Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder
An Updated Systematic Review and Meta-analysis

Alisson Paulino Trevizol, MD, Pedro Shiozawa, MD, PhD,* Ian A. Cook, MD,† Isa Albuquerque Sato, MD,* Caio Barbosa Kaku, MD,* Fernanda BS. Guimarães, MD,* Perminder Sachdev, MD, PhD,‡ Sujit Sarkhel, MD,§ and Quirino Cordeiro, MD, PhD**

Background: Transcranial magnetic stimulation (TMS) is a promising noninvasive brain stimulation intervention. Transcranial magnetic stimulation has been proposed for obsessive-compulsive disorder (OCD) with auspicious results.

Objective: To assess the efficacy of TMS for OCD in randomized clinical trials (RCTs).

Methods: Systematic review using MEDLINE and EMBASE from the first RCT available until March 11, 2016. The main outcome was the Hedges *g* for continuous scores for Yale-Brown Obsessive Compulsive Scale in a random-effects model. Heterogeneity was evaluated with the I^2 and the χ^2 test. Publication bias was evaluated using the Begg funnel plot. Metaregression was performed using the random-effects model modified by Knapp and Hartung.

Results: We included 15 RCTs (n = 483), most had small-to-modest sample sizes. Comparing active versus sham TMS, active stimulation was significantly superior for OCD symptoms (Hedges g = 0.45; 95% confidence interval, 0.2–0.71). The funnel plot showed that the risk of publication bias was low and between-study heterogeneity was low ($I^2 = 43\%$, $P = 0.039$ for the χ^2 test). Metaregression showed no particular influence of any variable on the results.

Conclusions: Transcranial magnetic stimulation active was superior to sham stimulation for the amelioration of OCD symptoms. Trials had moderate heterogeneity results, despite different protocols of stimulation used. Further RCTs with larger sample sizes are fundamentally needed to clarify the precise impact of TMS in OCD symptoms.

Key Words: meta-analysis, obsessive-compulsive disorder, transcranial magnetic stimulation, nonpharmacological therapies, systematic review

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The inability of obsessive-compulsive disorder (OCD) patients to suppress intrusive thoughts, impulses, images, and repetitive motor responses have been associated with excessive activity not only in orbitofrontostriatal regions, but also in medial and lateral frontal areas (eg, supplementary motor area, anterior cingulate, dorsolateral prefrontal cortex [DLPFC]) and in parietal regions.[1]

Based on the neurobiological findings, the use of transcranial magnetic stimulation (TMS) has been proposed as an adjunct therapy for modulating brain areas associated with OCD symptoms. Transcranial magnetic stimulation is a safe noninvasive treatment that uses electromagnetic fields to modulate cortical areas activity; in practice, a high-intensity current passes through a magnetic coil placed on the scalp, and this generates a time-varying pulsed magnetic field that penetrates the cranium approximately 2 cm from the scalp surface to cortical tissue. The neurobiological consequences of TMS depend upon the parameters of the magnetic field. Low-frequency TMS (~1 Hz) is generally thought to produce inhibitory effects, whereas high-frequency TMS (≥5 Hz) is excitatory to underlying neural tissue.[2] Different protocols have emerged focusing on left and right DLPFC, supplementary motor area and orbitofrontal cortex for OCD symptoms. In the present study, we performed a systematic review and meta-analysis on results of TMS for OCD.

MATERIALS AND METHODS

A systematic review and meta-analysis according to the recommendations of the Cochrane group and to the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines was conducted.[3] Two authors (A.P.T. and P.S.) performed independent systematic reviews and data extraction, and any discrepancy was resolved by consensus.

Literature Review

We reviewed the following references and databases:

a. MEDLINE database using the key words: (1) "transcranial stimulation," (2) "TMS," (3) "transcranial magnetic stimulation," (4) "noninvasive brain stimulation," (5) "NIBS," and (6) "obsessive-compulsive disorder." The Boolean terms were imputed: [(1) OR (2) OR (3) OR (4) OR (5)] AND [(6)]. We searched for publications listed in MEDLINE and EMBASE up to March 11, 2016.
b. Study references in retrieved articles and reviews, particularly those included in the meta-analyses by Ma et al[4] and Berlim et al.[5]

We also looked for controlled trials by contacting specialists in the field and by searching the website "clinicaltrials.gov" for additional unpublished/ongoing trials.

