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Review article

Repetitive transcranial magnetic stimulation for obsessive-compulsive disorder: A systematic review and pairwise/network meta-analysis

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ABSTRACT

Background We evaluated the efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) for obsessive-compulsive disorder (OCD), and ranked the relative efficacy of different stimulation protocols.

Methods We performed a search for randomised, sham-controlled trials of rTMS for OCD. The primary analysis included both a pairwise meta-analysis and a series of frequentist network meta-analyses (NMA) of OCD symptom severity. Secondary analyses were carried out on relevant clinical factors and safety.

Results 21 studies involving 662 patients were included. The pairwise meta-analysis showed that rTMS for OCD is efficacious across all protocols (Hedges' g=-0.502 [95%CI= -0.708, -0.296]). The first NMA, with stimulation protocols clustered only by anatomical location, showed that both dorsolateral prefrontal cortex (dlPFC) stimulation and medial frontal cortex stimulation were efficacious. In the second NMA, considering each unique combination of frequency and location separately, low frequency (LF) pre-supplementary motor area (preSMA) stimulation, high frequency (HF) bilateral dlPFC stimulation, and LF right dlPFC stimulation were all efficacious . LF right dlPFC was ranked highest in terms of efficacy, although the corresponding confidence intervals overlapped with the other two protocols.

Limitations Evidence base included mostly small studies, with only a few studies using similar protocols, giving a sparse network. Studies were heterogeneous, and a risk of publication bias was found.

Conclusions rTMS for OCD was efficacious compared with sham stimulation. LF right dlPFC, HF bilateral dlPFC and LF preSMA stimulation were all efficacious protocols with significant and comparable clinical improvements. Future studies should further investigate the relative merits of these three protocols.

Abbreviations: HF, high frequency; LF, low frequency; *r*, right; *l*, left; dlPFC, dorsolateral prefrontal cortex; preSMA, pre supplementary motor area; OFC, orbitofrontal cortex; mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; SMD, standardised mean difference (Hedges' g); OCD, Obsessive-compulsive disorder; rTMS, repetitive transcranial magnetic stimulation; iTBS, intermittent theta burst stimulation; cTBS, continuous theta burst stimulation; YBOCS, Yale-Brown Obsessive Compulsive Scale; CGI-S, Clinical Global Impression - Severity.

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1. Introduction

Obsessive-compulsive disorder (OCD) is a psychiatric disorder characterised by obsessions (intrusive, anxiety-inducing thoughts) and compulsions (repetitive actions or thoughts) (Foa et al., 1995; Shavitt et al., 2014). It has a lifetime prevalence of 2–3% (Ruscio et al., 2010) and causes significant disability and impairment of quality of life (Stein et al., 2019; Subramaniam et al., 2013). First-line treatments (psychotherapy, most commonly cognitive-behavioural therapy or exposure and response prevention; and pharmacotherapy, most commonly serotonergic reuptake inhibitors) are only fully effective in ~50% of patients (Hirschtritt et al., 2017). Highly treatment-resistant patients have the option to undergo deep brain stimulation; however, this is an extremely invasive procedure with potentially serious risks and side effects (Tastevin et al., 2019). There is a clear need for alternatives to expand this limited range of options for OCD patients who do not respond to first-line treatment.

Repetitive transcranial magnetic stimulation (rTMS) could be such an alternative treatment option. Repetitive TMS is a form of non-invasive brain stimulation that uses trains of magnetic pulses to focally stimulate specific brain regions (Rossi et al., 2009). It has been used as an experimental tool and as a treatment for neurological and psychiatric disorders for the past 30 years (Lefaucheur et al., 2020). Repetitive TMS has been officially recognised and established as a clinically effective treatment for treatment-resistant depression (specifically high frequency (HF) rTMS of the left dorsolateral prefrontal cortex (dlPFC) or low frequency (LF) rTMS of the right dlPFC) (Brunoni et al., 2017), and it is now part of nationally approved and reimbursed treatment regimens in an increasing number of countries.

Repetitive TMS has also been investigated as a potential treatment for OCD for around 20 years. Different stimulation targets have been explored, mainly the pre-supplementary motor area (preSMA) (Arumugham et al., 2018; Gomes et al., 2012; Harika-Germaneau et al., 2019; Mantovani et al., 2010; Pelissolo et al., 2016; Zhang et al., 2019) and the dlPFC(Alonso et al., 2001; Badawy et al., 2010; Elbeh et al., 2016; Haghighi et al., 2015; Jahangard et al., 2016; Mansur et al., 2011; Shayganfard et al., 2016), using both HF and LF protocols. In the last decade deep rTMS (a form of rTMS that is able to target deeper brain structures such as the anterior cingulate cortex (ACC) using specially modified TMS coils) has been developed (Carmi et al., 2018, 2019; McCathern et al., 2020). Despite several systematic reviews and meta-analyses on this subject (Rehn et al., 2018; Zhou et al., 2017), no consensus has been established on which of the many tested protocols (i.e. target site/stimulation frequency combination) is the most efficacious for OCD treatment. The recent publication of several new studies (including the aforementioned deep rTMS studies) warrants the performance of an updated meta-analysis.

Two meta-analyses (Liang et al., 2021; Perera et al., 2021) have recently examined the contribution of frequency and location to the efficacy of rTMS for OCD, coming to two different conclusions. One meta-analysis concluded that bilateral dlPFC stimulation is the superior treatment option, with comparable effects for HF and LF stimulation (Perera et al., 2021); whereas the other concluded that low frequency dlPFC stimulation is the best treatment option, with no hemisphere specified (Liang et al., 2021). This difference in interpretation could be because both studies decided not to separate and distinguish between unique combinations of frequency and location. Classically, HF rTMS and intermittent theta burst stimulation (iTBS) are thought to increase cortical excitability, while LF rTMS and continuous theta burst stimulation (cTBS) are thought to cause inhibition of the underlying brain tissue (Rossi et al., 2009). In the context of the treatment of depression, stimulation of left versus right dlPFC with HF versus LF rTMS can have different treatment effects (Brunoni et al., 2017). This indicates that frequency and location have an important and independent influence on the rTMS efficacy, and should therefore be considered separately when evaluating and comparing different protocols.

