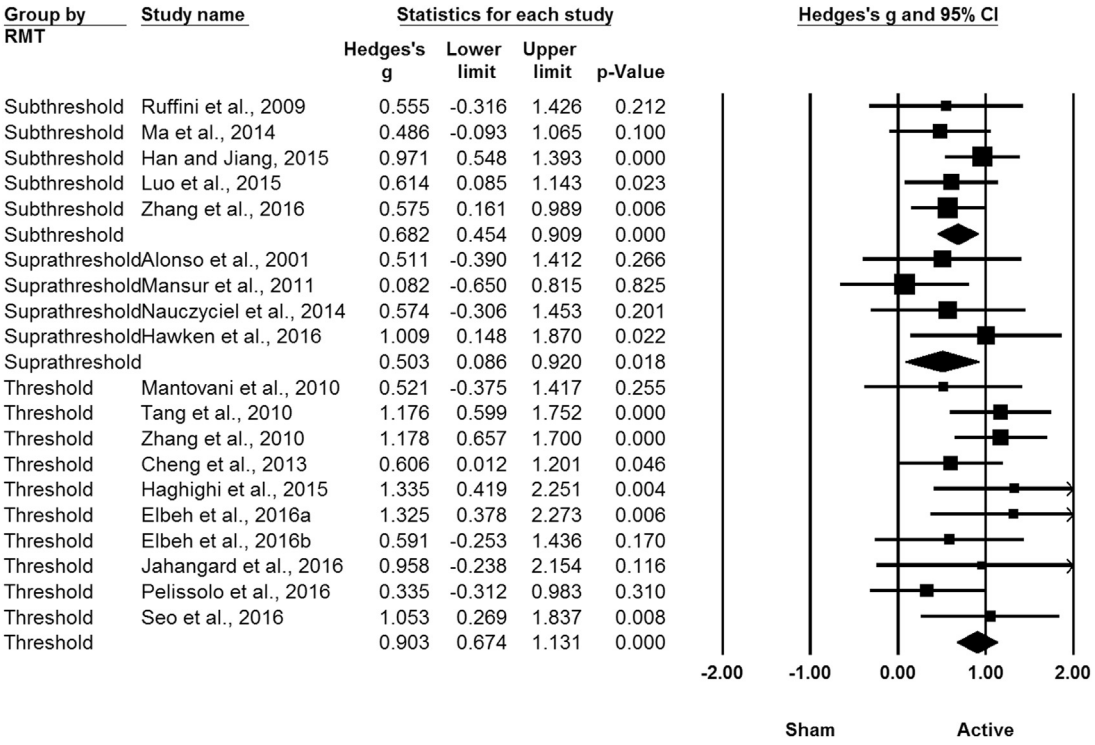

Fig. 8. Forest plot of subgroup analysis by stimulation intensity.

