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The Efficacy of Transcranial Magnetic Stimulation in the Treatment of Obsessive-Compulsive Disorder: An Umbrella Review of Meta-Analyses

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Abstract

Background. Repetitive transcranial magnetic stimulation (rTMS) has been increasingly used for treating obsessive-compulsive disorder (OCD). Although several meta-analyses have explored its effectiveness and safety, there is no umbrella review specifically focused on rTMS for OCD. This umbrella review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and analyzed relevant meta-analyses on rTMS for OCD.
Methods. Twenty-three articles were identified from PubMed, and after screening, 12 meta-analyses were included in the review. The studies analyzed in the meta-analyses ranged from 10 to 27, with total participants ranging from 282 to 791. The most commonly studied regions were the dorsolateral prefrontal cortex (DLPFC), supplementary motor area (SMA), and orbitofrontal cortex (OFC).
Result. The majority of the meta-analyses consistently supported the effectiveness of rTMS in reducing OCD symptoms when applied to the DLPFC and SMA. Encouraging results were also observed when targeting the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) through deep transcranial magnetic stimulation (dTMS). However, there was a high level of heterogeneity in the findings of nine out of 12 meta-analyses.
Conclusion. In conclusion, existing evidence suggests that rTMS targeting the DLPFC and SMA consistently reduces OCD symptoms, but targeting the mPFC and ACC through dTMS shows variable results. However, the high heterogeneity in the study findings indicates a need for further research and standardization in the field.

Introduction

Obsessive-compulsive disorder (OCD) is a prevalent mental illness, affecting approximately 2%–3% of the population. It typically manifests as a chronic condition and often exists with comorbidities, responds partially to treatment, leading to significant impairment.[1,2] A large network meta-analysis evaluating the efficacies of psychotherapeutic interventions and pharmacotherapies in OCD has revealed that the serotonergic medications, including selective serotonin reuptake inhibitors and clomipramine, exhibit similar efficacy, while the combination of pharmacological and psychotherapeutic interventions are more effective than individual treatment modalities.[3] After the initiation of treatment with serotonergic medications, significant clinical improvements can be observed (in comparison to placebo) within the initial 2 weeks. However, over time, clinical improvement gradually diminishes.[4] For individuals with OCD who did not respond favorably to conventional therapy or medication, neuromodulation techniques such as deep brain stimulation (DBS) and repetitive transcranial magnetic stimulation (rTMS) are proving to be promising therapeutic options.[1]

Neuroimaging studies consistently indicate the involvement of the cortico–striato–thalamo–cortical (CSTC) circuitry in patients with OCD.[5-7] Various neuromodulation techniques, ranging from invasive techniques like deep brain stimulation to convulsive techniques like electroconvulsive therapy, have been used in the management of OCD.[8] Studies report that among patients with OCD, all the neuromodulation techniques are used as an add-on treatment to ongoing pharmacological treatment.[9] Among these neuromodulation techniques, evidence suggests that DBS, targeting the ventral capsule, nucleus accumbens, or subthalamic nucleus,

exhibits the highest efficacy. Low-frequency rTMS over the supplementary motor area (SMA) or the orbitofrontal cortex has also been found effective in reducing the symptoms of OCD.[9,10]

rTMS has gained increasing popularity in the past decade as a means to manage OCD. Targeted brain areas for rTMS treatment include the dorsolateral prefrontal cortex (DLPFC), SMA, orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), and anterior cingulate cortex (ACC).[11] Notably, no major side effects were reported in the patients during or after rTMS sessions.[11] In most studies, rTMS treatments consisted of 10–30 sessions, with a frequency of five sessions per week.[11] In 2018, US Food and Drug Administration (FDA) permitted the use of BrainsWay Deep TMS as an adjunctive treatment for OCD, following positive results from a multicenter study.[12-14]

Both excitatory and inhibitory rTMS have been explored for the treatment of OCD. Low-frequency rTMS application is considered to have an inhibitory effect on the underlying cerebral cortex, while high-frequency rTMS exhibits an excitatory effect.[11] Recent developments of theta burst stimulation (TBS), in which bursts of three 50-Hz pulses each are delivered at a frequency of 5 Hz, have been found to produce similar effects on the underlying cortex. Continuous theta burst stimulation (cTBS) produces cortical inhibition, while intermittent theta burst stimulation (iTBS) leads to cortical excitation.[11]

OCD trials of rTMS targeting various brain areas such as DLPFC, SMA, OFC, mPFC, and ACC have reported varying response rates. According to Acevedo et al.,[15] stimulation of the SMA has the best response rate. However, most trials suffer from limitations, including small sample size and concomitant administration of pharmacotherapy. Several meta-analyses and systematic reviews have discussed the safety and efficacy of rTMS in the management of OCD. Here, we conduct an umbrella review [systematic review of the meta-analyses of randomized controlled trials (RCT)] to specifically examine the safety and efficacy of rTMS in OCD treatment.