In this systematic review with pairwise and network meta-analyses of rTMS for OCD, we evaluated the efficacy and safety of rTMS treatment compared with sham for adults with OCD, with a clinically informed focus on the relative efficacy of the unique combinations of frequency and location across the different rTMS protocols.

2. Materials & methods

The protocol for this study was pre-registered in the PROSPERO register (PROSPERO ID number: CRD42020207389) on 2 September 2020. This report was written according to the PRISMA 2020 statement; (PRISMA checklist is reported in Supplementary Table 1).

2.1. Search strategy

We searched the PubMed, EMBASE, APA PsycInfo, Web of Science, and Cochrane Central databases from inception up until 1 February 2021. We used the following search blocks, translated into the appropriate search terms for each database: ("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") (full search strategy per database is reported in Supplementary Table 2).

2.2. Eligibility criteria

We included published, peer-reviewed, randomised controlled trials enrolling patients with a primary diagnosis of OCD as diagnosed by a clinician or using a structured interview. All trials using any form of rTMS intervention (rTMS, iTBS, cTBS, deep rTMS and individual alpha rTMS) with at least 5 treatment sessions were included, with or without adjuvant/add-on treatment. Studies had to include a control or placebo group using any form of sham rTMS (i.e. sham coil, tilted coil, or deactivated coil); or comparison of active forms of rTMS. Primary outcome measure was post-treatment OCD severity. Exclusion criteria were conference abstracts, non-randomised study designs, OCD not as primary diagnosis, trials performing fewer than 5 treatment sessions or using a non-repetitive form of TMS such as single or double pulse TMS, or absence of an rTMS control group (such as waiting list or treatment as usual).

2.3. Study selection, data extraction, and outcome measures

Abstracts and full text articles were screened against inclusion/exclusion criteria using Rayyan (https://rayyan.qcri.org/) by two independent researchers (SF and OvdH). Any discrepancies were resolved in discussion. Data extraction was carried out using a structured Excel sheet by SF and checked by an independent researcher (KB, see acknowledgements). We extracted the following data from each study, where available, for assessment of: (A)treatment effect: Yale-Brown Obsessive-Compulsive Scale (YBOCS), response rates, other symptom scales (depression, anxiety, Clinical Global Impression - Severity (CGI-S)) (B) acceptability and safety: dropout rates, descriptions of side effects, (C) potential effect modifiers: age and sex of participants; treatment resistant or not; frequency and intensity of stimulation; coil type; number of pulses of rTMS (per session and total); number of sessions (per week and total); baseline motor threshold, stimulation location; method of identification of stimulation location; adjunctive therapy (medication or psychotherapy); symptom severity at baseline; type of sham condition. In cases where means and standard deviations were not available, we calculated these from the available data, following guidance in the Cochrane Handbook (Higgins et al., 2019b). Standard deviations that could not be calculated from the available data were imputed from the other studies in the meta-analysis according to Furukawa et al. (2006). When the primary outcome measure was not

adequately reported, we contacted the study authors with a request for the missing information. If we received no response, missing values were extracted from a recent meta-analysis when available (Zhou et al., 2017), or the study was excluded from the meta-analysis part of the review. We checked in each study whether the active and sham groups had balanced YBOCS scores at baseline to avoid biased treatment effect estimates (Fu and Holmer, 2016); we excluded studies with unbalanced YBOCS scores at baseline, unless summary statistics of an ANCOVA controlling for baseline differences were available, as recommended by Riley et al. (2013).

2.4. Risk of bias assessment

Individual risk of bias was assessed for each paper using a modified version of the Cochrane Risk of Bias tool (Brunoni et al., 2017; Sterne et al., 2019) by 2 independent researchers (SF, KB), and any discrepancies were resolved through discussion. We assessed risk of bias across groups of studies using the GRADE criteria (Guyatt et al., 2008). We also produced a comparison-adjusted funnel plot and ran Egger's Test to check for publication bias.

2.5. Data synthesis and analyses

2.5.1. Pairwise meta analyses

Conventional pairwise meta-analyses were carried out using Metafor for R (Viechtbauer, 2010). For our primary analysis, we performed pairwise meta-analyses using a random effects model to estimate the effect of active rTMS vs sham rTMS on the mean YBOCS directly post-treatment, expressing effect as Hedges' g (for all studies reporting mean and SD of YBOCS directly post-treatment). We decided to use the post-treatment score rather than change from baseline because this was the most frequently fully reported measure across all papers (standard deviation of change from baseline was only reported by 10/21 studies, and while it is possible to calculate SD from other metrics such as standard errors and confidence intervals (Higgins et al., 2019b) these were also frequently not reported). In the meta-analysis literature it is assumed that a comparison of post-intervention measurements will estimate the same quantity as a comparison of changes from baseline, as long as groups are balanced at baseline; according to the Cochrane Handbook (Deeks et al., 2019) "the difference in mean post-intervention values will on average be the same as the difference in mean change scores." According to one study, this approach may even confer an advantage over the use of pre-post change scores by avoiding possible inflation of effect size and providing a more conservative estimate of effect (Fu and Holmer, 2016). For crossover trials, we only considered the period before crossover. For studies with more than one type of rTMS, compared against sham, we split the sample size of the sham group as recommended in the Cochrane Handbook (Higgins et al., 2019a). One study (Badawy et al., 2010) had two active treatment groups (one medicated, one unmedicated), but only an unmedicated sham group – we excluded the medicated group from our analyses to allow a valid comparison between active and sham groups. We also carried out the following subgroup analyses of our pairwise meta-analysis: (1) studies with and without adjunctive psychotherapy; (2) studies with and without treatment resistant patients, and (3) type of sham coil. We also carried out a meta-regression to examine the effect of the number of sessions on rTMS efficacy. We carried out the following secondary analyses as random-effects pairwise meta-analyses: comparison of dropout rates between active and sham groups as a proxy for treatment acceptability; comparison of post-treatment depression scores between active and sham groups; and comparison of post-treatment CGI-S scores. Fewer than 10 studies reported follow-up YBOCS scores more than 2 weeks after the end of treatment, so a planned secondary meta-analysis of long term effect of rTMS was abandoned.

