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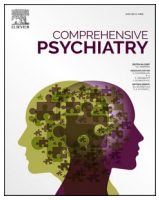

Repetitive transcranial magnetic stimulation (r-TMS) and selective serotonin reuptake inhibitor-resistance in obsessive-compulsive disorder: A meta-analysis and clinical implications

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ABSTRACT

Introduction: Despite promising results from several randomized controlled trials (RCTs) and meta-analyses, the efficacy of r-TMS as a treatment for OCD remains controversial, at least in part owing to inconsistency in the trial methodologies and heterogeneity in the trial outcomes. This meta-analysis attempts to explain some of this heterogeneity by comparing the efficacy of r-TMS in patients with or without resistance to treatment with selective serotonin reuptake inhibitors (SSRI), defined using standardized criteria.

Methods: We conducted a pre-registered (PROSPERO ID: 241381) systematic review and meta-analysis. English language articles reporting blinded RCTs were retrieved from searches using MEDLINE, PsycINFO, and Cochrane Library databases. Studies were subjected to subgroup analysis based on four stages of treatment resistance, defined using an adaptation of published criteria (1 = not treatment resistant, 2 = one SSRI trial failed, 3 = two SSRI trials failed, 4 = two SSRI trials failed plus one or more CBT trial failed). Meta-regression analyses investigated patient and methodological factors (age, duration of OCD, illness severity, stage of treatment-resistance, or researcher allegiance) as possible moderators of effect size.

Results: Twenty-five independent comparisons (23 studies) were included. Overall, r-TMS showed a medium-sized reduction of Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores (Hedge's *g*: -0.47; 95%CI: - 0.67 to −0.27) with moderate heterogeneity (I^2 = 39.8%). Assessment of publication bias using Trim and Fill analysis suggested a reduced effect size that remained significant (g: -0.29; 95%CI: −0.51 to −0.07). Subgroup analysis found that those studies including patients non-resistant to SSRI (stage 1) (g: -0.65; 95%CI: −1.05 to −0.25, k = 7) or with low SSRI-resistance (stage 2) (g:-0.47; 95%CI: −0.86 to −0.09, k = 6) produced statistically significant results with low heterogeneity, while studies including more highly resistant patients at stage 3 (g: −0.39; 95% CI: −0.90 to 0.11, k = 4) and stage 4 (g: -0.36; 95%CI: −0.75 to 0.03, k = 8) did not. Intriguingly, the only significant moderator of the effect size found by meta-regression was the severity of baseline depressive symptoms. All trials showed evidence of researcher allegiance in favour of the intervention and therefore caution is required in interpreting the reported effect sizes.

Conclusion: This meta-analysis shows that r-TMS is an effective treatment for OCD, but largely for those not resistant to SSRI or failing to respond to only one SSRI trial. As a consequence, r-TMS may be best implemented earlier in the care pathway. These findings would have major implications for clinical service development, but further well-powered RCTs, which eliminate bias from researcher allegiance, are needed before definitive conclusions can be drawn.

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1. Introduction

Obsessive Compulsive Disorder (OCD) represents a significant cause of mental health related morbidity [1]. Several evidence-based consensus statements and treatment guidelines recommend selective serotonin reuptake inhibitors (SSRIs) or cognitive behaviour therapy (CBT) with Exposure and Response Prevention (ERP) as first line treatments [2,7,70]; however, a significant minority of patients (roughly 40–60%) fail to achieve an adequate response even after accessing these strategies [1,50].

Research into alternative treatments using non-invasive brain stimulation techniques has focused on repetitive transcranial magnetic stimulation (r-TMS) targeting putative OCD-related dysfunctions in orbitofronto-striato-thalamic neuro-circuitry, including the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), supplementary motor area (SMA), orbitofrontal cortex (OFC), and medial prefrontal cortex [1,12,18]. r-TMS is thought to induce effects on cortical activity, with low frequency ($\leq$ 1 Hz) stimulation inducing inhibition and high frequency ($\geq$ 5 Hz) producing excitation [16]. Theta Burst Stimulation (TBS) is a relatively new and time efficient form of r-TMS which uses pulses of stimulation and thereby significantly reduces the total stimulation duration [15].

Several randomized controlled trials (RCTs) of r-TMS (including theta burst) in OCD have been performed. The results so far have been promising but inconsistent, probably related at least in part to the wide variety of stimulation protocols (e.g., target, laterality, frequency, duration and length of treatment) used. Thus, whereas low frequency (LF) or inhibitory r-TMS targeting the SMA produced a significant benefit in some RCTs [17–19], this protocol failed to show a significant effect in others [20–22]. RCTs targeting the OFC with LF r-TMS have yielded more consistently positive results [19,23]; however, the studies recruited small numbers of patients and therefore confidence in these findings is low. DLPFC stimulation yielded highly inconsistent results, with some studies [36–38,45] producing a large significant effect size which was not replicated in the remaining studies [22,40,42–44]. Studies of deep r-TMS, targeting the ACC [35] and delivered using a specific (H) coil in conjunction with behaviour therapy produced a significant effect resulting in US Food and Drug Administration (FDA) permitted marketing of the Brainsway Deep Transcranial Magnetic Stimulation System for the treatment of OCD [51].