Methodology

This study presents a systematic review of all meta-analyses on TMS in OCD available in the PubMed database from inception until 15 September 2023. The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two authors (SKK & AA) independently conducted a comprehensive search in the PubMed database using the search terms: (((obsessive compulsive disorder) OR (OCD)) AND ((((TMS) OR (Transcranial magnetic stimulation)) OR (repetitive transcranial magnetic stimulation)) OR (rTMS))), along with applying the filter for Meta-Analysis. A total of 22 articles were identified from the search. One more article was included after manual search. Only articles published in English were included. The metadata of these articles were extracted and imported into the Rayyan software. Two researchers independently screened these articles, blinded to the screening performed by the other researcher. All articles that are meta-analyses on the use of TMS intervention in patients with OCD, regardless of their clinical outcomes (e.g., safety, efficacy, comparative effectiveness), were included. Additionally, some meta-analyses that discuss non-invasive brain stimulations in the management of psychiatric disorders, but analyzed the role of TMS in OCD, specifically, were also included. After the independent screening, both investigators discussed the screened articles to reach a consensus. Figure 1 shows the PRISMA guidelines in a graphical flow.

Results

A total of 12 meta-analyses were included in this systematic review after screening 23 articles. The excluded articles were primarily focused on psychiatric disorders other than OCD. Of the 23 screened articles, 20 were meta-analyses, and a systematic review was conducted in 12 of these articles. Of the 23 articles screened, 22 were in English and one was in Dutch. Table 1 provides a summary of the meta-analyses included in this study.

The number of studies included in the meta-analyses ranges between 10 and 27. The majority of these meta-analyses (8 of 12) were published in the past 2 years (2021–2022). Among the studies, DLPFC emerged as the most frequently targeted region of interest, followed by SMA and OFC. The meta-analyses consistently conclude that rTMS applied to DLPFC and SMA effectively reduces the symptoms of OCD. Targeting mPFC and ACC through dTMS gives encouraging results. The reported effect sizes of the meta-analyses range between Hedge's g of 0.42 and 0.79 and after correcting the heterogeneity, it ranges between 0.29 and 0.49. The summary of the common targets and outcomes of the meta-analyses are provided in Table 2.

The meta-analyses included here have number of participants ranging from 282 to 791. The majority of the meta-analyses (9 of 12) report high heterogeneity of the findings. The effect sizes reported are moderate to large (Table 3).

The majority of the meta-analyses reported about estimating the risk of bias of the published studies included. However, only 6 of the 12 meta-analyses gave a detailed account of the risk of bias estimation (Table 4).

Discussion

This systematic review examines the safety and efficacy of different rTMS protocols for the treatment of OCD, based on meta-analyses of randomized controlled trials. Twelve eligible meta-analyses were included in this review.[16–27] The different rTMS stimulation procedures were organized according to two main categories: (1) the prefrontal area stimulated: DLPFC, SMA, OFC, and mPFC/ACC; including their respective laterality (right, left, or bilateral); and (2) the type of paradigm of stimulation: Low-frequency rTMS (= < 1 Hz); High-frequency rTMS (> = 5 Hz); Theta-burst Stimulation (TBS)—either continuous-TBS (cTBS) or intermittent-TBS (iTBS); Deep TMS (it is a form of high-frequency rTMS, it just uses a different coil to target the mPFC/ACC).

According to all the meta-analyses included, rTMS for OCD is safe. The reported side effects were mild (mostly mild headache, discomfort, or neck pain), and the dropout rate was low.