2.5.2. Network meta-analysis

In order to further explore our primary outcome (efficacy of rTMS for OCD as measured by post-treatment YBOCS), we carried out a series of frequentist random-effects network meta-analyses using the netmeta package in R (Rücker et al., 2020). We first broadly clustered the studies into three groups based only on anatomical stimulation target area: medial frontal cortex (including the preSMA and medial prefrontal cortex (mPFC)/ACC); dorsolateral prefrontal cortex (comprising bilateral, left and right dlPFC stimulation); and orbitofrontal cortex (left and right stimulation). We then carried out a more fine-grained grouping based on unique combinations of stimulation frequency and precise anatomical location (stimulation protocols). In both cases, the network meta-analysis allowed us to compare the different types of TMS with each other indirectly and to retrieve a ranking of treatment effect for both YBOCS and CGI-S scores. We used the results of the network meta-analysis to rank the different anatomical clusters and stimulation protocols according to size of treatment effect compared with sham, depicting the ranks on a forest plot to check for overlap in confidence intervals and significant treatment effect compared with sham.

Heterogeneity of the network was assessed using the I^2 statistic. Within- and between-network inconsistency was evaluated using the Q statistic. A net-splitting approach was used to evaluate inconsistency in the estimates of individual comparisons in the network.

2.5.3. Side effects

Since side effects were not systematically reported across the collected articles, these are reported in a qualitative summary.

3. Results

3.1. Characteristics of included studies

Of 1688 references found in our search, 21 full text articles were included in this review (Arumugham et al., 2018; Badawy et al., 2010; Carmi et al., 2018, 2019; Elbeh et al., 2016; Gomes et al., 2012; Haghighi et al., 2015; Harika-Germaneau et al., 2019; Hawken et al., 2016; Jahangard et al., 2016; Kang et al., 2009; Ma et al., 2014; Mansur et al., 2011; Mantovani et al., 2010; Nauczyciel et al., 2014; Pelissolo et al., 2016; Ruffini et al., 2009; Sachdev et al., 2007; Seo et al., 2016; Shayganfard et al., 2016; Zhang et al., 2019) (Fig. 1; Supplementary Table 3 for full details). We excluded two studies (Alonso et al., 2001; Naro et al., 2019) for which we could not obtain the primary outcome measure (YBOCS directly post-treatment) via the techniques listed in *Materials and Methods*; and one study which had unbalanced YBOCS scores between the active and sham groups at baseline (Prasko et al., 2006; Fu and Holmer, 2016; Riley et al., 2013).

The 21 included studies treated a total of 368 patients with active rTMS and 294 with sham rTMS (Table 1). Most trials (18/21) recruited only treatment-resistant patients (who had failed first line treatment with medication and/ or psychotherapy), continued medication throughout the rTMS treatment (20/21), and performed a minimum of 10 rTMS sessions over 2 weeks (Table 1; Supplementary Table 3). Eleven different stimulation protocols (combinations of stimulation location and stimulation frequency) were investigated across the 21 studies (Table 1).

3.2. Primary outcome: meta-analysis of YBOCS following rTMS

3.2.1. Pairwise meta-analysis

For post-treatment YBOCS, Hedges' g=−0.502 [95%CI=−0.708, −0.296] (Fig. 2), indicating a significantly greater improvement in YBOCS following active rTMS than following sham rTMS. Clinically, this translates to four points more decrease in the YBOCS severity score when using rTMS compared with sham rTMS (assuming that the standard deviation of the YBOCS severity score in the clinical population equals 8). Heterogeneity was moderate (Q(df=22)=34.104, I^2=35.03%, p =

