

Original Article

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

Zhong-Rui Ma¹, Li-Jun Shi²

¹Department of Neurology, Chengdu Fifth People's Hospital, Chengdu, China; ²Department of Hematology, Chengdu Fifth People's Hospital, Chengdu, China

Received September 20, 2014; Accepted November 25, 2014; Epub December 15, 2014; Published December 30, 2014

Abstract: Background and objective: Randomized controlled trials (RCTs) on repetitive transcranial magnetic stimulation (rTMS) as augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant obsessive-compulsive disorder (OCD) have yielded conflicting results. Therefore, this meta-analysis was conducted to assess the efficacy of this strategy for SSRI-resistant OCD. Methods: Scientific and medical databases, including international databases (PubMed, MEDLINE, EMBASE, CCTR, Web of Science, PsycINFO), two Chinese databases (CBM-disc, CNKI), and relevant websites dated up to July 2014, were searched for RCTs on this strategy for treating OCD. Mantel-Haenszel random-effects model was used. Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score, response rates and drop-out rates were evaluated. Results: Data were obtained from nine RCTs consisting of 290 subjects. Active rTMS was an effective augmentation strategy in treating SSRI-resistant OCD with a pooled WMD of 3.89 (95% CI = [1.27, 6.50]) for reducing Y-BOCS score and a pooled odds ratio (OR) of 2.65 (95% CI = [1.36, 5.17]) for response rates. No significant differences in drop-out rates were found. No publication bias was detected. Conclusion: The pooled examination demonstrated that this strategy seems to be efficacious and acceptable for treating SSRI-resistant OCD. As the number of RCTs included here was limited, further large-scale multi-center RCTs are required to validate our conclusions.

Keywords: Repetitive transcranial magnetic stimulation, rTMS, obsessive-compulsive disorder, OCD, selective serotonin reuptake inhibitors, SSRIs, meta-analysis

Introduction

Obsessive-compulsive disorder (OCD) is a chronic and severe neuropsychiatric disorder characterized by obsessions and compulsions. Typical symptoms include persistent and recurrent thoughts or mental images and compulsions in the form of repetitive, time-consuming behaviors or mental acts [1, 2]. The prevalence of OCD in the general population is estimated at 1% to 3%, and this disorder is usually associated with low quality of life, social impairment, and continuous mental distress [3, 4]. OCD can seriously disrupt normal daily routine leading to dramatic impairments in interpersonal and occupational roles [5]. Therefore, this disorder becomes one of the most disabling medical conditions with considerable direct and indirect economical costs on society [6].

Currently, high doses of selective serotonin reuptake inhibitors (SSRIs) given over long periods of time, cognitive-behavioral therapy (CBT), or a combination of the two was the main first-line treatment strategy for OCD [7, 8]. However, there are still about 60% of subjects with OCD that do not experience satisfactory outcomes with SSRIs [9]. In those resistant subjects, pharmacological treatment strategy has been broadened to include serotonin-norepinephrine reuptake inhibitors (SNRIs), low doses of atypical antipsychotics or intravenous citalopram (SSRI). Unfortunately, even though such therapeutic options can improve the prognosis of OCD, 30-60% of subjects either unable to stand medication side effects or respond partially. Therefore, more effective and safer alternative strategies are highly necessary for the treatment of severe resistant OCD.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that induces currents in focal brain areas to modulate cortical and subcortical function by electromagnetic stimulation [10, 11]. This type of focal neuromodulatory intervention may be helpful of subjects with severe resistant forms of OCD [8]. Depending on the stimulation frequency, rTMS can either decrease or increase cortical excitability in relatively focal areas. [12] Previous studies have found high-frequency rTMS (~5-10 Hz) to be typically excitatory and low-frequency rTMS (≤ 1 Hz) to be typically inhibitory [13]. Because OCD may be related to increased neural activity in prefrontal subcortical circuits, the inhibitory effect of rTMS was hypothesized to be beneficial in OCD treatment. In 1997, Greenberg and colleagues introduced rTMS as a new treatment approach for OCD, and hypothesized that inhibition of the prefrontal activity with rTMS might reduce obsessive-compulsive symptoms [14]. Since then, several studies have investigated the clinical utility of rTMS as augmentation for SSRI-resistant OCD.