A significant milestone in the history of rTMS in OCD treatment was the 2018 FDA approval,[14] which was based on the multicenter, prospective, randomized, double-blinded placebo-controlled trial. This trial examined the efficacy of bilateral, high-frequency (20 Hz)) deep-TMS targeting the mPFC/ACC using an H7 coil, combined with personalized symptom provocation at the beginning of each stimulation sessions.[28] Results showed that at 1-month follow-up, 45.2% of the patients in the active treatment group responded, compared to 17.8% in the sham treatment group.[28] All the studies conducted before and after the FDA approval of TMS for OCD treatment have focused on the abnormal function of the cortico-striato-thalamo-cortical (CSTC) circuitry, which plays a crucial role in the mechanisms of OCD.[6,7] Similar abnormal neural oscillations have also been observed in other brain areas associated with neuropsychiatric conditions.[29,30]

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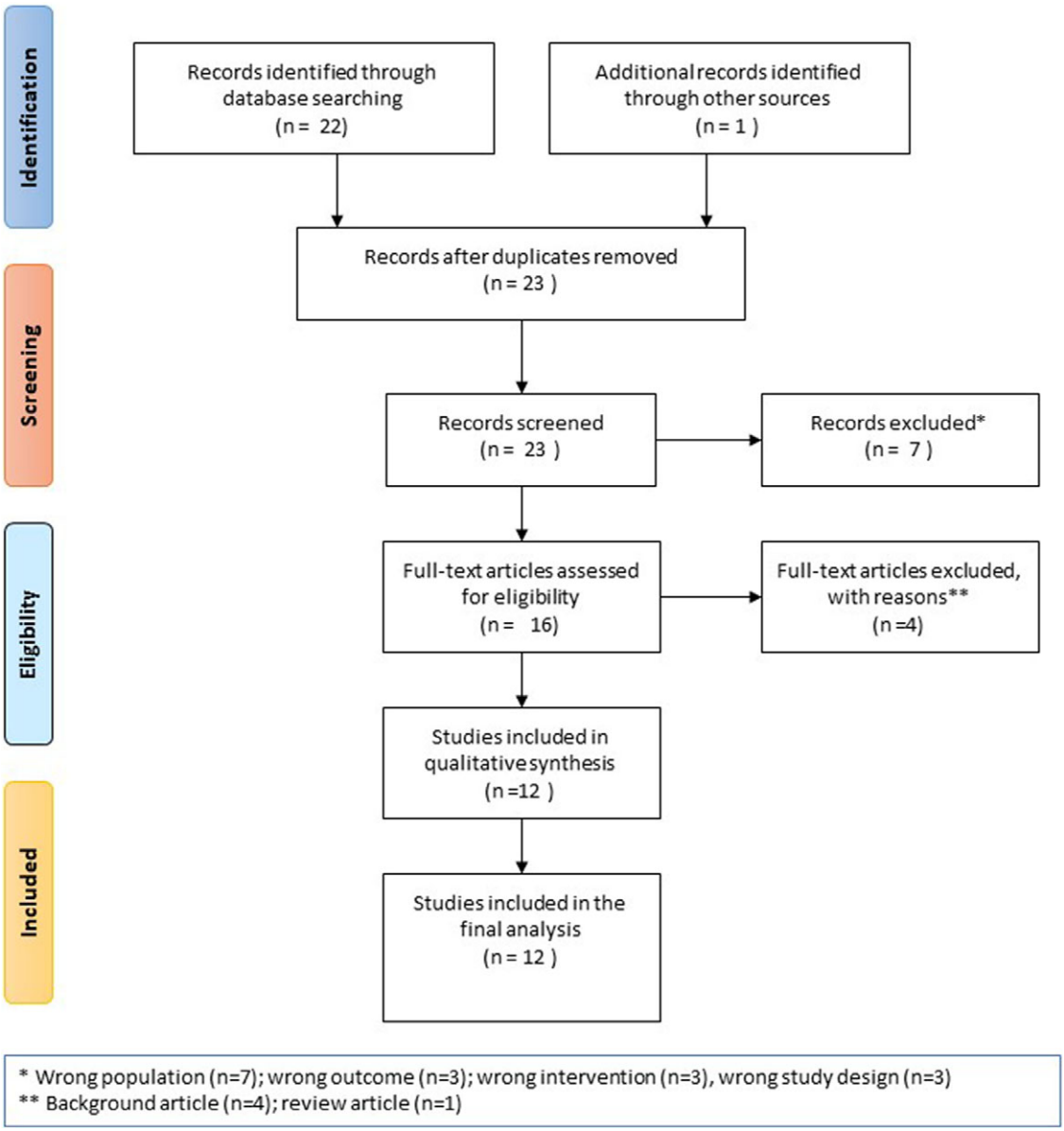

Figure 1. PRISMA flow diagram showing the selection of the meta-analyses.