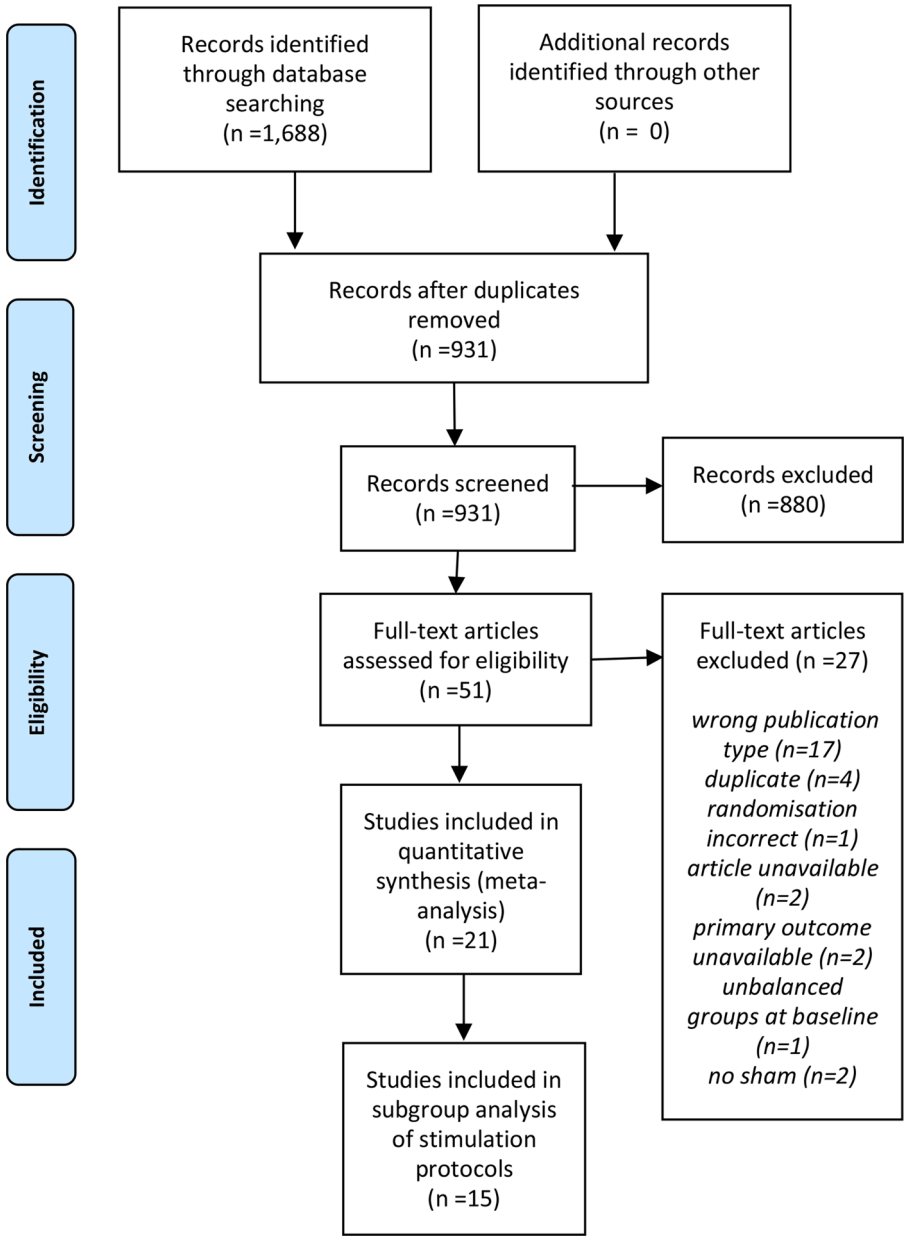


Fig. 1. PRISMA diagram describing search and screening results.

0.048).

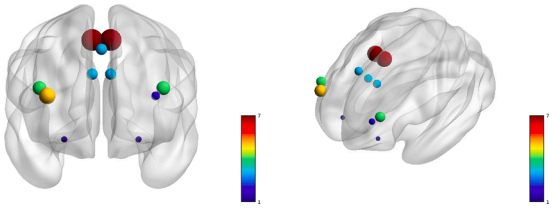
3.2.2. Network meta-analyses

We first divided all studies into three groups based only on anatomical target region: medial frontal cortex (including the preSMA and mPFC/ACC stimulation sites); dorsolateral prefrontal cortex (comprising bilateral, left and right dlPFC stimulation); and orbitofrontal cortex (left and right stimulation) (Table 1). One study (Kang et al., 2009) had to be excluded from this analysis as it stimulated both dlPFC and SMA. A network analysis (Fig. 3A) using this brain region grouping revealed that dlPFC and medial frontal cortex stimulation are significantly more efficacious than sham, whereas OFC stimulation is not (Fig. 3B). Global heterogeneity in the network was low (I^2= 38.1%). Within-design heterogeneity (heterogeneity between studies that were in the same anatomical cluster) was significant (Q(df=19)=30.71, p = 0.04).

While this anatomical grouping confirms what has been shown by previous meta-analyses (i.e. that preSMA and dlPFC are both promising stimulation locations for OCD (Liang et al., 2021; Perera et al., 2021)), it does not answer practical questions such as which stimulation frequency and precise location would be the optimal choice for rTMS treatment of OCD. The heterogeneity within these broad anatomical clusters was also relatively high, possibly due to the combination of multiple brain regions and stimulation frequencies within clusters. We therefore carried out a second network meta-analysis in which we divided anatomical area protocols into subgroupings defined by precise anatomical location and stimulation frequency (Fig. 4A). Results of comparisons between all pairs of protocols can be seen in Supplementary Table 4 – demonstrating that LF right dlPFC stimulation, HF bilateral dlPFC stimulation, and LF preSMA stimulation are all significantly efficacious compared with sham stimulation. Examination of the ranked forest plot (Fig. 4B), and the comparisons shown in Supplementary Table 4, further revealed that these three efficacious stimulation protocols have overlapping confidence intervals, indicating that there no significant difference in clinical efficacy between them. Global heterogeneity in the network was low (I^2= 35.1%), as was network inconsistency (Q(df=3)= 1.71, p = 0.64).

Table 1
Summary of study characteristics for the 21 studies in this review.

	Active	Sham
Total participants in this review	368	294
Sample size per study (mean± SD)	15.33 ± 8.70	14.00 ± 9.17
Age (mean ± SD)	33.52 ± 5.74	35.37 ± 5.46
Total treatment sessions per study (mode, range)		10, 10–30
Weeks of treatment per study (mode, range)		2, 1–6
Studies including only treatment resistant patients		18 (86%) of 21 studies
Baseline YBOCS of all participants (mean, SD)		29.55 ± 3.07
Baseline CGI of all participants (mean, SD)		5.27 ± 0.43
Number of studies per stimulation protocol, clustered by anatomical region (location, frequency)		



dlPFC cluster	r dlPFC and preSMA, LF	1
	bilateral dlPFC, HF	4
	R dlPFC, HF	2
	R dlPFC, LF	2
	L dlPFC, HF	2
Medial frontal cluster	bilateral preSMA, cTBS	1
	bilateral preSMA, LF	6
	mPFC and ACC (dTMS), LF	1
	mPFC and ACC (dTMS), HF	2
OFC cluster	R OFC, LF	1
	L OFC, LF	1