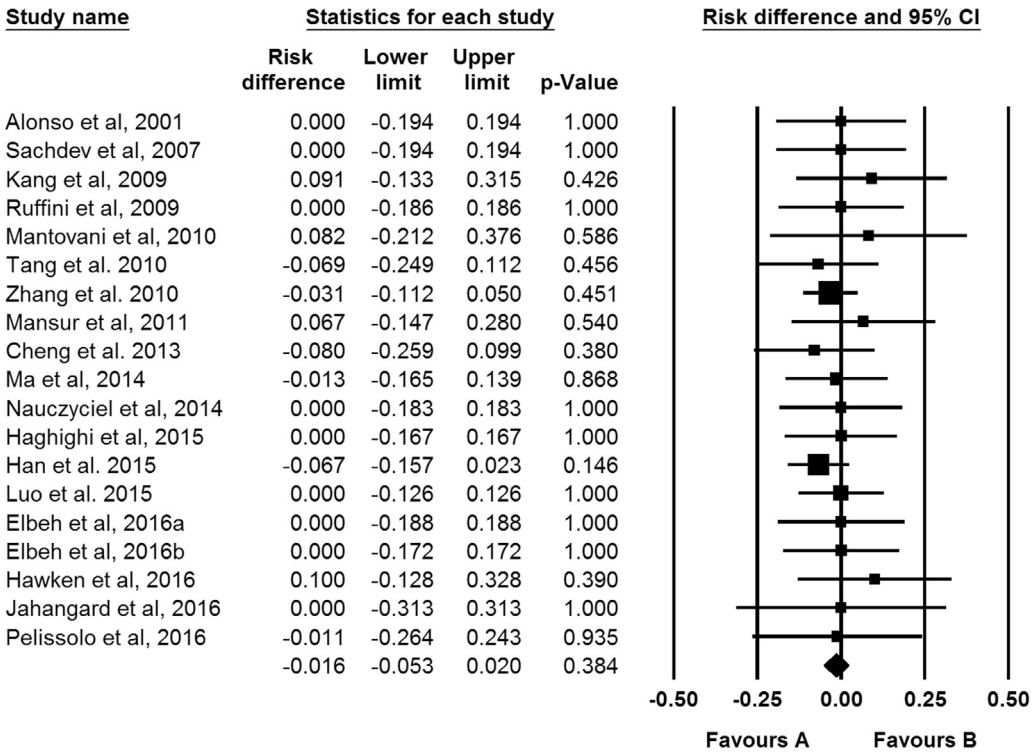

Fig. 9. Forest plot of meta-analysis for all-cause dropouts.

assumptions require further investigation.

We also conducted subgroup analyses according to different sham conditions, i.e., a tilted coil or sham coil. The tilted-coil subgroup (g=0.83) had a larger effect size than the sham-coil subgroup (g=0.44), indicating that sham coils may produce larger placebo effects than tilted coils. One explanation for this difference could be that only a few studies excluded participants who had previous experience with rTMS treatment, and because a tilted coil is not placed in the same position as the active coil, it may be more difficult to blind subjects to the use of tilted coils. Second, compared with a tilted coil, the auditory sensation of a sham coil is more similar to that of an active coil (Lefaucheur et al., 2014), and sensorial focus has been shown to increase placebo effects (Price et al., 2008). Even when using sham coils as the sham condition, the treatment effect of active rTMS could be overestimated because sham coils cannot induce scalp sensations. In an optimal sham condition, the auditory and somatic sensations should be the same as

those of active rTMS, with the exception that active stimulation is provided to cortical areas. The development of optimal sham conditions requires further investigation.

5. Limitation

None of the continuous variables were significantly associated with therapeutic effects, and this lack of association may have been due to other uncontrollable variables and confounding factors, as well as to the limited number of available studies. Only the short-term effects and their influencing factors were assessed in this meta-analysis, and the result may be different for medium- and long-term effects. Only two studies were included in the non-resistant subgroup and the OFC subgroup, and this small sample may limit our ability to evaluate the effect sizes in those groups; accordingly, we must cautiously interpret the results for those subgroups. Given the lack of an ideal sham condition, the therapeutic effects of rTMS may be overestimated in relation to current sham conditions. Though the Egger's regression was non-significant, a publication bias is more likely to exist, because only published studies were included in this meta-analysis. Because of the methodological heterogeneity (different patient characteristics and rTMS parameters) and methodological shortcomings (most of studies performed per-protocol analysis), the results of this meta-analysis should be treated cautiously.

6. Conclusion

Based on this study, the short-term therapeutic effects of rTMS are superior to those of sham treatments. Targeting the right DLPFC seems produce larger therapeutic effects than targeting other regions. LF and HF rTMS produce similar effects, both of which show an improvement over sham control treatments. For the stimulation intensity, treatments at 100% of the RMT appear to provide the best results. Notably, these finding are only exploratory, and they must be treated cautiously. Head-to-head RCTs are needed to verify our results. Future RCTs should extend the follow-up period to explore the medium- or long-term effects. Since the sample sizes of the previous studies were small, more RCTs with larger sample sizes that investigate different rTMS protocols and different patient characteristics are needed. Investigations of the latent mechanism underlying the effects of rTMS for treating OCD and of optimal sham conditions are urgently needed.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jad.2017.03.033.

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