In OCD, an imbalance between the direct and indirect pathways of the CSTC circuitry contributes to the generation and perpetuation of obsessions and compulsions, which are the key symptoms of OCD. It was found that the mPFC/ACC is hyperactive in OCD patients. Interestingly, the type of stimulation used was high-frequency, which is thought to be excitatory, and does not further hyperactivate this region. Instead, it is believed that the high-frequency stimulation may disrupt the abnormal circuitry activity in OCD,[31] which is consistent with the literature on using high-frequency stimulation to disrupt abnormal brain oscillations in other neuropsychiatric disorders, such as the use of 500-Hz stimulation to disrupt abnormal brain oscillation in epilepsy models.[32,33] In addition to the stimulation protocol targeting the mPFC/ACC, the remaining target areas that have been studied include bilateral and right DLPFC, which have shown the highest quality of evidence according to Zhou et al, Liang et al, Perera et al, and Fitzsimmons.[18,20-22]. On the other hand, results for left DLPFC, SMA, and OFC have been more heterogeneous.[16,19,20] According to the meta-analysis of Perera et al., the reason for the largest significant effect size in the BL-DLPFC group, in contrast to meta-analyses reporting a higher effect size for the SMA group, is that Perera et al. included an additional study with a high effect size to the BL-DLPFC group and four studies with low effect size to the SMA group. Similarly, Hyde et al., reported that BL-DLPFC produces maximum therapeutic efficacy in the management of OCD.[25] The most recent meta-analysis by Thatikonda et al., emphasizes the superiority of DLPFC targets than non-DLPFC targets.[27] Suhas et al., in their network meta-analysis found the superiority of deep TMS than conventional TMS treatments in the management of OCD.[26]

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Table 1. Summaries of the Meta-Analyses on the Use of TMS in OCD

	References	Title	Journal	Date till articles screened & included	Databases included	Search terms used	Other search strategies employed	Language restrictions	Unpublished studies included
1.	Berlim et al.[16]	Repetitive transcranial magnetic stimulation (rTMS) for obsessive-compulsive disorder (OCD): an exploratory meta-analysis of randomized and sham-controlled trials.	Journal of psychiatric research	31/12/2012	Medline, Embase, APA, Cochrane, Scopus	(randomized controlled trial OR ((randomized OR randomized) AND controlled AND trial)) AND ("magnetic stimulation" OR rTMS) AND (obsess* OR compuls* OR OCD)	Bibliography of RCTs, Meta analysis and reviews	English	No
2.	Trevizol et al.[17]	Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: An Updated Systematic Review and Meta-analysis.	Journal of ECT	11/03/2016	Medline, Embase, Clinicaltrials	(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)].	Bibliography of selected articles, Communication with experts	English, Spanish, Portuguese	Yes (unpublished and ongoing trials)
3.	Zhou et al.[18]	An updated meta-analysis: Short-term therapeutic effects of repeated transcranial magnetic stimulation in treating obsessive-compulsive disorder.	Journal of affective disorders	18/09/2016	PubMed, Embase, Cochrane, Wanfang, CKNI, Sinomed	"magnetic stimulation" or "rTMS" or "transcranial magnetic" and "obsessive" or "compulsive" or "OCD".	Bibliography of meta-analyses	English or Chinese	No
4.	Rehn et al.[19]	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).	The Psychiatric quarterly	01/12/2016	PubMed, WoS, Medline, APA, Scholar	'obsessive-compulsive disorder' or 'OCD' or 'obsessions' or 'compulsions' AND 'transcranial magnetic stimulation' or 'TMS'	Bibliography of systemic review and meta analyses	None	No
5.	Liang et al.[20]	Efficacy and tolerability of repetitive transcranial magnetic stimulation for the treatment of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis.	Translational Psychiatry	25/03/2020	PubMed, WoS, Embase, APA, Cochrane	obsessive compulsive disorder" or "OCD" or "obsessions" or "compulsions" AND "magnetic stimulation" or "rTMS" or "transcranial magnetic".		None	No