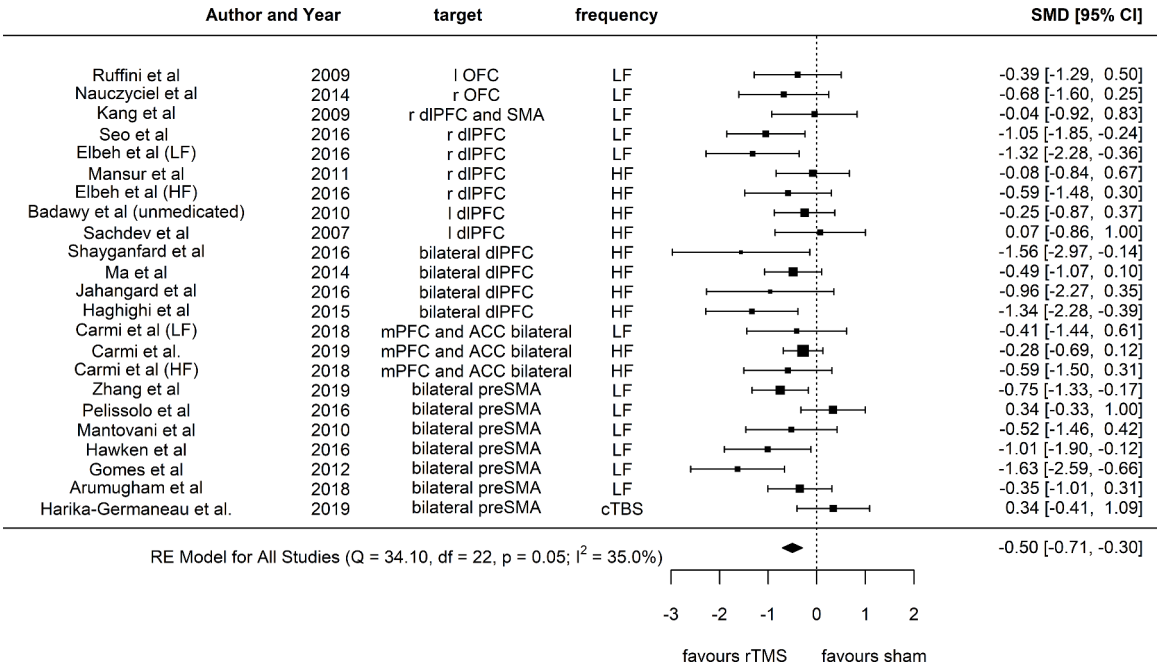


Fig. 2. Pairwise meta-analysis forest plot: Random effects meta-analysis of YBOCS following rTMS for OCD for active vs sham rTMS. SMD=standardised mean difference (Hedges' g). HF= high frequency, LF= low frequency, *l*=left, *r*=right, dlPFC = dorsolateral prefrontal cortex; preSMA = pre-supplementary motor area; OFC = orbitofrontal cortex, mPFC = medial prefrontal cortex; ACC = anterior cingulate cortex, SMD=standardised mean difference (Hedges' g).

Within-design heterogeneity (heterogeneity between studies that performed the same protocol) was non-significant (Q(df=9)= 16.77, p = 0.052). Net-splitting revealed no inconsistencies between direct and indirect estimates of effect in our network (all $p > 0.400$).

3.2.3. *Clinical moderators of improvement in OCD symptoms*

The effect of adjunctive psychotherapy, treatment resistance, type of sham stimulation and number of sessions on rTMS outcome was examined using subgroup analyses and meta-regression of the initial pairwise meta-analysis (Supplementary Table 5). No differences in rTMS effect were found with adjunctive psychotherapy, treatment resistant vs non-treatment resistant patients, or with type of sham coil. A lower number of rTMS sessions correlated with a greater treatment effect, but this did not survive correction for multiple comparisons (p = 0.025, corrected α=0.0125).

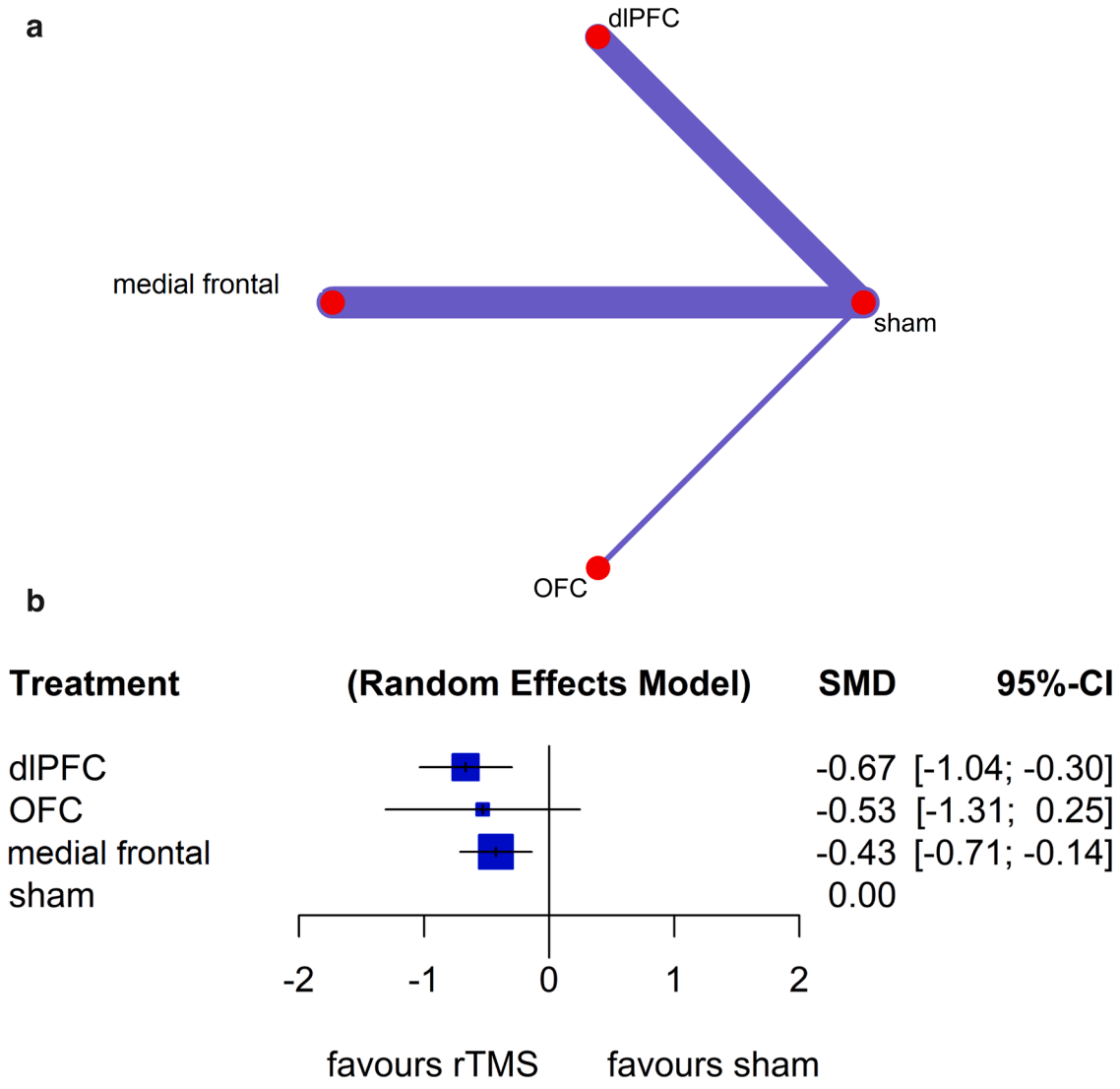


Fig. 3. (A) Network diagram for network meta-analysis of anatomically defined stimulation locations. Each line in the diagram represents a direct comparison between the two stimulation types. The thickness of the line is proportional to the number of studies providing data for that comparison. (B) Ranking plot for network meta-analysis of anatomically defined stimulation locations compard to sham group. The size of the blue square represents the weight (larger squares = larger sample size, lower variance) per protocol. SMD = standardised mean difference (Hedges' g). dlPFC = dorsolateral prefrontal cortex. OFC = orbitofrontal cortex.