However, it is unclear whether the addition of rTMS to ongoing medication treatment (SSRIs) is an effective augmentation strategy in SSRI-resistant OCD, as studies that have explored the efficacy of this strategy have shown inconsistent results. For example, one randomized controlled study (RCT) reported that this strategy had no significant improvement of OCD, [15] and one RCT reported that this strategy have been associated with significant improvements in OCD when compared to sham rTMS [16]. Another RCT found that there were significant improvements of OCD in both active and sham rTMS [17]. These discrepant findings may be caused by the lack of statistical power among some of the individual RCTs [18]. Therefore, we used meta-analytical approaches to examine the efficacy and acceptability of this strategy in SSRI-resistant OCD. This approach should obtain more accurate results by integrating the findings from multiple studies [19].

Methods

Search strategy

The first step of this meta-analysis was a selective article search. Scientific and medical data-

bases, including international databases (PubMed, MEDLINE, EMBASE, CCTR, Web of Science, PsycINFO), two Chinese databases (CBM-disc, CNKI), and relevant websites dated up to July 2014, were searched for randomized controlled trials (RCTs) on repetitive transcranial magnetic stimulation (rTMS) for treating obsessive-compulsive disorder (OCD). The search terms used were "OCD", "obsessive-compulsive disorder", "TMS", and "transcranial magnetic stimulation". To mitigate language bias, no language restriction was imposed. To avoid omitting relevant RCTs, conference summaries and reference documents listed in the articles were also researched manually.

Study selection

Among the studies identified in the initial search, the following inclusion criteria were applied for subsequent analysis [20]:

- ◆ Randomized single- or double-blinded sham-controlled trials on rTMS for OCD.
- ◆ Only data from the initial randomization of parallel or crossover design studies being used.
- ◆ At least five subjects over 18 years with selective serotonin reuptake inhibitors (SSRI)-resistant OCD randomized per study arm.
- ◆ Primary OCD was diagnosed by Diagnostic and Statistical Manual of Mental Disorders IV [21] or International Classification of Diseases [22] criteria.
- ◆ rTMS given for ≥ 5 sessions as an augmentation strategy for OCD.
- ◆ Not performed rTMS concomitantly with a new psychotropic medication (e.g., antidepressants, antipsychotics).
- ◆ Provided pre- and post-rTMS Y-BOCS scores.

Outcome measures

Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score change was chosen as the primary outcome. The response rate was chosen as the secondary outcome. Response was based on the RCT's definition (global reduction > 25% in Y-BOCS score or at least a 50% reduction in the absolute Y-BOCS score). The drop-out rate was chosen as the tertiary outcome to assess

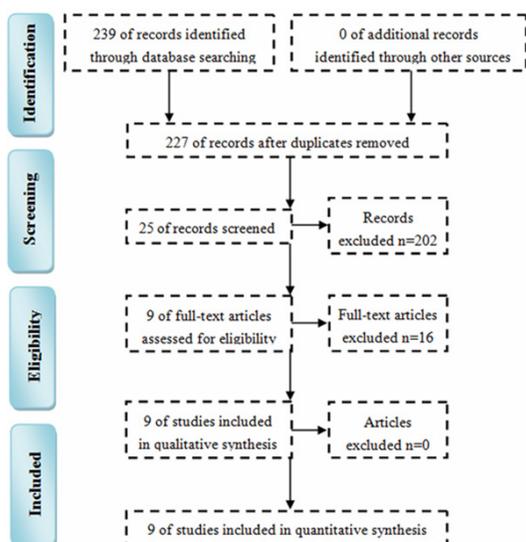


Figure 1. Workflow of literature search.

the acceptability of rTMS treatment. These outcome measures were the most consistently reported estimates of treatment's efficacy and acceptability. The treatment endpoint was preferentially viewed as the study endpoint.

Bias risk in individual studies

Two primary authors of this study served as reviewers to independently assess the quality of each eligible RCT according to the Cochrane Collaboration criteria [23]. Bias risk was determined by: (1) randomization quality; (2) blinded assessment of outcome; (3) allocation concealment; and (4) reported incomplete outcome data. Studies with two or more bias risks were excluded from the meta-analysis.