Eligibility Criteria

We adopted the following inclusion criteria: (1) manuscript written in English, Spanish, or Portuguese; (2) randomized, sham-controlled trials; (3) provided data (on the manuscript or upon request) for the estimation of the main outcomes, that is, mean (SD) values and response and remission rates. We excluded case reports and series of cases, noncontrolled trials, and trials assessing conditions other than OCD or interventions other than TMS.

Data Extraction

The following variables were extracted according to a structured checklist previously elaborated by the authors: (1) metadata

From the *Interdisciplinary Center for Clinical Neuromodulation, Santa Casa School of Medical Sciences, São Paulo, Brazil; †Neuromodulation Division, Departments of Psychiatry and Bioengineering, University of California, Los Angeles, CA; ‡Neuropsychiatric Institute, Prince of Wales Hospital, Sydney, Australia; and §Institute of Psychiatry, Kolkata, India.

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Reprints: Alisson Trevizol, Department of Psychiatry, Santa Casa Medical School, Rua Major Maragliano, 241, Vila Mariana, ZIP: 0460001, São Paulo, Brazil (e-mail: alisson.trevizol@hotmail.com.br).

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(ie, authorship, publication date, and so on); (2) demographics (ie, sample size in each group, age, sex), (3) disorder characteristics (baseline Yale-Brown Obsessive Compulsive Scale [YBOCS]; use of medication; psychometric scales, interviews, and checklists used for diagnosis and assessment of anxiety and depressive symptoms), (4) characteristics of the TMS technique (ie, frequency, motor threshold, period of stimulation, train, intertrain interval, number of sessions, cortical target stimulated, side of brain), (5) research methods (ie, randomization protocol, sham technique, blinding assessment).

Although categorical outcomes might be more readily interpretable than continuous ones (despite the fact that the odds ratio is frequently misinterpreted as risk ratio), the primary outcome was based on YBOCS scores as a continuous outcome measure. We considered that a continuous effect size would better synthesize the included studies, and the primary outcome of all included studies was based on continuous measure outcomes.

Quality Assessment

We assessed methodological quality of each trial by assessing: (1) methods of randomization—whether the study was correctly randomized and/or the authors reported the randomization method; (2) sham TMS—how sham TMS was performed.

Quantitative Analysis

Main Outcomes

All analyses were performed using the statistical packages for meta-analysis of Stata 13.1 for Mac OSX. For the main outcome (YBOCS scores), we initially calculated the standardized mean difference and the pooled standard deviation of each comparison. This procedure is convenient because it standardizes the effect sizes across all studies based on the standard deviation of each study. In the studies by Ruffini et al[6] and Nauczyciel et al.[7] The YBOCS scores were assessed by graphic evaluation. In the study by Sachdev et al[8] and Sarkhel et al,[9] data were provided by the authors. In all other studies, data were reported in the articles. The studies conducted by Nauczyciel et al[7] and Haghighi et al[10] had a cross-over design. Due to possible late effects of the TMS stimulation, we used only data from the first cross-over phase from both studies. In that way, patients would have undergone only one protocol (either active or sham). An unstandardized mean difference analysis was performed with the difference on the YBOCS score for a more immediate clinical interpretation.

Quantitative Assessment of Heterogeneity and Bias

Heterogeneity was evaluated with the I^2 (>35% for heterogeneity) and the χ^2 test ($P < 0.10$ for heterogeneity). Publication bias was evaluated using the funnel plot, which displays confidence interval boundaries to assist in visualizing whether the studies are within the funnel, thus providing an estimate of publication bias (eg, whether studies are distributed asymmetrically and/or fall outside the funnel). Sensitivity analysis, which assesses the impact of each study in the overall results by excluding 1 study at a time, was also performed.

Metaregression

Metaregression was performed using the random-effects model modified by Knapp and Hartung,[11] using only one variable at a time.

Safety Evaluation

We used patients' dropouts as most severe outcome for safety evaluation. A categorical analysis was used for odds ratio assessment between groups.