3.3. Secondary outcomes

3.3.1. Safety: dropout rates

For the studies which clearly reported dropout rates (all but (Seo et al., 2016) and (Carmi et al., 2018)), these were examined using a pairwise meta-analysis across the whole group of studies as a possible indicator of treatment acceptability. There was no difference between dropout rates for active vs sham rTMS (OR=0.906, [95%-CI=0.452, 1.815].

3.3.2. Safety: summary of side effects

Twelve studies reported side effects of rTMS for OCD. Side effects were not reported consistently across studies, so no quantitative synthesis could be made. Reported side effects included the following: Headache, sedation, concentration difficulties, scalp pain, weakness, fatigue, mood swings, memory impairment, dizziness, fainting, facial nerve stimulation. No studies reported serious adverse events.

3.3.3. Depression score: pairwise meta-analysis

For depression severity, as measured by the Hamilton Depression Rating Scale and the Montgomery Åsberg Depression Rating Scale, Hedges' g=−0.21 [95%CI=−0.40, −0.02] (Supplementary Fig. 1), indicating a small but statistically significant improvement in comorbid depression symptoms following active rTMS compared with sham rTMS. Heterogeneity was low (Q(df =12) = 10.31, I^2=0.00%, p = 0.59). Due to relatively few studies reporting depression symptom scores (1–2 studies per protocol type), we did not carry out a subgroup or network meta-analysis for this outcome.

3.3.4. CGI-S scores: pairwise and network meta-analysis

For symptom severity as measured by the CGI-S, the pairwise meta-analysis showed that Hedges' g=−0.86 [95%CI=−1.36, −0.35] (Supplementary Fig. 2A), indicating a large and significant improvement in CGI-S following active rTMS compared with sham rTMS. Heterogeneity was high (Q(df =14) = 58.34, I^2=80.4%, p=< 0.0001) due to one small outlying study (Gomes et al., 2012). Results of the network meta-analysis (Supplementary Fig. 2B) mirrored those of the YBOCS network meta-analysis, with bilateral dlPFC HF stimulation (Hedges' g=−1.52 [95% CI=−2.38, −0.65]) and LF preSMA stimulation (Hedges' g=−0.83 [95% CI=−1.55, −0.11]) giving a significantly greater improvement in CGI-S than sham, and LF R dlPFC stimulation approaching significance (Hedges' g=−1.02 [95% CI=−2.07, 0.02]).