Data extraction

Two reviewers in our group independently verified all potentially suitable RCTs by the aforementioned inclusion criteria, and assessed the bias risk of the identified RCTs, and completed the data abstraction. Any disagreement about the study quality or data extraction was resolved by consensus in the group. Data retrieved from the RCTs included the first author, the year of publication, country of origin, study design, parameters of rTMS, demographic and clinical characteristics of subjects, therapy period, and outcomes. For data that could not be directly extracted, good faith efforts were applied to obtain the data by dispatching e-mails to the

author, or by calculating using the statistical method [24].

Statistical analysis

This meta-analysis was performed using RevMan 5.1 (Cochrane Information Management System [IMS]) and according to the recommendations of Sacks *et al* [25]. Baseline scores, standard deviations (SDs), and endpoint means were used to estimate the number of responsive patients under the condition that dichotomous efficacy outcomes could not be directly extracted [24]. Worst-case scenario analysis of drop-outs was used to perform a clinically sound analysis. For continuous data, weighted mean difference (WMD) was calculated based on the comparison of the mean changes in pre-treatment to post-treatment using the means and SDs. For discontinuous data, odds ratio (OR) was calculated [26]. We used a Mantel-Haenszel random-effects model, as it was assumed that the included studies probably had varying true treatment effects [27]. If needed, subgroup analysis and sensitivity analysis were conducted. Heterogeneity was assessed using the Q statistic and I^2 index [28]. Finally, funnel plots and Egger's test were used to assess the potential presence of publication bias.

Results

Literature search

We performed a systematic review of the available literature according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines. The initial Internet search obtained 227 potentially relevant studies after removing 12 duplicates. Among these, 166 studies were removed because the titles did not meet the inclusion criteria. Then, 36 additional studies were excluded by abstract review. Finally, a total of 16 additional studies were excluded after two reviewers independently read the full texts. Therefore, nine RCTs met all inclusion criteria and were used to perform meta-analysis [15-17, 29-34]. The whole selection process was described in **Figure 1**. Meanwhile, references from these RCTs were researched for possibly omitted RCTs. All screening steps were independently completed by two reviewers, and any disagreements were resolved by discussion.

rTMS as augmentation for SSRI-resistant OCD

Table 1. Demographic and clinical characteristics of included randomized controlled trials

Study	Active rTMS			Sham rTMS			Outcome measures	Response criteria	Resistant OCD?	Depression comorbidity	Country
	N	Age (S.D.)	F/M	N	Age (S.D.)	F/M					
Alonso, 2001	10	39.2 (13.0)	8/2	8	30.3 (9.5)	4/4	YBOCS, HDRS	> 40% YBOCS reduction	YES ^a	None	Spain
Prasko, 2006	20	28.4 (7.4)	5/15	14	33.6 (8.4)	8/6	YBOCS, HARS, BAI, CGI	N.A	YES ^b	None	Czech Republic
Kang, 2009	10	28.6 (12.7)	2/8	10	26.2 (10.5)	1/9	Y-BOCS, MADRS, HARS, BDI, STAI-S	> 25% YBOCS reduction	YES ^c	35%	Korea
Mantovani, 2010	9	39.7 (8.6)	4/5	9	39.4 (10.2)	3/6	YBOCS, CGI	> 25% YBOCS reduction	YES ^d	56%	USA
Mansur, 2011	13	42.1 (11.9)	6/7	14	39.3 (13.9)	8/6	YBOCS, HAMA, HAMD, CGI	> 30% YBOCS reduction	YES ^e	85%	Brazil
Gomes, 2012	12	35.5 (7.5)	8/4	10	37.5 (6.0)	5/5	YBOCS, HAMA, BDI HAMD, CGI	> 25% YBOCS reduction	YES ^f	77%	Brazil
Zhang, 2010	34	31.3 (8.4)	14/20	31	28.3 (9.9)	14/17	YBOCS, HAMA	> 30% YBOCS reduction	YES ^g	N.A	China
Cheng, 2013	23	27.3 (6.9)	11/12	21	25.7 (5.5)	10/11	YBOCS	N.A	YES ^h	N.A	China
Ma, 2014	25	27.2 (8.9)	8/17	21	29.7 (9.5)	8/13	YBOCS, HAMA, HRSD, CGI	> 35% YBOCS reduction	YES ^h	None	China

OCD: obsessive-compulsive disorder, N.A: not available. ^a72.2% (n = 13) of subjects had SSRI-resistant OCD. ^bNon-response after a 8-week trial of a selective serotonin reuptake inhibitor (SSRI). ^cFailure of at least 2 adequate trials of SSRIs and cognitive behavior therapy (CBT). ^dResidual OCD symptoms despite an adequate trial of an SSRI and CBT (for at least 12 and 8 weeks, respectively). ^ePatients scoring ≤ 30% on the Yale-Brown Obsessive Compulsive Scale after ≥ 3 complete courses of SSRIs (including clomipramine) and 20 h of CBT. ^f60% (n = 13) of subjects had SSRI-resistant OCD. ^gNon-response after a 12-week trial of SSRIs. ^hNon-response after at least 6-week trial of SSRIs.