Table 1. *Continued*

	References	Title	Journal	Date till articles screened & included	Databases included	Search terms used	Other search strategies employed	Language restrictions	Unpublished studies included
6.	Perera et al.[21]	Repetitive Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: A Meta-analysis of Randomized, Sham-Controlled Trials.	Biological psychiatry	31/10/2020	Pubmed, WoS, Medline, APA	obsessive-compulsive disorder, OCD, non-invasive brain stimulation, repetitive transcranial magnetic stimulation, rTMS, theta burst stimulation, and TBS	Bibliography of selected articles	English	No
7.	Fitzsimmons et al.[22]	Repetitive transcranial magnetic stimulation for obsessive-compulsive disorder: A systematic review and pairwise/network meta-analysis.	Journal of affective disorders	01/02/2021	PubMed, WoS, Embase, APA, Cochrane	Obsessive-Compulsive Disorder" OR "obsessive compulsive*" OR "OCD" OR "obsessional*") AND ("Transcranial Magnetic Stimulation" OR "transcranial magnetic stimulation*" OR "rTMS" OR ("TBS" AND "stimulation") OR "theta burst stimulation*" OR "iTBS" OR "cTBS" OR "TMS"	None		No
8.	Pellegrini et al.[23]	Repetitive transcranial magnetic stimulation (r-TMS) and selective serotonin reuptake inhibitor-resistance in obsessive-compulsive disorder: A meta-analysis and clinical implications.	Comprehensive psychiatry	31/07/2021	Pubmed, APA, Cochrane	: ['obsessive compulsive disorder' OR 'OCD' or 'obsessions' OR 'compulsions'] AND ['transcranial magnetic stimulation' OR 'TMS']	Bibliography of selected articles	English	No
9.	Gao et al.[24]	A meta-analysis of the effects of non-invasive brain stimulation on obsessive-compulsive disorder.	Psychiatry research	14/03/2021	PubMed, Embase, Cochrane	("Obsessive-Compulsive Disorder" OR "Disorder, Obsessive-Compul sive") AND ("Non-invasive Brain Stimulation" OR "Repetitive Trans cranial Magnetic Stimulation" OR "Transcranial Direct Current Stimulation"OR "Transcranial Alternating Current Stimulation" OR "Transcutaneous Vagus Nerve Stimulation" OR "NIBS" OR "tDCS" OR "rTMS" OR "tACS" OR "TNS" OR "tVNS") AND ("Randomized Controlled Trial" OR "Randomized" OR "Placebo").	Bibliography of meta analyses	English	No

Table 1. *Continued*

	References	Title	Journal	Date till articles screened & included	Databases included	Search terms used	Other search strategies employed	Language restrictions	Unpublished studies included
10.	Hyde et al.[25]	Efficacy of neurostimulation across mental disorders: systematic review and meta-analysis of 208 randomized controlled trials	Molecular Psychiatry	26/04/2021	PubMed, WoS, Embase, APA, Medline	"(random*) AND ("TMS" OR rTMS OR tDCS OR TMS)" *[combined with a list of ICD-11 mental health conditions, adapted for each database]*	Bibliography of included studies	None	No
11.	Suhas et al.[26]	Treatment strategies for serotonin reuptake inhibitor-resistant obsessive-compulsive disorder: A network meta-analysis of randomized controlled trials	The World Journal of Biological Psychiatry	01/03/2022	Medline, WoS, Scopus, EBSCO	'((obsess* OR compuls* OR OCD) AND (RTMS OR Repetitive transcranial Magnetic stimulation OR *[various other terms for augmenting agents])*	None	English	No
12.	Thatikonda et al.[27]	Efficacy of Repetitive Transcranial Magnetic Stimulation on Comorbid Anxiety and Depression Symptoms in ObsessiveCompulsive Disorder: A Meta-Analysis of Randomized Sham-Controlled Trials	The Canadian Journal of Psychiatry	31/07/2021	PubMed, APA PsycINFO, Cochrane central register	("obsessive compulsive disorder" OR "OCD" OR "obsessions" OR "compulsions") AND ("transcranial magnetic stimulation" OR "TMS" OR "magnetic stimulation" OR "rTMS.")	Bibliography of meta analyses and relevant articles	English	No