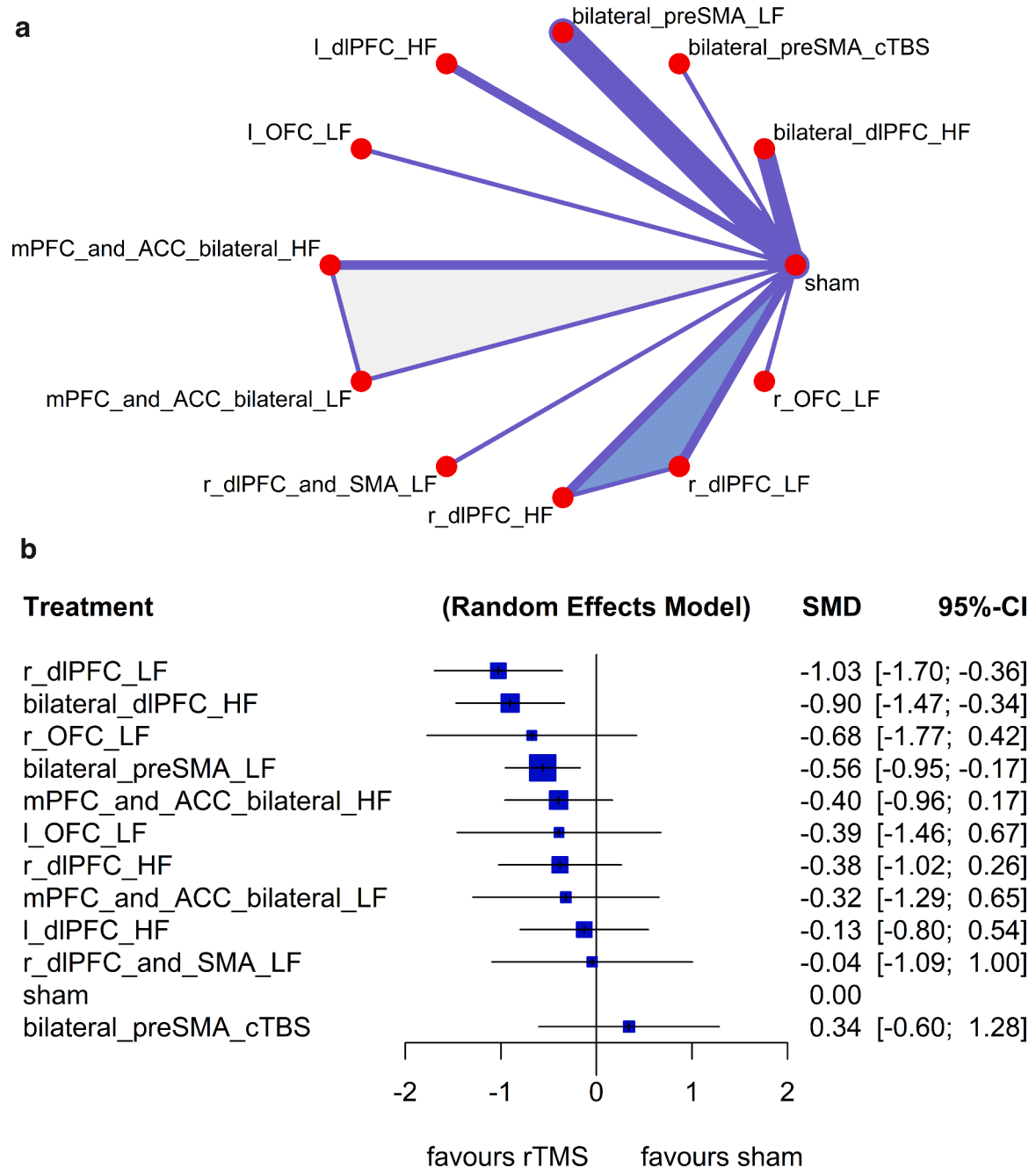


Fig. 4. (A) Network diagram for network meta-analysis of unique treatment protocols (stimulation target/frequency combinations). Each line in the diagram represents a direct comparison between the two stimulation types. The thickness of the line is proportional to the number of studies providing data for that comparison. (B) Ranking plot for random-effects network meta-analysis for all stimulation protocols in comparison to sham group. The size of the blue square represents the weight (larger squares = larger sample size, lower variance) per protocol. HF= high frequency, LF= low frequency, *l*=left, *r*=right, dlPFC = dorsolateral prefrontal cortex; preSMA = pre supplementary motor area; OFC = orbitofrontal cortex, mPFC = medial prefrontal cortex; ACC = anterior cingulate cortex, SMD=standardised mean difference (Hedges' g).

3.4. Risk of bias – individual and across studies

While Egger's test for publication bias was borderline non-significant, ($p = 0.059$), the comparison-adjusted funnel plot (Supplementary Fig. 3) for the primary outcome (post-treatment YBOCS) was asymmetrical, indicating a risk of publication bias (small studies that favour sham or no effect are less likely to be published).

In the risk of bias assessment for individual studies (Supplementary Table 6), 5/21 studies were rated as Low Risk, 12/21 as Uncertain Risk, and 4/21 as High Risk (due to incomplete outcome data). The result of the primary pairwise meta-analysis was unchanged after excluding the four High Risk studies in a sensitivity analysis(Hedges' $g = 0.546$ [95% CI=−0.793, −0.299]).

The results of the evaluation of the entire body of evidence and the stimulation protocols in the subgroup analysis using the GRADE criteria are reported in Table 2. The GRADE certainty rating for all studies is rated as Moderate, due to the presence of likely publication bias.

4. Discussion

This systematic review and meta-analyses aimed to evaluate the efficacy of rTMS OCD therapy, and compare and rank the various rTMS

Table 2
GRADE assessment of evidence for the efficacy of rTMS for OCD: all studies and evaluated protocols with >1 study per protocol, primary outcome measure (YBOCS) only.

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rTMS	sham	SMD (95% CI)		
Change in YBOCS following rTMS: all studies											
21	randomised trials	not serious [a]	not serious	not serious	not serious	publication bias strongly suspected [b]	368	294	−0.50 (−0.71, −0.30)	⨁⨁⨁◯ MODERATE	IMPORTANT
bilateral dlPFC, HF											
3	randomised trials	not serious	not serious	not serious	serious [c]	none	20	21	−0.91 (−1.50, −0.33)	⨁⨁⨁◯ MODERATE	IMPORTANT
bilateral pre SMA, LF											
6	randomised trials	serious [d]	not serious	not serious	not serious	none	95	88	−0.57 (−0.97, −0.16)	⨁⨁⨁◯ MODERATE	IMPORTANT
mPFC/ACC, HF											
2	randomised trials	not serious	not serious	not serious	not serious	none	63	54	−0.40 (−0.99, 0.19)	⨁⨁⨁⨁ HIGH	IMPORTANT
rdlPFC, HF											
2	randomised trials	serious [d]	not serious	not serious	not serious	none	28	21.5	−0.38 (−1.05, 0.28)	⨁⨁⨁◯ MODERATE	IMPORTANT
rdlPFC, LF											
2	randomised trials	not serious	not serious	not serious	not serious	none	29	20.5	−1.03 (−1.72, −0.33)	⨁⨁⨁⨁ HIGH	IMPORTANT

CI: Confidence interval; **SMD:** Standardised mean difference.
Explanations.
a. only 4 studies of 21 are rated as high risk, due to lack of ITT analysis, and excluding these does not result in a change to the result of the main meta-analysis.
b. Publication bias likely - lack of smaller studies favouring sham.
c. very broad confidence intervals.
d. 1 study rated as High Risk due to non-ITT analysis.

stimulation targets and protocols currently discussed in the literature as promising rTMS treatment options for OCD. Based on a rather limited and heterogeneous evidence base (small sample size, inconsistency across studies with regard to precise frequency used), we found that rTMS is an efficacious treatment for OCD, giving on average a 4-point decrease in YBOCS compared with sham across 21 studies. The NMAs showed that dlPFC and medial frontal cortex stimulation were efficacious compared with sham, specifically the protocols HF bilateral dlPFC, LF bilateral preSMA, and LF right dlPFC rTMS. While LF right dlPFC rTMS was the highest ranked, the overlapping confidence intervals in the ranking indicated that all three protocols have a similar efficacy. The significant reductions in YBOCS with these protocols are also mirrored in the reductions of CGI-S scores, underlining the clinical meaningfulness of these results. The reported side effects and meta-analysis of dropout rates indicate that rTMS is safe, with only mild side effects being reported. Studies were generally of reasonable quality, with most receiving a Low or Unknown risk of bias score, and the GRADE rating was Moderate for rTMS as a whole and Moderate to High for the different stimulation protocols.