Table 2. RTMS parameters of included randomized controlled trials

Study	Frequency	% rMT	TPPS	Duration	Strategy	Brain target	Coil type
Alonso, 2001	1 Hz	110	2160	6 weeks	Mixed ^a	R-DLPFC	circular coil
Prasko, 2006	1 Hz	110	N.A.	2 weeks	Augmentation	L-DLPFC	fig-8 coil
Kang, 2009	1 Hz	110	1200	2 weeks	Augmentation	R-DLPFC + SMA	fig-8 coil
Mantovani, 2010	1 Hz	100	2400	4 weeks	Mixed ^a	SMA	fig-8 coil
Mansur, 2011	10 Hz	110	60000	6 weeks	Augmentation	R-DLPFC	fig-8 coil
Gomes, 2012	1 Hz	100	12000	2 weeks	Augmentation	SMA	fig-8 coil
Zhang, 2010	10 Hz	100	60000	6 weeks	Augmentation	R-DLPFC	fig-8 coil
Cheng, 2013	20 Hz	100	60000	4 weeks	Augmentation	B-DLPFC	fig-8 coil
Ma, 2014	8-12 Hz	80	6480-8720	2 weeks	Augmentation	B-DLPFC	circular coil

RTMS: repetitive transcranial magnetic stimulation, rMT: resting motor threshold, L: left rTMS, R: right rTMS, B: bilateral rTMS, TPPS: total pulse per session, N.A., not available. ^a72.2% (n = 13) of subjects were currently on medication.

Table 3. Bias risk in the included randomized controlled trials

Study	Bias issues			
	RD	AL	BD	ID
Alonso, 2001	None	None	None	None
Prasko, 2006	None	None	None	None
Kang, 2009	None	None	None	None
Mantovani, 2010	None	None	None	None
Mansur, 2011	None	None	None	None
Gomes, 2012	None	None	None	None
Zhang, 2010	None	None	None	None
Cheng, 2013	None	None	None	None
Ma, 2014	None	None	None	None

N.A: not available, RD: randomization, AL: allocation, BD: blinding, ID: incomplete data.

Main characteristics

These nine RCTs contained an aggregate of xxx adult subjects with SSRI-resistant OCD, composed of 154 active rTMS and 136 sham rTMS subjects. Subjects in three RCTs were from China, two RCTs from Brazil, and other four RCTs recruited patients from Spain, Czech Republic, Korea and USA, respectively. With the exception of a small subset (n = 5, 27.7%) of the Alonso 2001 study, all included subjects that displayed some degree of SSRI-resistant OCD were treated by a combination of rTMS and SSRI medication. The mean duration of rTMS treatment was 3.8 weeks (S.D. = 1.9 weeks). The detailed characteristics of the included RCTs are described in **Tables 1** and **2**.

rTMS as augmentation for SSRI-resistant OCD

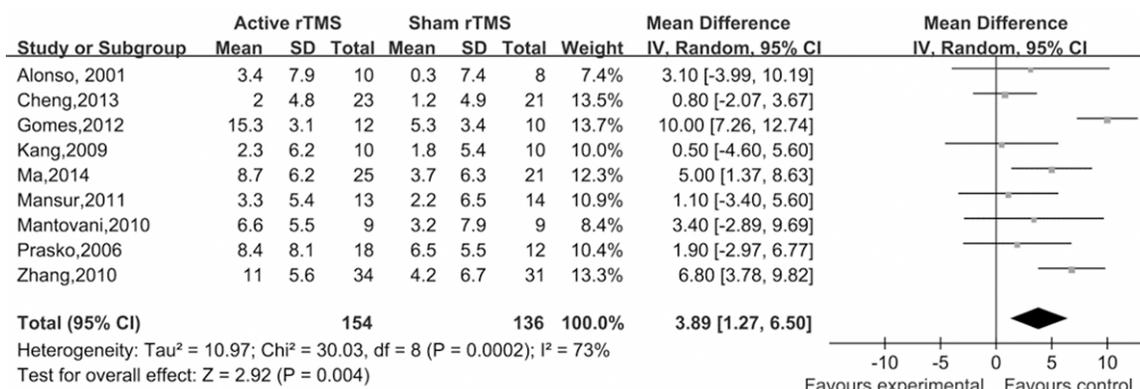


Figure 2. Meta-analysis of Y-BOCS score change.