Table 2. Efficacy of rTMS in OCD and the Targets of Intervention

	Author	No. of RCTs selected	Targets/ROI[a] (No. of RCTs)	Conclusion about the efficacy of ROI
1.	Berlim et al.[16]	10	Rt DLPFC:4 Lt DLPFC:3 SMA: 3	LF rTMS (particularly targeting the SMA or the OFC) seems to be the most promising approach
2.	Trevizol et al.[17]	15	No subgroup analysis conducted.	No discussion about ROI in the conclusion
3.	Zhou et al.[18]	20	BL DLPFC: 5 Rt DLPFC:8 Lt DLPFC: 2 SMA: 3 OFC: 2	Targeting the right DLPFC seems to produce larger therapeutic effects than targeting other regions.
4.	Rehn et al.[19]	18	BL DLPFC:3 Rt DLPFC: 6 Lt DLPFC: 3 SMA: 4 OFC: 2	SMA is the most effective target
5.	Liang et al.[20]	22	BL DLPFC: 4 Rt DLPFC:6 Lt DLPFC:3 SMA: 5 OFC: 2 ACC/mPFC: 2	LF rTMS over DLPFC, LF rTMS over SMA, HF rTMS over DLPFC are better than sham.
6.	Perera et al.[21]	26	BL DLPFC: 4 Rt DLPFC:5 Lt DLPFC: 4 SMA: 8 OFC: 2 mPFC: 2	BL DLPFC is the most effective approach.
7.	Fitzsimmons et al.[22]	21	DLPFC: 11 SMA + mPFC: 10 OFC: 2	DLPFC is the most efficacious approach.
8.	Pellegrini et al.[23]	23	No subgroup regarding target of interest conducted.	No discussion about ROI in conclusion
9.	Gao et al.[24]	14	DLPFC: 11 SMA: 4	DLPFC is a better site for neuromodulation.
10.	Hyde et al.[25]	27[a]	BL DLPFC: 4 SMA: 6	BLDLPFC shows maximum efficacy
11.	Suhas et al.[26]	15	Deep TMS: 2 rTMS: 13	Deep TMS is efficacious but not rTMS at other sites
12.	Thatikonda et al.[27]	20	DLPFC: 8 SMA: 7 OFC: 3 mPFC: 1	DLPFC was found to be the only efficacious target for stimulation

Abbreviations: ACC, anterior cingulate cortex; BL DLPFC, bilateral dorso-lateral prefrontal cortex; HF, high frequency; LF, low frequency; Lt DLPFC, left dorso-lateral prefrontal cortex; mPFC, medial prefrontal cortex; OFC, orbito-frontal cortex; RCT, randomized control trial; ROI, region of interest; Rt DLPFC, right dorso-lateral prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation; SMA, supplementary motor area.
[a]Subgroup analysis based on stimulation parameters plus ROI.

Regarding the type of stimulation paradigm, both HF and LF rTMS are effective. The more recent TBS, either continuous or intermittent, was ineffective, at least according to the few RCTs on this paradigm. Similar results are also obtained from other research.[34,35] The reasons, why conventional rTMS is effective, but, cTBS and iTBS are ineffective in the management of treatment-refractory OCD is illusive and needs more research.

Regarding bias, all the eligible meta-analyses reported the presence of publication bias, indicating that small studies favoring sham or no effect are less likely to be published. However, Perera et al.[21] considered the publication bias low after removing two outlier RCTs. Pellegrini et al.[23] noted the presence of researcher allegiance in favor of the intervention, and recommended caution in interpreting the reported effect sizes. Liang et al. and Gao et al.[20,24] reported detection and attrition bias in their analyses. However, Fitzsimmons et al. reported a high-to-moderate level of certainty in their assessment of the evidence using the GRADE criteria.[22]

In terms of study heterogeneity, nine studies reported high heterogeneity,[16,17,19-21,24-27], two studies found moderate heterogeneity,[22,23] and only one reported low heterogeneity.[18] Several factors may contribute to the significant differences in the RCT outcomes: (1) the intrinsic heterogeneous nature of the disorder: OCD has four subtypes—symmetry (26.7%), taboo thoughts (21.0%), contamination (15.9%), and hoarding (15.4%).[7] Each of these clusters of OCD symptoms is related to

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Table 3. Reported effect Sizes Comparing Active vs Sham rTMS across Studies