Attempts have been made to achieve greater clarity about the relative efficacy of these different targets and protocols by pooling data and applying meta-analysis. There have been eight meta-analyses assessing the efficacy of r-TMS in OCD [29; 52; 27; 26; 53; 15; 54; 55] each demonstrating some utility of the procedure. Indeed, the pooled effect size for r-TMS has ranged from Hedge's $g = 0.45$ [27] to Hedge's $g = 0.79$ [53]. Earlier meta-analyses identified the OFC [29] as the most efficacious target, but, as studies accrued, later meta-analyses favored first the SMA [29; 26; 53] and then the bilateral DLPFC as the most effective target [15,54,55]. However, the high levels of heterogeneity in clinical outcomes seen across all the previous meta-analyses, most evident in the most recent analyses including the largest number of trials (I^2: 73.5% in Liang et al., 2021 [54]; I^2: 62% in Perera et al., 2021 [15]; I^2: 35.1% in Fitzsimmons et al., 2022 [55]), and thought to be associated with major differences in individual trial design and methodology, has continued to undermine confidence in the positive findings. As a result, r-TMS has not been universally adopted as an evidence-based treatment for OCD. For example, in the UK, the National Institute for Health and Care Excellence (NICE) recently commented that the "evidence on its efficacy is inadequate in quantity and quality" (https://www.nice.org.uk/guidance/ipg676).

Along with differences in stimulation parameters and targets, there have been marked between-trial differences in the characteristics of the patient participants. Variables such as age, gender, duration of illness, baseline symptoms severity, comorbidities have been subjected to meta-regression analyses [26; 27], but no significant moderating or mediating effect of these variables on study outcomes has been found.

Established clinical treatments for OCD are usually delivered according to a 'sequenced' approach, with SSRIs or CBT offered first, based on accepted levels of efficacy and tolerability, and other treatments such as combination treatments reserved for those who have not responded to these 'first line' interventions [1,56]. r-TMS is usually cited as an intervention for 'treatment-resistant OCD' [1,51]. Definitions have been proposed for different degrees of OCD-treatment resistance [57,58]. For example, failure to improve by 25% on the Yale Brown Obsessive-Compulsive Scale (Y-BOCS) [67] following treatment with at least two SSRIs given at maximally tolerated licensed doses for a minimum of 12 weeks has been proposed as a clinically meaningful threshold for SSRI-resistance, for application in treatment trials [59]. However, the resistance status of the participants as reported in the RCTs of r-TMS for OCD is extremely variable, with some studies even failing to report prior treatment status [41;48]. As the presence of SSRI-resistance could be expected to influence the effectiveness of forms of treatment other than SSRIs, such as r-TMS, there are grounds for investigating the effect of SSRI-resistance on r-TMS outcomes as another potential source of between-trial heterogeneity. Such an analysis may also fill the gap in evidence determining the optimal stage in the sequenced care pathway at which r-TMS should be offered.

Three meta-analyses have investigated the effect of treatment-resistance on r-TMS outcomes [26; 52; 54]. However, none of these meta-analyses provides an adequate definition for treatment resistant OCD and confidence in their findings is limited. Thus, whereas Zhong-Rui Ma & Li-Jun Shi, 2014 [52], reported that r-TMS was effective in 'SSRI-resistant' patients (odds ratio (OR) of 2.65 [95%CI: 1.36–5.17] for clinical response status), their meta-analysis included not only RCTs with a wide range of definitions for treatment resistance but also RCTs in which no definition of resistance was provided. Indeed, in this meta-analysis the heterogeneity of the effect size was exceptionally high (I^2 = 73%). In contrast, in Zhou et al., 2017 [26], a subgroup analysis of those studies including patients with treatment resistant OCD was performed, which produced a large effect size (g = 0.85, 95%CI: 0.5 to 1.2). However only two studies were included in the treatment-resistant subgroup and the resistance status of the subjects in these trials was not corroborated by any form of definition. In the third, more recent meta-analysis [54], a subgroup analysis for treatment resistance was again performed (although, no forest-plot was provided). Interestingly, the analysis of studies applying LF r-TMS to the DLPFC found that the intervention was significantly more effective than sham only in the treatment *non*-resistant subgroup. However, as in the previous meta-analyses, the authors appeared to take at 'face value' the OCD resistant status of the subjects and did not apply any form of standardized definition.

Thus, although several meta-analyses report positive effects for r-TMS in OCD, uncertainty remains both about its overall efficacy (https://www.nice.org.uk/guidance/ipg676) and about which patients are likely to benefit most. The current meta-analysis was therefore conducted to differentiate, for the first time, the effects of r-TMS in patients with SSRI-resistant and non-resistant OCD using standardized criteria, in order to better determine the place of r-TMS in the sequenced care-pathway for OCD. As the corpus of trials continues to grow, with four RCTs published since the latest moderator analyses were performed, we included a fresh analysis of candidate moderators including gender, age, duration of illness, baseline symptom severity, in an attempt to re-assess previous null findings [26,27].

Researcher allegiance bias represents a latent bias among trial lists in favour of the success of the investigational agent that may further undermine confidence in trial findings. Research allegiance bias can be detected by examining the way the published paper is written [33] and is known to significantly moderate clinical outcomes in OCD trials [49]. While most meta-analyses have carried out a risk of bias assessment of included studies, none so far have looked at the effect of researcher allegiance. Therefore, we additionally included an analysis of researcher

allegiance bias, which has not so far been investigated for r-TMS in OCD.