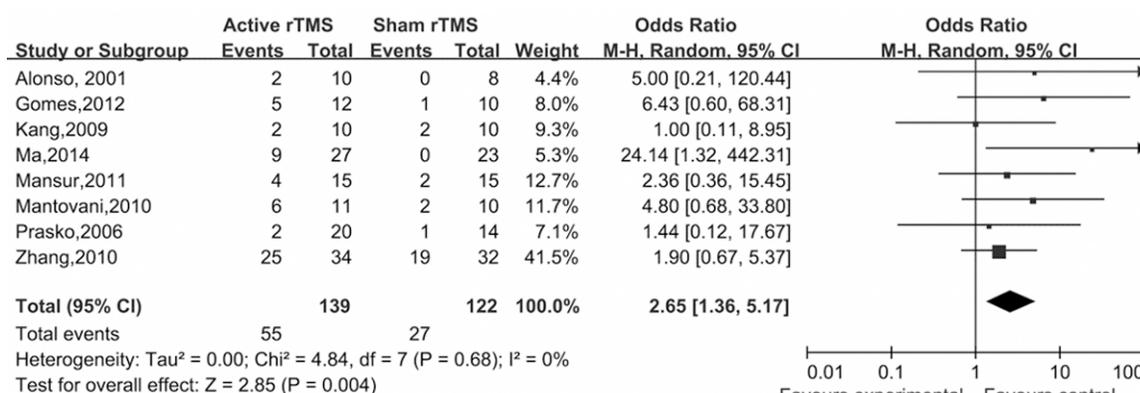


Figure 3. Meta-analysis of response rates.

Bias risk assessment

All nine included RCTs were randomized and applied double blind method. The incomplete data was reported in the RCTs that had subjects withdraw. As these nine RCTs displayed minimal or no bias risk, the data from all nine studies were included in this meta-analysis (Table 3).

Y-BOCS score change

Nine RCTs compared active rTMS to sham rTMS on reducing this primary outcome (Figure 2). In these RCTs, 154 subjects received active rTMS and 136 subjects received sham rTMS. The pooled WMD was 3.89 with 95% CI = [1.27, 6.50] for the random effect model. These results indicated that the addition of rTMS to ongoing medication treatment (SSRIs) was an effective augmentation strategy in SSRI-resistant OCD. Heterogeneity was existed (P = 0.0002, I² = 73%). There were 27.7% (n = 5) and

40% (n = 9) subjects in Alonso 2001 and Gomes 2012, respectively, that had no SSRI-resistant OCD. Therefore, we excluded these two RCTs to perform sensitivity analysis. The results did not changed much (WMD = 3.00, 95% CI = [0.89, 5.11]), but there was no significant heterogeneity any more (P = 0.08, I² = 47%).

Response rates

Response rates at the treatment end point were available for all eight RCTs (Figure 3). In these RCTs, 55 of 139 active rTMS subjects (39.6%) and 27 of 122 sham rTMS subjects (22.1%) responded. The pooled odds ratio (OR) was 2.65 (95% CI = [1.36, 5.17]), indicating that active rTMS could have higher response rates in treating resistant-OCD. Significant heterogeneity in effect size was non-existent (P = 0.68, I² = 0%). Furthermore, visual inspection of the inverted funnel plots of these RCTs appeared to be closely symmetrical. Consi-