RESULTS

Overview

Our systematic review yielded 123 studies after duplicates were removed. Among them, 109 articles did not match eligibility criteria (Fig. 1). Fifteen studies[4,6–10,12–20] (483 patients) were selected for the quantitative analysis. Across all subjects, the mean

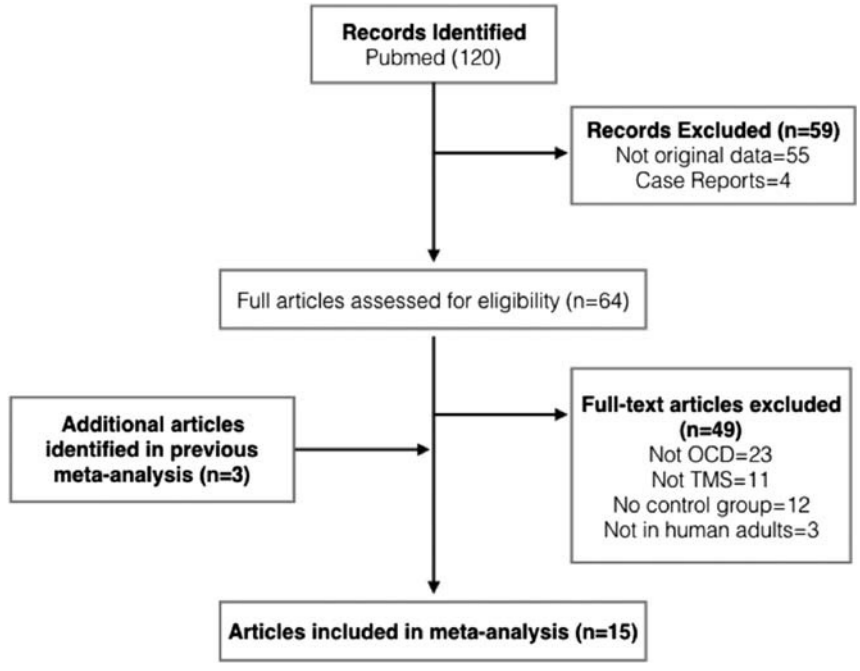

FIGURE 1. Preferred Reporting Items for Systematic Review and Meta-Analysis outflow chart.

TABLE 1. Demographics and Clinical Characteristics

	Active TMS			Sham TMS			TMS Parameters				
Study	**n**	**Fem (n)**	**Age, y**	**n**	**Fem (n)**	**Age, y**	**Brain Cortex Region**	**F, Hz**	**No. Pulses**	**MT (%)**	**Duration**
Alonso et al., 2001	10	8	39.2	8	4	30.3	R-DLPFC	1	21600	110	6 wk
Prasko et al., 2006	18	5	28.9	12	7	33.4	L-DLPFC	1	18000	110	2 wk
Sachdev et al., 2007	10	3	29.5	8	5	35.8	L-DLPFC	10	15000	na	2 wk
Kang et al., 2009	10	2	28.6	10	1	26.2	R-DLPFC + SMA	1	12000	110	2 wk
Ruffini et al., 2009	16	6	41.5	7	3	39.3	L-OFC	1	9000	80	3 wk
Badawy et al., 2010	40	20	26.9	20	13	28.9	L-DLPFC	20	12000	na	3 wk
Sarkhel et al., 2010	21	11	29.3	21	8	31.9	R-DLPFC	10	8000	110	2 wk
Mantovani et al., 2010	11	4	39.7	10	3	39.4	SMA	1	24000	100	4 wk
Zhang et al., 2010	34	14	31.3	31	14	28.3	R-DLPFC	10	60000	100	6 wk
Mansur et al, 2011	15	6	42.1	15	8	39.3	R-DLPFC	10	60000	110	6 wk
Gomes et al., 2012	12	8	35.5	10	5	37.5	SMA	1	12000	100	2 wk
Cheng et al., 2013	23	11	27.3	21	10	25.7	B-DLPFC	20	60000	100	4 wk
Ma et al., 2014*	27	8	27.1	23	8	29.8	B-DLPFC	8–12	6480–8720	80	2 wk
Nauczyciel et al., 2014	9	7	40	10	8	39	R-OFC	1	12000	120	1 wk
Haghighi et al., 2015	10	3	34.9	11	6	36.55	B-DLPFC	20	7500	100	4 wk

SMA indicates supplementary motor area; OFC, orbitofrontal cortex; L-DLPFC, left DLPFC; R-DLPFC, right DLPFC; B-DLPFC, bilateral DLPFC; R-OFC, right OFC; L-OFC, left OFC.

age was 31.87 (SD = 7.58) years, and 44.1% of participants were women. No main treatment drug washout was performed. Demographics and stimulation protocols are displayed in Table 1. Study sample size ranged from 18 to 65 subjects (average, 16.1; SD = 8.45).