2. Methods

2.1. Design and search strategy

This systematic review and meta-analysis was pre-registered at the International Prospective Register of Systematic Reviews (PROSPERO ID 241381: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=241381).

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in conducting and reporting our findings [31]. Three databases were searched: Pubmed, Cochrane Library, and PsycINFO from the earliest publication until July 2021. The search keywords consisted of: ['obsessive compulsive disorder' OR 'OCD' or 'obsessions' OR 'compulsions'] AND ['transcranial magnetic stimulation' OR 'TMS']. The reference lists of retained articles was also scrutinized for additional relevant publications.

2.2. Study selection

Studies were eligible for inclusion if they: a) assessed participants meeting any ICD/DSM OCD diagnostic criteria b) included adolescents and/or adults; c) were randomized controlled trials employing a therapeutic intervention against sham TMS; and d) were written in English.

The first stage of the analysis focused on removing duplicate studies. Once this had been completed, researchers reviewed the title of the selected studies and excluded those that were ineligible. Next, the abstracts of the studies were assessed and based on their summary of contents, those that were inapplicable were excluded. Finally, the remaining studies were subject to a full text review.

The searches and extraction were conducted independently by three researchers (LP, KG, AE). In the occurrence of any disagreements, the reasons were discussed among the research team and a consensus formed.

2.3. Data extraction

Data from the RCTs meeting inclusion criteria were extracted and placed in a Microsoft Excel spreadsheet. The inputting of study data into tabulated spreadsheets was conducted by one researcher (LP) and was double-checked by two other researchers (AE, KG) before the data was cleaned. We decided to use as primary outcomes the following scale: Yale Brown Obsessive-Compulsive Scale (Y-BOCS). If the questionnaire was not available, the primary outcome measures of the specific studies were used.

Secondary measures, including measures of depression and anxiety symptoms were entered into a separate spreadsheet. Potential moderator variables such as: gender, mean age, duration of illness and treatment, as well as OCD scores at baseline for both intervention and control groups were also extracted.

The data was cleaned using Data Extraction for Complex Meta-Analysis, DECiMAL [32]. Data cleaning consisted of removing non-numerical information from the extraction spreadsheet and substituting this information with numerical values. This allowed for transference to a Comprehensive Meta-Analysis file.

2.4. SSRI-resistance

SSRI-resistance was defined a priori and pre-registered using criteria published by Pallanti et al., (2006) [57]. In the original publication, 10 different levels of treatment resistance are posited. We adapted these criteria to simplify the number of stages of resistance into four, namely, stage 1: not resistant, stage 2: one SSRI trial failed, stage 3: two SSRI trials failed, stage 4: two SSRI trials failed plus one or more CBT trial failed. Studies were allocated to these groupings based on the inclusion and exclusion criteria used and the reported treatment history of trial participants. In the case where no information about previous treatment was given, patients were allocated to stage 1 by default.

2.5. Researcher allegiance bias

Researcher allegiance was assessed for all trials using the 'researcher allegiance assessment tool' developed by Cuijpers et al., 2012 [71]; see also Turner et al. 2014 [33] (see Table 2).

According to this tool, we posed the questions listed in Table 2 to evaluate the presence of researcher allegiance. If the answer to any of these questions was 'yes', the study was deemed at risk of researcher allegiance bias.

2.6. Statistical analysis

The statistical database package used in this meta-analysis was Comprehensive Meta-Analysis V3 software (66). Hedge's *g* based on random effects was used to calculate the effect sizes. Following Cohen's convention, an effect size of 0.2 was considered small, 0.5 as moderate, and 0.8 as large.

Hedge's *g* was calculated using the mean, standard deviation and sample sizes of the intervention and control groups at the end-of-trial. When multiple time points were available for assessment in studies, post-treatment values were favored. Where studies did not provide these data, Hedge's *g* was calculated using sample sizes and a *t*-value or sample sizes and an independent groups *p* value.

When trials had more than one single intervention (e.g., r-TMS at different frequencies), control sample sizes were divided by the number of comparisons made to avoid biasing effect size weighting. Heterogeneity was assessed using the I^2 statistic, and for interpretation we followed Cochrane guidance [61], where I^2 values of 0%–40% identified as might not be important; 30–60% as may represent moderate heterogeneity; 50–90% may represent substantial heterogeneity; 75%–100% representing considerable heterogeneity.

Subgroup analyses were conducted for categorical moderator variables and meta-regression analyses were conducted for continuous moderator variables. Although no definitive minimum number of studies is required for meta-regression, we followed the general recommendations of at least 6 to 10 studies for a continuous variable [62; 61], and for a categorical subgroup variable, a minimum of 4 studies per group [62]. We used the method of moments approach for meta-regressions to accommodate random effects. Publication bias was assessed by observing funnel plots to test for any asymmetry. Test statistics such as Duval and Tweedie's trim and fill method [63], Begg's rank test [64], and Egger's [65] regression test were used to infer the potential of there being publication bias within the literature.

3. Results

Twenty-three studies (providing 25 independent comparisons) were included in this meta-analysis (see Table 1).