While several meta-analyses on rTMS and OCD have been published, our approach has several advantages over the most recent studies (Liang et al., 2021; Perera et al., 2021; Zhou et al., 2017). By using a network meta-analysis approach, we were able to (indirectly) compare and rank different stimulation protocols against each other, which is not possible in a conventional pairwise meta-analysis. A recent network meta-analysis used anatomical groupings without specifying the laterality of the stimulation sites, limiting the clinical utility of their study (Liang et al., 2021). In contrast, we use fine-grained groupings of specific stimulation locations and frequencies, allowing us to identify precisely the most efficacious stimulation location-frequency combinations for the treatment of OCD. Unlike other recent meta-analyses (Liang et al., 2021; Perera et al., 2021) we also investigate other clinical outcomes, finding improvement of both CGI scores and depression scores following rTMS treatment, further adding to the clinical relevance of our study. We use post-treatment YBOCS as our primary outcome, which avoids the inflation of effect size which may occur with the use of change-from-baseline scores (Fu and Holmer, 2016), as used in Liang et al. (2021) and Perera et al. (2021). Finally, we do not include a biased study with unbalanced groups at baseline (Prasko et al., 2006), which other recent meta-analyses do include (Liang et al., 2021; Perera et al., 2021).

Our findings are in agreement with previous systematic reviews and meta-analyses of rTMS for OCD that show efficacy for rTMS against sham (Berlim et al., 2013; Rehn et al., 2018; Trevizol et al., 2016; Zhou et al., 2017). Our effect size for the pairwise meta-analysis is somewhat lower than that found by other recent meta-analyses (Rehn et al., 2018; Zhou et al., 2017) – this could be due to a number of negative studies being published in the past two years, and also the fact that we were not able to find several Chinese-language studies included in Zhou et al. (2017) in our database searches. Our results also replicate findings reported in a recently published network meta-analysis on rTMS for OCD (Liang et al., 2021) (that LF dlPFC stimulation, HF DLFPC stimulation and LF preSMA stimulation are significantly more efficacious than sham stimulation), which used a Bayesian approach rather than a Frequentist

approach in their network meta-analysis, indicating that these findings are robust to alternative analysis methods. Notably, we do not find a significant effect of deep TMS to the mPFC/ACC in the two studies from Carmi et al. (2018), (2019), while a significant effect was reported in another review(Liang et al., 2021) and in the papers themselves. This may be due to the fact that we imputed the SDs for these studies; if the imputed SD is higher than the original, this can bias towards lack of effect (Higgins et al., 2019b).

There is a significant effect of rTMS protocol on post-treatment YBOCS compared with sham, equal to a reduction of approximately 4 points more on the YBOCS scale across all active protocols. The relative contributions of the different rTMS protocols should, however, be interpreted with caution due to small numbers of studies in each subgroup. LF right dlPFC rTMS was placed first when ranking all protocols in the NMA, but there are only two studies applying this protocol, with relatively wide confidence intervals. HF bilateral dlPFC stimulation is also efficacious compared with sham, but this is based on only three studies from the same research group with very wide confidence intervals and small sample sizes, all with unclear risk of bias. LF preSMA stimulation is the largest subgroup (six studies and 183 participants) with generally the best quality evidence (3/6 studies at low risk of bias), though with one study at high risk of bias. The highly overlapping confidence intervals of these three stimulation protocols also indicate that all three protocols may have clinical value on the group level. Possible solutions to this unclear relative efficacy would be to carry out larger clinical trials of these three highly ranked protocols in order to strengthen the evidence base for each protocol, and to carry out more direct comparisons of the different protocols in multi-arm clinical trials. Other relevant issues for the clinical application of rTMS for OCD that future studies should investigate include clarifying the added value of adjunctive CBT and medication, and identification of biomarkers to aid prediction of rTMS responders.

There are a number of limitations to this review. Primary outcome data were not available and could not be retrieved upon request for three studies (Alonso et al., 2001; Naro et al., 2019; Prasko et al., 2006), meaning that these had to be excluded from the meta-analysis. The primary pairwise meta-analysis indicated moderate heterogeneity, which can be explained by the heterogeneous methods and protocols used in rTMS studies (see also Supplementary Table 3). Repetitive TMS studies are notoriously variable in methodology. This review includes 12 different stimulation protocols, most of which are only investigated by one study; all but two of the studies (Harika-Germaneau et al., 2019; Pelissolo et al., 2016) use a head surface measurement or EEG cap-based technique to define the stimulation location as opposed to neuronavigation, meaning that it is not certain that the intended brain area is being stimulated, possibly leading to smaller apparent efficacy (Fitzgerald et al., 2009); and several studies use a tilted coil as a sham condition (as opposed to a realistic sham coil) which gives a poor placebo response and is known to increase the apparent efficacy of the active condition (Zhou et al., 2017). Since most of the studies only include treatment resistant patients, these findings are not necessarily generalizable to a population that includes non-treatment resistant patients (though our secondary analyses found no indication of different treatment effect in treatment resistant vs non treatment resistant patients). We also found a risk of publication bias, indicating a lack of publication of smaller negative studies. Finally, while our network meta-analysis included some closed loops, it was a fairly sparse network with few direct comparisons between active protocols, which may lead to spuriously wide confidence intervals (Brignardello-Petersen et al., 2019).

5. Conclusion

rTMS is efficacious compared with sham across three different rTMS protocols (HF bilateral dlPFC, LF preSMA, and LF right dlPFC) for the treatment of OCD. Given the comparable relative efficacy of these protocols, however, it is not possible to give a clear recommendation at this point for one stimulation type over the others – all three may have clinical value. Future trials should aim to standardise methods and investigate these three stimulation protocols with large multi-arm randomised clinical trials in order to homogenize the evidence base.

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CRediT authorship contribution statement

Sophie M.D.D. Fitzsimmons: Conceptualization, Formal analysis, Writing original draft. **Ysbrand D. van der Werf:** Conceptualization, Writing review & editing, Supervision. **A. Dilene van Campen:** Writing review & editing. **Martijn Arns:** Conceptualization, Writing review & editing. **Alexander T. Sack:** Conceptualization, Writing review & editing. **Adriaan W. Hoogendoorn:** Conceptualization, Formal analysis, Writing review & editing. **other members of the TETRO Consortium:** Writing review & editing. **Odile A. van den Heuvel:** Conceptualization, Writing review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors have no conflicts of interest to declare

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Supplementary materials

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