Quality assessment revealed that all studies were randomized, sham-controlled, with patient and evaluator blinded. Sham TMS was performed in 5 different ways: (1) a sham coil that produced a similar acoustic artifact and scalp sensation as the active coil; (2) a sham magnetic coil that looked and sounded identical to the active coil, but that produced no scalp sensation; (3) the coil was held 90 degrees vertically over the stimulated head area (minimal magnetic field was induced, just the auditory artifact); (4) the coil was placed at a 45 degree angle to the head, producing nerve and muscle stimulation on the face and scalp; (5) deactivated coil was used.

Primary Outcome

We calculated the effect size for endpoint. We found that active TMS was significantly superior to sham TMS in this data set (D = 2.94; 95% confidence interval [95% CI], 1.26–4.62) (Fig. 2).

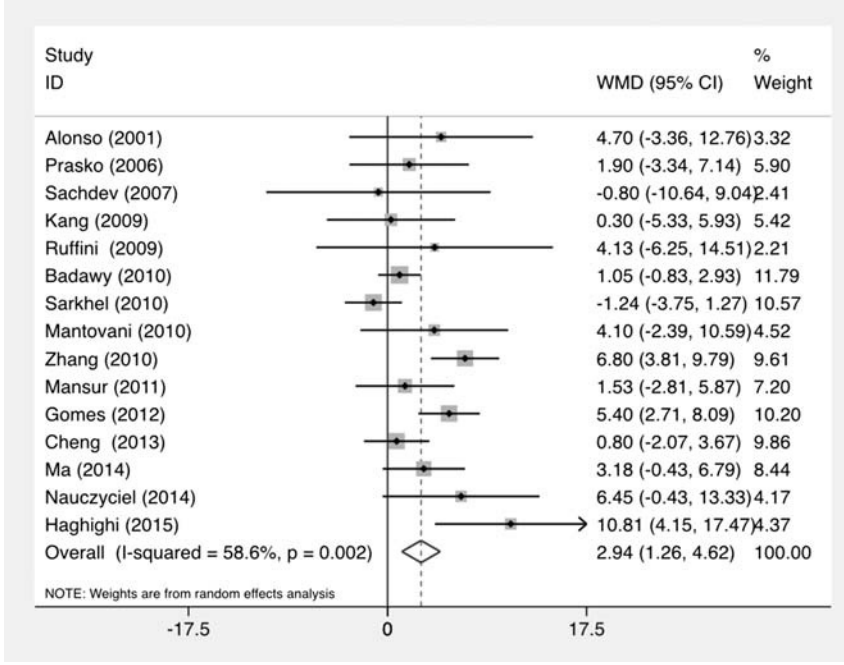

FIGURE 2. Forest plot of effect sizes (Hedges g). The forest plot was used to graphically illustrate the relative strength of treatment effects for each elected study; the vertical line represents the overall effect.

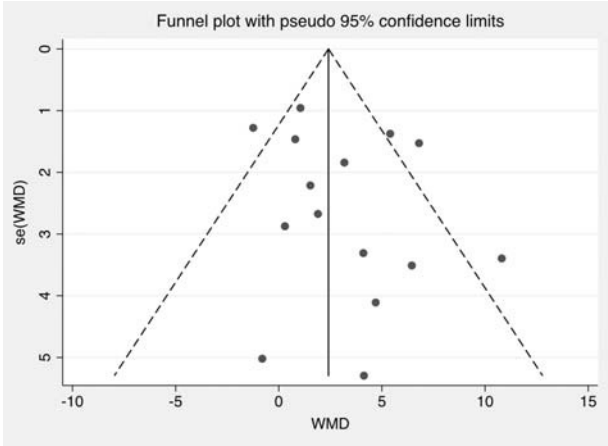

FIGURE 3. Begg funnel plot. The funnel plot was used to evaluate the existence of publication bias. All studies are within the limits determined by the graphic except for one, indicating low bias.

Quantitative Assessment of Heterogeneity and Bias

Heterogeneity was moderate in our analysis ($I^2 = 58.6\%$, $P = 0.002$ for the χ^2 test). The funnel plot displays that studies were evenly distributed throughout the funnel, with 3 studies located out (Fig. 3). However, the exclusion of each study did not have a significant impact on the results, with resulting effect sizes close to the overall effect size (Fig. 4). Therefore, no particular study could be driving the results of our analysis.

Metaregression

Metaregression showed no particular influence of any variable on the results (Table 2).

Safety Evaluation

A categorical analysis of safety, using dropout as most severe possible outcome, was performed. No difference between groups was observed (odds ratio, 1.02; 95% CI, 0.76–1.36). Evaluation of most common side effects was not possible due to lack of detailed data provided in the articles.