Overall, r-TMS produced a significant moderate reduction of Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores (N = 23 studies, k = 25 comparisons) (Hedge's *g*: -0.47; 95%CI: - 0.67 to −0.27) $p < 0.001$: see Fig. 1) with a moderate effect size heterogeneity ($I^2 = 39.8\%$). Observation of the funnel plot indicated some asymmetry and Trim and Fill analysis highlighted the presence of publication bias. The adjusted effect size was reduced but remained significant (g: -0.29; 95%CI: −0.51 to −0.07). Egger's regression intercept was also significant (intercept = −2.02, $p = 0.04$). (See Fig. 2.)

Subgroup analysis (see Fig. 3) investigating SSRI-resistance as a possible moderator (according to our a priori criteria: stage 1 = not resistant; stage 2 = one SSRI trial failed; stage 3 = two SSRI trials failed; stage 4 = two SSRI trials failed plus one or more CBT trial failed) found that studies meeting criteria for stage 1 or 2 produced significant results,

Table 1
Characteristics of the studies.

	Active			Sham			
Study	N	age (SD)	gender (%female)	N	age (SD)	gender (%female)	Treatment resistance*
Alonso et al, 2001 [34]	10	39.2 (13.0)	0,8	8	30.3 (9.5)	0,5	1
Arumugham et al, 2018 [20]	19	27.74 (7.88)	0,16	17	30.71 (10.43)	0,294	2
Badawy et al, (2010) [70]	20	26 (5.7)	0.60	20	28.9 (5.7)	0.65	1
Carmi et al, 2019 [35]	47	41.1 (11.97)	0,574	47	36.5 (11.38)	0,596	2
Elbeh et al, 2016 [36]	15	26,8 (5.2)		7,5	25,5 (4.0)	0,33	1
Gomes et al, 2012 [18]	12	35.5 (7.5)	0,67	10	37.5 (16)	0,5	3
Haghigi et al., 2015 [37]	10	34.9 (5.91)	0,7	11	36.55 (3.95)	0,55	4
Harika-Germaneau et al., 2019 [22]	14	46.3 (10.1)	0,64	14	48.2 (12.9)	0,43	3
Hawken et al., 2016 [19]	10	33.0 (10.0)	0,5	12	34.0 (14.0)	0,5	2
Jahangard et al., 2016 [38]	5	32.4 (9.0)	0,8	5	33.8 (5.8)	0,6	4
Kang et al., 2008 [39]	10	28.6 (12.66)	0,2	10	26.2 (10.52)	0,1	4
Mansur et al., 2011 [40]	13	42.1 (11.9)	0,46	14	39.3 (13.9)	0,57	4
Mantovani et al., 2010 [17]	9	39.7 (8.6)	0,44	9	39.4 (10.2)	0,33	2
Naro et al., 2019 [41]	5	52 (5)	0.5	5	52 (5)	0,5	1
Nauczyciel et al., 2014 [23]	9	40 (N/A)	0.75	10	39 (N/A)	0,79	4
Pelissolo et al., 2016 [21]	20	39.1 (10.4)	0,65	16	42.3 (10.6)	0,58	3
Prasko et al., 2006 [42]	18	28.9 (7.7)	0,28	12	33.4 (8.7)	0,58	2
Ruffini et al., 2009 [24]	16	41.5 (NA)	0.6	7	39.3 (NA)	0.75	4
Sachdev et al., 2007 [43]	10	29.5 (9.9)	0,7	8	35.8 (8.2)	0,375	4
Seo et al., 2015 [45]	14	34.6 (9.8)	0,43	13	36.3 (12.5)	0,54	3
Shayganfard et al., 2017 [46]	5	33.8 (9.6)	0,8	5	33.2 (7.9)	0,4	4
Xiaoyan et al., 2014 [47]	25	27.12 (8.9)	0,32	21	29.86 (9.5)	0,38	2
Zhang et al., 2019 [48]	25	32.2 (13.3)	0,4	24	39.38 (17.0)	0,42	1

* Resistance defined according to an adaptation of Pallanti's criteria: 1 = not treatment resistant, 2 = one SSRI trial failed, 3 = two SSRI trials failed, 4 = two SSRI trials failed plus one or more CBT trial failed.