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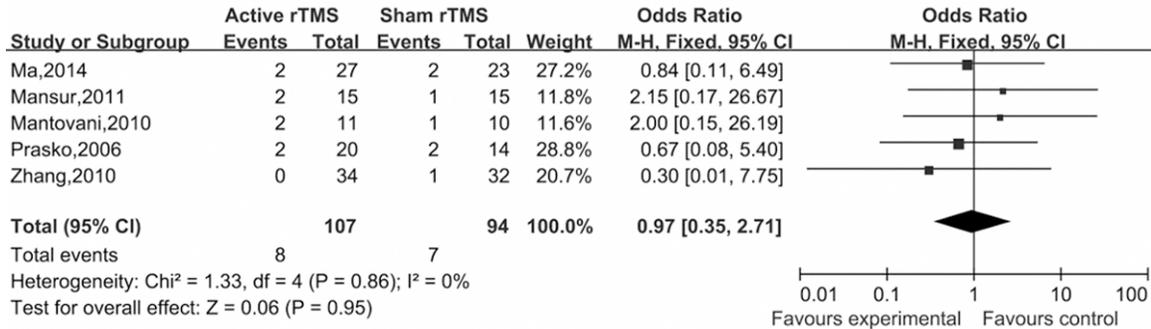


Figure 4. Meta-analysis of drop-out rates.

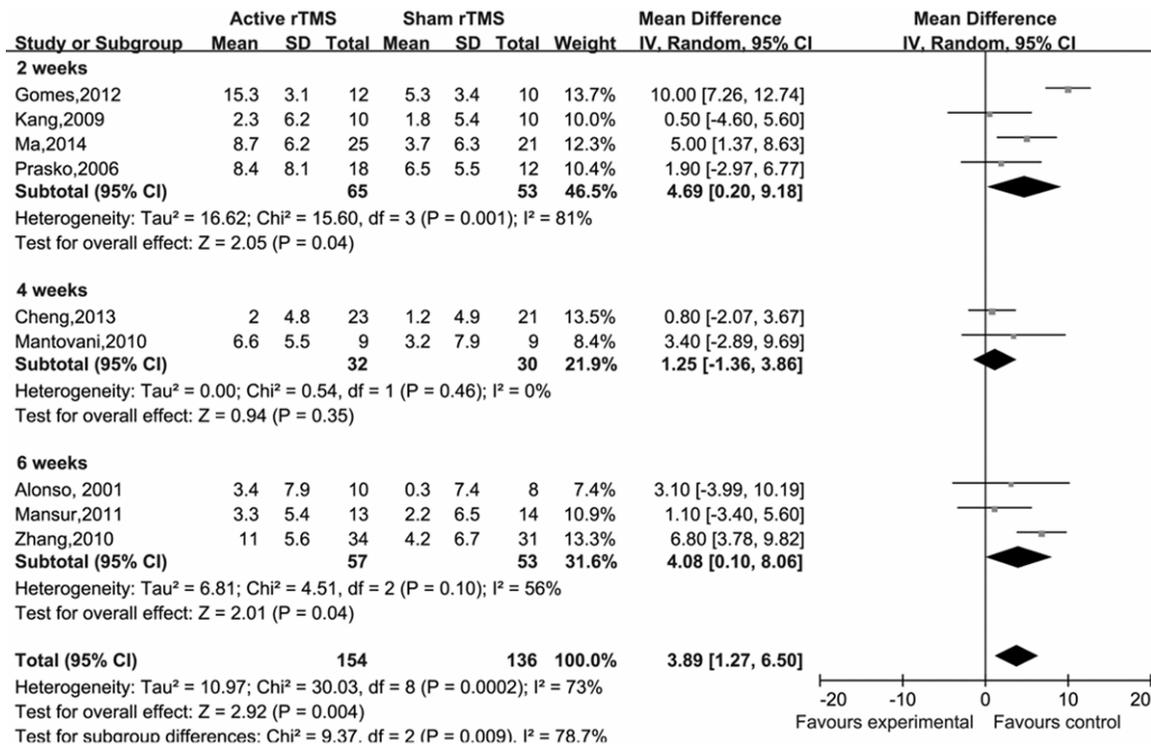


Figure 5. Subgroup analysis of Y-BOCS score change.

dering the nine selected RCTs may not have provided enough power to show a clear asymmetry, the Egger's test was conducted. This test showed that the result ($P = 0.23$) was not influenced by publication bias.

Acceptability of rTMS treatment

Drop-out rates from active rTMS versus sham rTMS were available in five RCTs (Figure 4). In these RCTs, 8 of 107 active rTMS subjects (7.5%) and 7 of 94 (7.5%) sham rTMS subjects withdrew. No significant difference was observed in drop-out rates between these two

treatment modalities. The pooled OR was 0.97 (95% CI = [0.35, 2.71]).