DISCUSSION

In this systematic review that included 15 randomized clinical trials (RCT)[4,6–10,12–20] (n=483), we found that active TMS was significantly superior to sham TMS for the treatment of OCD (D = 2.94; 95% CI, 1.26–4.62). This result was apparent in our main analysis that used a continuous effect size measure. The funnel plot assessment showed that the risk of publication bias was also low and between-study heterogeneity was moderate ($I^2 = 58.6\%$). Our results are in accordance to previous meta-analysis.[5] However, we aid to enlarge the pooled sample of this previous review in 71.3% with the inclusion of 5 further trials.

Interventional protocols were heterogeneous. In fact, study protocols either stimulated or inhibited the left or right DLPFC, the DLPFC bilaterally, the supplementary motor area and the orbitofrontal cortex. One study included inhibited the right DLPFC and the supplementary motor area.[15] Metaregression did not identify clinical and/or methodological predictors for TMS responsiveness. Demographics and stimulation protocols are summarized in Table 1. Metaregressions were performed to identify the possibility of different results if protocols were evaluated separately. No treatment protocol was identified as predictor to TMS nonresponsiveness (Table 2). Moreover, as to verify the influence of each study on the overall effect, we used the "metaninf" Stata tool. No study individually influenced the overall effect (Fig. 4). A key limitation of the present report is the small number of evaluable sham controlled RCTs in OCD. Another limitation is that all studies used TMS as an adjunct to other treatments, so the incremental advantage of active over sham intervention may has been obscured by the effects of the underlying primary treatment.

CONCLUSIONS

Based upon this meta-analysis of published double-blinded RCTs, we found that active TMS is clinically and statistically superior to sham TMS in the treatment of OCD. Notwithstanding,

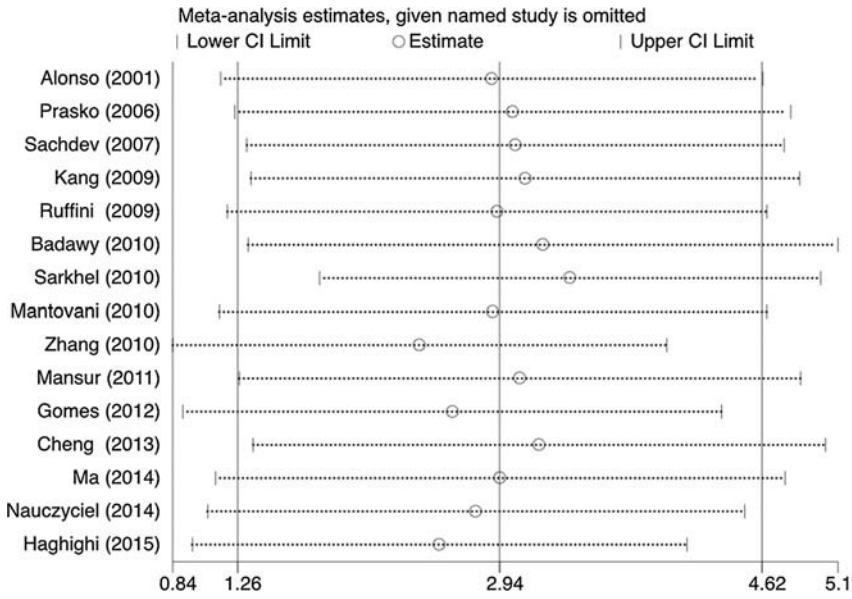

FIGURE 4. Sensitivity analysis. The sensitivity analysis assesses the impact of each study in the overall results by excluding one study at a time.

TABLE 2. Metaregression

Metaregression	*P*	Metaregression	*P*
Age sham	0.968	Total number of pulses	0.666
Age active	0.061	Frequency	0.522
Duration of illness sham	0.07	No. sessions	0.671
Duration of illness active	0.141	Motor threshold	0.998
YBOCS sham baseline	0.064	No. weeks of stimulation	0.674
YBOCS active baseline	0.099	Blinding	0.284
Depression sham baseline	0.451	Alpha guided TMS	0.849
Depression active baseline	0.983	Side of brain stimulated	0.388
Scale of depression used	0.684	R-DLPFC/L-DLPFC/B-DLPFC/L-OFC/R-OFC/SMA/SMA+DLPFC	0.414
DLPFC/SMA/OFC/DLPFC+SMA	0.664		

the number of trials published to date was relatively small, so further phase III studies assessing broader samples are fundamentally needed to clarify the potential impact of TMS in the treatment of OCD symptoms in daily clinical practice.

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