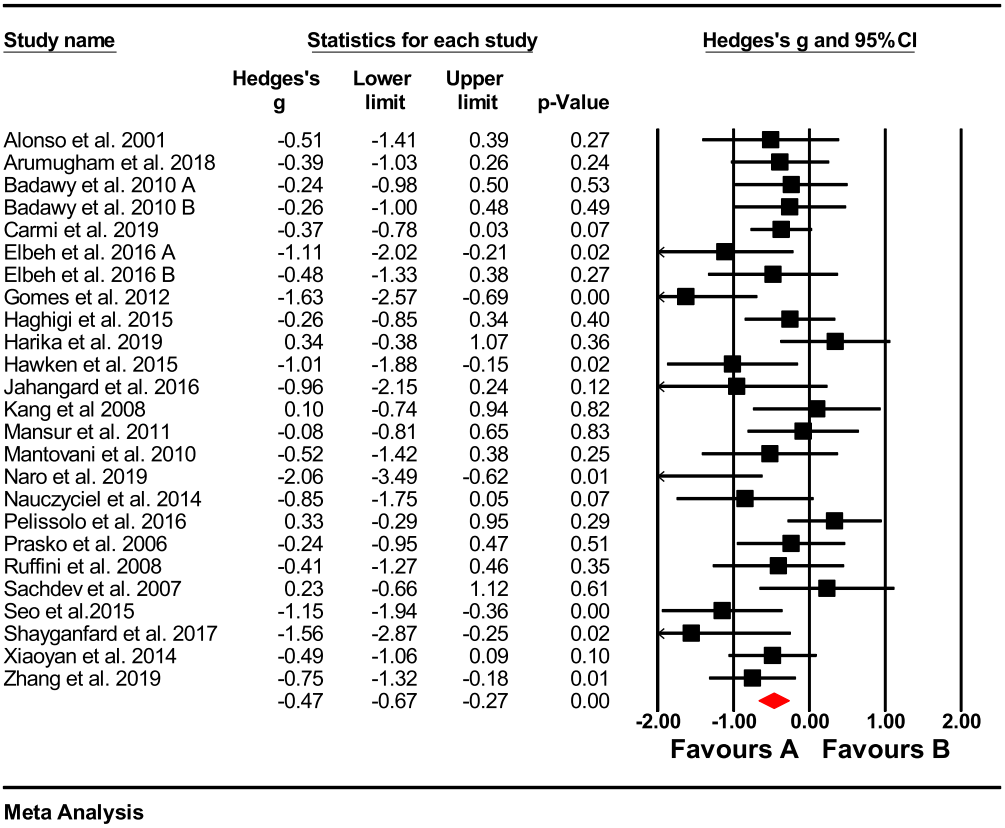

Fig. 1. Forest plot of all the studies.

while studies meeting criteria for stage 3 or 4 produced non-significant results: Stage 1 (k = 7) g: -0.65 (95%CI: −1.05 to −0.25) $p < 0.001$, $I^2 = 17.4\%$; Stage 2 (k = 6) g: -0.47 (95%CI: −0.86 to −0.09), $p = 0.02$, $I^2 = 0\%$; Stage 3 (k = 4) g: -0.39 (95%CI: −0.90 to 0.11), $p = 0.13$, $I^2 = 84.3\%$; Stage 4 (k = 8) g: -0.36 (CI: −0.75 to 0.03), $p = 0.07$, $I^2 = 20\%$.

The magnitude of between-trial heterogeneity in effect size was significantly reduced when those trials including patients at stage 1 ($I^2 = 17.4\%$), stage 2 ($I^2 = 0\%$) and stage 4 ($I^2 = 20\%$) were analysed separately, compared to the heterogeneity seen when all the studies were analysed together ($I^2 = 39.8\%$); while heterogeneity was increased

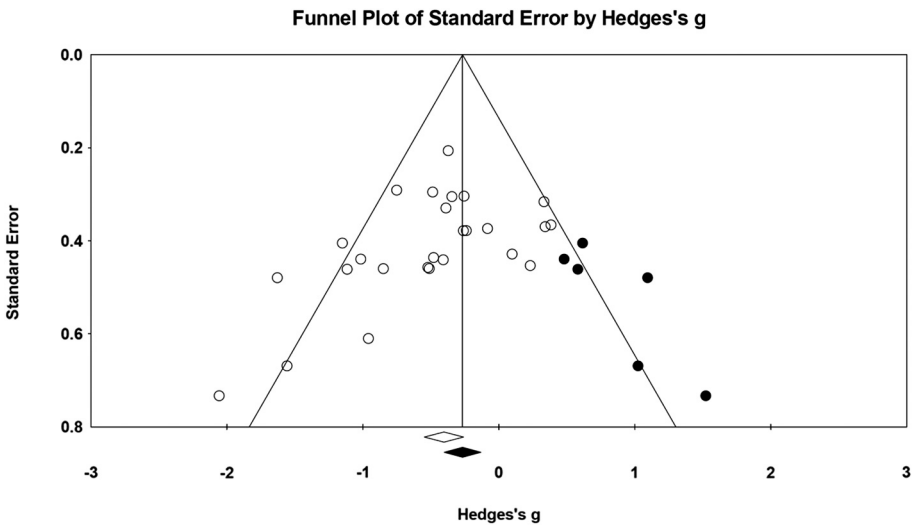

Fig. 2. Funnel plot for publication bias.
Funnel plot indicated some asymmetry and Trim and Fill analysis highlighted the imputed studies that should be added to balance this asymmetry (black circles). The adjusted effect size was reduced but remained significant (g: -0.29; 95%CI: −0.51 to −0.07). Egger's regression intercept was also significant (intercept = −2.02, $p = 0.04$).