	References	No. of RCTs selected	No of participants	Effect size reported	Heterogeneity	New effect size after modifying for heterogeneity
1.	Berlim et al.[16]	10	282	Hedge's g = 0.59 (95% CI = 0.17–1.01), p = 0.006	Q = 25.7, I^2 = 65%, p = 0.002, High heterogeneity	Hedge's g = 0.4 (*95%CI* = 0.15–0.64), p = 0.001
2.	Trevizol et al.[17]	15	483	WMD = 2.94 (95% CI = 1.26–4.62)	I^2 = 58.6%, p = 0.002, High heterogeneity	–
3.	Zhou et al.[18]	20	791	Hedge's g = 0.71 (95% CI = 0.55–0.87), p < 0.001	I^2 = 10%, Low heterogeneity	–
4.	Rehn et al.[19]	18	484	Hedge's g = 0.79 (95% CI = 0.43–1.15), p < .001	I^2 = 71.32%, p < 0.001, High heterogeneity	–
5.	Liang et al.[20]	22	698	Not reported	I^2 = 73.5%, High heterogeneity	–
6.	Perera et al.[21]	26	781	Hedge's g = 0.64 (95% CI = 0.39–0.89), p < 0.0001	I^2 = 62.06%, Q = 64.52, p < .0001, High heterogeneity	Hedge's g = 0.49, (95% CI = 0.32–0.66), p < 0.0001
7.	Fitzsimmons et al.[22]	21	662	Hedge's g = 0.502 (95% CI = 0.708–0.296)	I^2 = 35.03%, p = 0.048, Moderate heterogeneity	–
8.	Pellegrini et al.[23]	23	639	Hedge's g = 0.47 (95% CI = 0.27–0.67), p < 0.001	I^2 = 39.8%, Moderate heterogeneity	Hedge's g = 0.29 (95% CI = 0.0–0.51)
9.	Gao et al.[24]	14	376	SMD = 0.72 (95% CI = 0.37–1.06), p < 0.0001	I^2 = 58%, High heterogeneity	–
10.	Hyde et al.[25]	27*	760	SMD = 0.66 (95% CI = 0.41–0.91), p < 0.001	Q = 72.18 I^2 = 65%, High heterogeneity	SMD = 0.65 (95% CI = 0.36–0.95
11.	Suhas et al.[26]	2 (deep TMS) 13 (rTMS)	65 174	SMD = 2.15 (95% CI = 1.85–2.45) SMD = 0.37 (95% CI = 0.33–0.40)	I^2 = 98.7%, High heterogeneity I^2 = 94%, High heterogeneity	–
12.	Thatikonda et al.[27]	20	668	Hedge's g = 0.43 (95% CI = 0.20–0.65), p < 0.001	Q = 40.14, I^2 = 52.7%, High heterogeneity	Hedge's g = 0.54 (95% CI = 0.18–0.89)

Abbreviations: I^2, I^2 Index; Q, Cochrane's Q Statistic; SMD, standardized mean difference; WMD, weighted mean difference.

distinct neural substrates. However, only a few RCTs included in the meta-analyses clearly state the subtype of OCD symptoms; (2) The degree of resistance to SSRIs: According to Pellegrini et al.,[23] patients with stage 1 or 2 of SSRI resistance tend to have better responses to TMS, while the effect is not significant in patients with stage 3 or 4 of SSRI resistance; (3) Frequency of the stimulus: Low-frequency (= < 1 Hz) is considered to be inhibitory, and high frequency (> = 5 Hz) is considered to be excitatory. However, different RCTs use different frequency ranges (e.g., 10 Hz, 20 Hz, or stimulation synchronized with alpha wave activity); (4) Number of TMS pulses per session: the amount of TMS pulses administered in each session varies among studies; (5) Total number of TMS sessions delivered in total (summation of total number of pulses delivered in all sessions); (6) Application of symptom provocation: Not all RCTs applied this method as Carmi et al.[28,31] in the deep TMS, HF, for mPFC/ACC; (7) Timing of assessment; and (8) Comorbid depressive symptoms at baseline: the presence of comorbid depressive symptoms can impact the outcomes.

Our study has limitations that should be acknowledged. First, the search for articles was conducted only in the PubMed database, and only meta-analyses in English were included. This decision was made considering that most of the meta-analyses are published in English and indexed in PubMed. Second, since the meta-analysis included RCTs with significant heterogeneity and publication bias, including researcher allegiance, caution should be taken when interpreting the results.