Subgroup analysis

A subgroup analysis was conducted based on the time of treatment: two, four and six weeks (Figure 5). With regard to Y-BOCS score change, four RCTs conducted two weeks treatment, two RCTs conducted four weeks treatment and three RCTs conducted six weeks treatment. The pooled WMD was 4.69 with 95% CI = [0.20, 9.18] in two weeks, 1.25 with 95% CI = [-1.36, 3.86] in four weeks and 4.08 with 95% CI =

[0.10, 8.06] in six weeks. These results indicated that after two or six weeks' treatment by the combination of rTMS and SSRIs, subjects with SSRI-resistant OCD had a significant decreased Y-BOCS score, but this change was not presented in subjects receiving four weeks' treatment. This difference might be caused by the small included RCTs in the subgroup of four weeks.

Discussion

Repetitive transcranial magnetic stimulation (rTMS), as augmentation or monotherapy, has been successfully used to treat neuropsychiatric disorders [35-38]. This is the first meta-analysis assessing the efficacy and acceptability of rTMS augmentation of SSRIs for SSRI-resistant OCD. This meta-analysis was based on nine RCTs composed of 290 subjects randomly assigned to either active rTMS or sham rTMS. Our findings show that the addition of active rTMS to ongoing medication treatment (SSRIs) was an effective augmentation strategy in treating SSRI-resistant OCD with pooled WMD of 3.89 (95% CI = [1.27, 6.50]) for reducing Y-BOCS score. Subgroup analysis also showed the similar results. Moreover, this strategy had higher response rates. Meanwhile, active and sham rTMS groups did not differ in terms of drop-out rates at treatment end. Based on these results, the addition of active rTMS to ongoing medication treatment (SSRIs) could significantly reduce overall OCD-related anxiety and depressive symptomatology following a mean of 3.8 weeks treatment, and could be acceptable.

It is possible that the benefit will be greater than that indicated above because the baseline Y-BOCS scores for the active rTMS group were significantly higher. The baseline in six RCTs showed that the Y-BOCS scores of the active rTMS group were higher than that of the sham rTMS group. Although most of these imbalances were not significant in individual trials, the cumulative effect might have been significant. Thus, an underestimation of the benefit of rTMS as augmentation of SSRI might occur.

All relevant RCTs were almost included in this review. However, some articles published in journals that were not indexed by international databases might have been missed. Fortunately, these studies are likely to be of low

quality and would not significantly affect the results of this review [39]. Meanwhile, we excluded some low-quality RCTs, which were mostly from China. Because these studies were always lack of truly randomization and analysis of complete data, resulting in a potential risk of gross imbalance.

Previously studies have reported that the therapeutic efficacy of rTMS was tied to its stimulus parameters [40, 41]. Therefore, it is possible that the optimum stimulus parameters of rTMS as augmentation for SSRI-resistant OCD remain unclear. Future studies should investigate different parameters combination to enhance the effects of rTMS on OCD, such as the identification of more clinically-relevant stimulation parameters (e.g., frequency, motor threshold, number of daily stimuli and treatment period). Meanwhile, researchers should use additional evaluation methods to better predict which patients might benefit from this strategy.

A few limitations of this meta-analysis should be addressed here. First, a relatively small sample size of subjects with SSRI-resistant OCD was included. Second, the efficacy of rTMS as augmentation of SSRI was examined only in RCTs with treatment duration of 2-6 weeks. Thus, long-term effects could not be assessed. Third, the efficacy of rTMS as monotherapy could not be assessed.

In conclusion, this meta-analysis indicates that the addition of active rTMS to ongoing medication treatment (SSRIs) could statistically significant reduce Y-BOCS score compared to sham rTMS in subjects with SSRI-resistant OCD, and is well tolerated in PD patients. Therefore, rTMS could be an efficacy and acceptability augmentation added on to SSRI therapies. Future large-scale studies are needed to assess the long-term effect of this strategy and the effect of rTMS as monotherapy.

Acknowledgements

We thank Min Liu from The Chinese Cochrane Center for retrieving the studies for this review.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Zhong-Rui Ma, Department of Neurology, Chengdu Fifth People's

Hospital, 33 Mashu Street, Wenjiang Zone, Chengdu 611130, Sichuan Province, China. Tel: +86-18382053607; Fax: +86-28-82722252; E-mail: zjian33@163.com

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