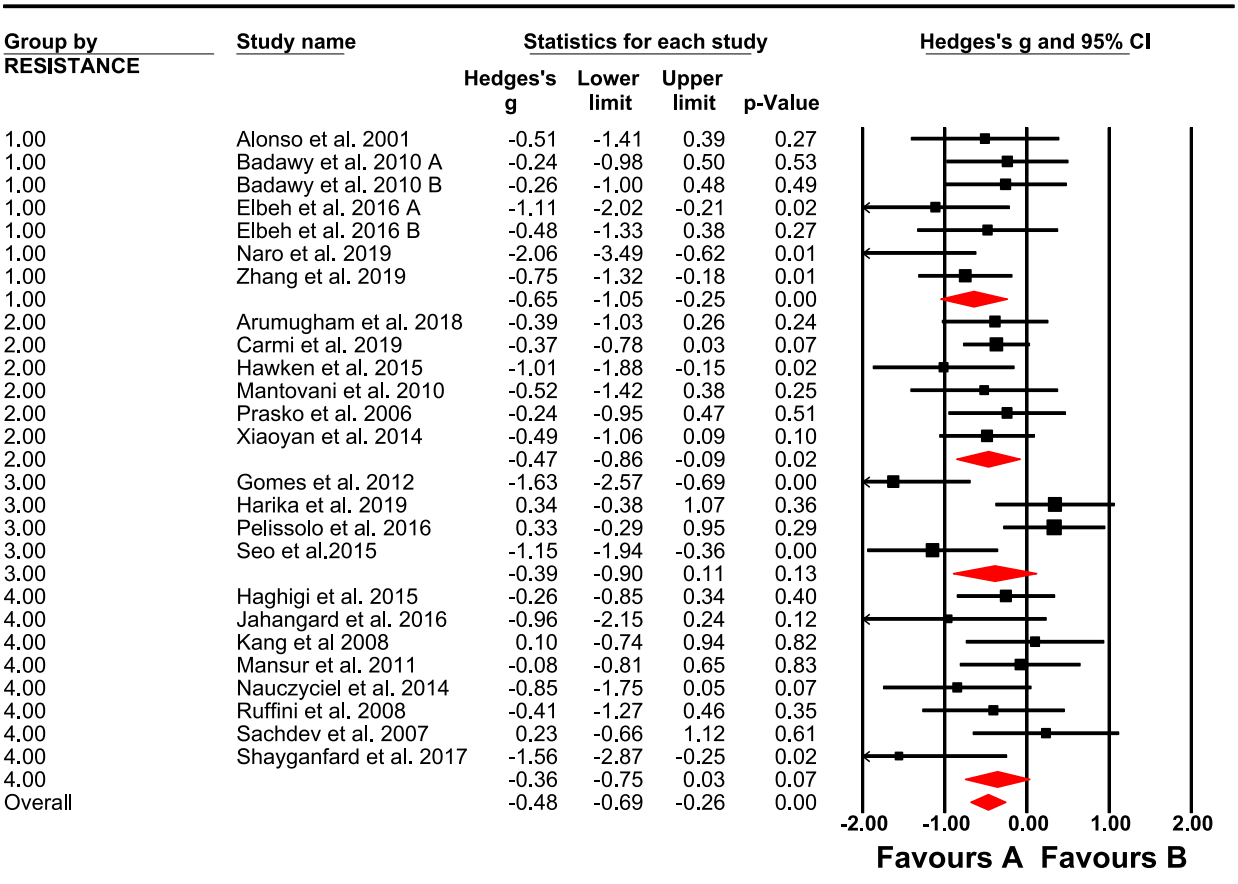

Fig. 3. Subgroup analysis for treatment resistance.
Group 1: not resistant, Group 2: one SSRI trial failed, Group 3: two SSRI trials failed, Group 4: two SSRI trials failed plus one or more CBT trial failed.

in those studies including patients at stage 3 ($I^2 = 84.3\%$), in which subgroup a bimodal distribution in effect size was demonstrated, with some trials showing a large effect and others a null effect. Moreover, the effect size was numerically reduced in the presence of any form of SSRI-resistance (see Fig. 3).

Intriguingly, the only significant moderator of the effect size for Y-BOCS was the baseline severity of depressive symptoms as measured by the Hamilton Depression Rating Scale ($N = 7$ studies, $F = 6.92$, $p = 0.04$, see Fig. 4). Four of the studies included in this meta-regression stimulated the SMA, and the other three stimulated the DLPFC (see supplementary material Table 1). However, not all the studies used the Hamilton Depression Rating Scale (HAM—D) and meta-regression based

on other depression rating scales such as the Montgomery and Asberg Depression Rating Scale (MADRS) did not produce significant results (F = 0.72, $p = 0.4$, k = 7) (see supplementary material).

Continuous variables such as percentage of females, age, baseline anxious symptoms, baseline OCD severity and duration of OCD were not found to be significant moderators of treatment through meta-regression analyses (see supplementary material Table 2).

All studies met at least one criterion suggesting the presence of researcher allegiance (see Table 2). Indeed, all the studies met at least 2 criteria for researcher allegiance, casting doubt on the presence of this type of bias in all the studies included (see supplementary table 3).

Table 2
Researcher allegiance criteria - researcher allegiance tool from Cujipers at el., 2012 [71].

- Is only one of the interventions mentioned in the title?
- In the introduction, is one of the interventions explicitly described as being the main experimental intervention?
- Was one intervention specifically described as a control condition?
- Is there an explicit hypothesis that one treatment is expected to be more effective than the other?

If the answer to any of these questions is yes, the study is deemed at risk of researcher allegiance.

4. Discussion

This meta-analysis of r-TMS in OCD is the only one known to the authors to have compared the effects in SSRI resistant and non-resistant subgroups using standardized criteria and to have assessed bias due to researcher allegiance.