The findings of our systematic review, which encompassed 12 meta-analyses evaluating the effects of rTMS stimulation of different prefrontal regions and various paradigms of stimulations in OCD patients, revealed that both low- and high-frequency rTMS to be effective. In contrast, TBS, either continuous or intermittent, was found to be ineffective. Bilateral and right DLPFC, and mPFC/ACC are the most effective areas to be stimulated in the TMS treatment of OCD. However, the left DLPFC, SMA, and OFC stimulation results are heterogeneous. Moreover, TMS in OCD patients with low SSRI resistance (stage 1 or 2), in other words, in the early stages of the course of the illness, is more effective than in patients with more resistance to SSRI (stage 3 or 4). According to Pelligrini et al.,[23] the use of TMS in OCD patients with less resistance should be considered in future guidelines for TMS in OCD treatment. Deep TMS is another emerging modality, found to have superiority over the conventional TMS modalities; however, the number of studies using deep TMS is less. More research using deep TMS in OCD may give better insight into its efficacy in the management of OCD.

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Table 4. Risk of Bias Assessed in Meta-Analyses

	References	Methods used for bias assessment	Publication bias assessed (Yes/No) [method used]	Selection bias assessed (Yes/No)	Performance bias assessed (Yes/No)	Reporting bias assessed (Yes/No)	Randomization bias assessed (Yes/No)	Other biases assessed
1.	Berlim et al.[16]	Not reported	Yes [Egger's Regression, Trim and Fill procedure, Funnel plot, Fail safe N]	Not reported	Not reported	Not reported	Not reported	No
2.	Trevizol et al.[17]	Not reported	Yes [Funnel Plot]	Not reported	Not reported	Not reported	Not reported	No
3.	Zhou et al.[18]	Cochrane handbook 5.1.0	Yes [Egger's Regression, Funnel plot]	Yes	Not reported	Yes	Yes	No
4.	Rehn et al.[19]	Not reported	Yes [Egger's Regression, Trim and Fill procedure]	Not reported	Not reported	Not reported	Not reported	No
5.	Liang et al.[20]	Cochrane risk of bias tool, Bias assessment tool by Chaimani et al.	Yes [Funnel plot]	Yes	Yes	Yes	Not reported	Detection bias, Attrition bias
6.	Perera et al.[21]	Not reported	Yes [Egger's Regression, Funnel plot	Not reported	Not reported	Not reported	Not reported	No
7.	Fitzsimmons et al.[22]	Cochrane risk of bias tool	Yes [Egger's Regression, Funnel Plot]	Not reported	Not reported	Not reported	Not reported	No
8.	Pellegrini et al.[23]	Not reported	Yes [Egger's Regression, Trim and Fill, Funnel plot]	Not reported	Not reported	Not reported	Not reported	Allegiance bias
9.	Gao et al.[24]	Cochrane handbook 5.1.0	Yes [Egger's Regression, Funnel plot]	Yes	Yes	Yes	Not reported	Detection bias, attrition bias
10.	Hyde et al.[25]	Cochrane risk-of-bias tool	Yes [Egger's Regression, Funnel plot]	Not reported	Not reported	Not reported	Not reported	Missing data
11.	Suhas et al.[26]	Not reported	Yes [Funnel plot]	Yes	Not reported	Not reported	Not reported	No
12.	Thatikonda et al.[27]	Cochrane risk-of-bias tool	Yes [Egger's Regression, Funnel plot]	Not reported	Not reported	Not reported	Yes	Missing data

Conclusion

This systematic review provides insights into the positive and negative aspects of the existing evidence on the effectiveness of rTMS in OCD. These findings can guide clinicians in their decision-making process when considering the use of rTMS in OCD, as well as assist researchers in planning future studies. The intensity of OCD symptoms, such as obsessional thoughts, compulsive behaviors, and anxiety, is significantly decreased by rTMS treatment that targets the DLPFC and SMA. However, there is significant heterogeneity in the trial results, leading to varying conclusions regarding the efficacy of rTMS for OCD. This heterogeneity can be attributed to differences in study design, patient characteristics, rTMS parameters, outcome measures, and timing across studies. Consequently, it is difficult to draw definitive conclusions about rTMS effectiveness. To determine the ideal parameters and identify predictors of response to rTMS in OCD, further research is warranted, especially large-scale randomized controlled trials with standardized techniques. While existing research suggests that rTMS can reliably alleviate OCD symptoms, additional research is needed to determine the best procedures and variables affecting therapy response in OCD sufferers.

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