The definition of treatment-resistance in OCD is not unequivocal [58] and has varied widely across the r-TMS in OCD trials. Thus, while some studies defined treatment-resistance as having failed one pharmacotherapy trial [35], others specified that the patients had to fail 3 pharmacotherapy trials and 1 CBT trial [40]. Accordingly, we applied established definitions for stages of SSRI-resistance, as proposed by Pallanti et al., 2006 [50], which we simplified into four clinically relevant stages, with the threshold for clinically relevant SSRI-resistance [59] represented by stage 3 i.e., a failure to respond to two prior courses of SSRI, based on the authors' (NF, LC, AE, KG, UA) clinical experience of treating resistant OCD at a specialist level in two different European countries (UK, IT).

Our analysis showed that r-TMS is an effective treatment for OCD (Hedge's *g*: -0.47; 95%CI: −0.67 - -0.27, $p < 0.001$; Fig. 1). However, it should be noted that we found evidence of publication bias and in the Trim & Fill analysis the effect size was smaller (g: -0.29; 95%CI: −0.51 to −0.07), even if still significant. Moreover, a significant effect was only seen in patients without established SSRI-resistance (stages 1 g: −0.65, stage 2 g: −0.47). Studies with established levels of SSRI resistance (stages 3 and 4) did not demonstrate significant impact of r-TMS on OCD symptoms, compared to sham. These results indicate that the threshold for determining r-TMS effectiveness lies somewhere between having failed one SSRI trial (possible SSRI-resistance) and two SSRI trials (definite SSRI-resistance), with greater benefit for lesser degrees of SSRI-resistance. Moreover, the heterogeneity in effect size was low (<20%) in each of the two low resistance subgroups, providing further confidence in this finding.

Thus, r-TMS appears efficacious in non-resistant OCD and may therefore be best implemented earlier in the stepped care pathway, possibly alongside SSRIs or CBT, with major implications for clinical service development, as r-TMS is not routinely available as a treatment for OCD in many health services. As r-TMS is known to have few side effects and is well tolerated in treatment trials [53], it may even represent a rational alternative to SSRIs or CBT for specific subgroups of patients for whom SSRIs or CBT are unsuitable or have known contra-indications for established first-line treatments.

Prior meta-analyses of r-TMS in OCD have failed to identify any significant mediating or moderating factors through meta-regressions [26,27]. Indeed, the apparent absence of moderators suggests either that r-TMS is equally effective irrespective of age, gender, severity etc. or that there have been too few trials to detect an effect using a moderator

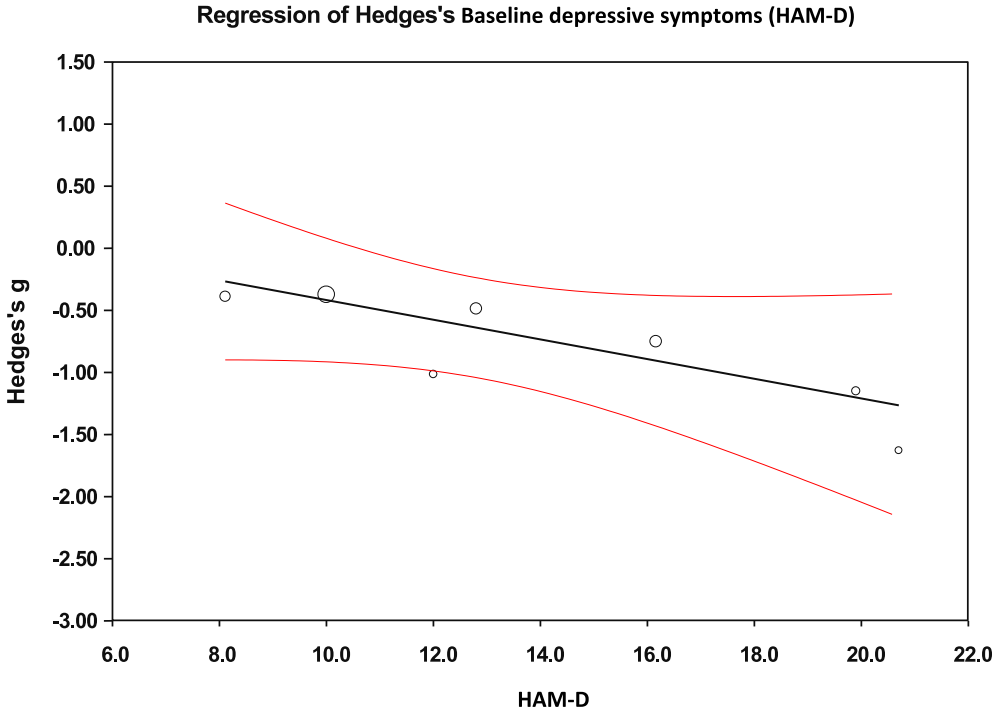

Fig. 4. Meta-regression for baseline depressive symptoms.
Scatter plots showing the significant association (black line) between the effect size (y axis) and the severity of baseline depressive symptoms measured through the HAM-D (x axis). Each circle represents a study ($N = 7$).

analysis. In contrast, in our meta-analysis, baseline depression, as measured by the Hamilton Depression Rating Scale, was found to significantly moderate the effect of r-TMS on OCD outcomes, predicting a better r-TMS response. Interestingly, none of the studies included in this meta-regression targeted the OFC – a cortical node within neural circuitry specifically implicated in reward processing, stimulation of which may induce antidepressant effects alongside improvement in OCD [68], but instead targeted the DLPFC and SMA, which are brain regions implicated in cognitive and behavioral control. The brain-based mechanism mediating this effect is therefore hard to explain based on current translational neuroscience theories. Possibly the greater baseline Hamilton Depression Scale scores reflected greater global illness severity and thereby greater scope for symptomatic improvement. Yet no significant moderating effect was seen using the baseline Y-BOCS nor using the MADRS, in the latter case, possibly because the number of studies available was too small. Alternatively, unlike the MADRS which probes core depression, the Hamilton Depression Rating Scale contains several anxiety items, hence it may have reflected higher baseline anxiety acting as a potential moderator of r-TMS responsiveness.

Some caution, however, is required in interpreting the effectiveness data, as all RCTs of r-TMS in OCD have so far employed an inadequate sample size. In order to detect an effect size of 0.47 at 0.8 power, a 2-tailed test requires 95 participants per group. So, none of the existing trials are adequately powered to detect the effect size reported. The low power is consistent with our Trim and Fill analysis, which suggests the presence of publication bias.

Importantly, all the studies additionally showed evidence of researcher allegiance bias [49]. As researcher allegiance is likely to have biased the results in favour of the intervention [49,60], caution is again required in interpreting the reported effect sizes of r-TMS across the OCD database as a whole. Researcher allegiance operates in many ways, including via study design features not only favouring the preferred treatment, but also influencing the preferred control comparison [49]. For example, the use of sham stimulation in r-TMS studies has been criticised for introducing bias by not adequately controlling for sensory aspects of the active stimulation. However, the effects of researcher allegiance may persist even 'beyond designing the study in a way which benefits the preferred treatment' [69], reflecting 'researcher enthusiasm or expertise for a preferred treatment that is not fully represented in the variables commonly coded as methodological characteristics' [49]. The implication is that patients treated in centres whose expertise does not focus on r-TMS may experience inferior outcomes. Thus, well powered RCTs that eliminate all major forms of bias are still needed before conclusions about the overall efficacy of r-TMS and its relative efficacy across different OCD patient groups can be drawn and cost-effectiveness comparisons made with other first line treatments such as SSRIs and CBT.

4.1. Limitations

Our study has certain limitations. We used an adaptation of the Pallanti criteria [50] (originally 10 different criteria, reduced to four), as stated in our pre-registered protocol, because there were insufficient studies to analyse across the 10 subgroups.

Another limitation is that most studies do not give comprehensive information on treatment resistance, and we believe our simplified and adapted version of Pallanti's Criteria is the best one to capture the different levels of resistance in this group of studies.

In addition, the studies included in our meta-analysis were very heterogenous from a protocol perspective (high and low frequency, duration of stimulation, inhibitory versus excitatory, stimulation target).

We decided to include in our analysis the study by Carmi et al. 2019, even if this this study adopts deep TMS, in line with previous meta-analyses [15,54].

A further limitation is the fact that only 9 of 23 trials provided information on prior treatment with psychological therapy (i.e., CBT). Therefore, we were unable to comment adequately on CBT- resistance and thus focused our analysis on SSRI-resistance, where most studies (21 out of 23) provided adequate information. However, two studies provided inadequate information about prior SSRI treatment and were therefore listed among the seven studies in the non-resistant (stage 1) grouping.

5. Conclusions

Our meta-analysis signals the effectiveness of r-TMS in those patients with OCD who have *not* failed to respond to previous treatment with SSRI. The importance of these findings lies in considering the implications and potential advantages of applying this intervention early in the clinical care pathway, thereby opening up patient choice, and not reserving r-TMS for SSRI-resistant cases. Indeed, those with SSRI-resistant OCD did not show any significant benefit from r-TMS. Nonetheless, we also identified methodological shortfalls in the existing trials database, in particular the use of small sample sizes and the presence of researcher allegiance bias, that could not be adequately controlled for using meta-analysis. Therefore, further well-powered studies of r-TMS in OCD, including well defined resistant and non-resistant patient groups that demonstrate elimination of all major sources of bias, are needed before conclusions can be drawn with certainty.

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Declaration of Competing Interest

Prof. Fineberg in the past three years has received research funding paid to her institution from the NIHR, COST Action and Orchard. She has received payment for lectures on psychiatric diagnosis from the Global Mental Health Academy and for expert advisory work on psychopharmacology from the Medicines and Healthcare Products Regulatory Agency, publishing royalties from Oxford University Press and an honorarium from Elsevier for editorial work as Editor in Chief, Comprehensive Psychiatry. She has received financial support to attend meetings from the British Association for Psychopharmacology, European College for Neuropsychopharmacology (ECNP), Royal College of Psychiatrists, International College for Neuropsychopharmacology, COST, World Psychiatric Association, International Forum for Mood and Anxiety Disorders, American College for Neuropsychopharmacology. In the past she has received funding from various pharmaceutical companies for research into the role of SSRIs and other forms of medication as treatments for OCD and for giving lectures and attending scientific meetings.

Prof. Albert declares that in the past 3 years has been a consultant and/or a speaker for Angelini, Neuraxpharm, Janssen Cilag, Lundbeck, Innova Pharma.

Prof. Laws, Dr. Pellegrini, Dr. Garg, Dr. Enara and Dr. Gottlieb have no conflict to declare.

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Appendix A. Supplementary data

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