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Transcranial Magnetic Stimulation for Anxiety Symptoms: An Updated Systematic Review and Meta-Analysis

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Abstract

Background: Transcranial magnetic stimulation (TMS) is a promising non-invasive brain stimulation intervention. TMS has been proposed for the treatment of Anxiety Disorders and disorders in which anxiety symptoms are prevalent, such as Obsessive-Compulsive Disorder (OCD) and Post-traumatic Stress Disorder (PTSD).

Objective: To assess the efficacy of TMS for anxiety symptoms in Specific and Social Phobia, Generalized Anxiety Disorder, Panic Disorder (PD), OCD and PTSD in randomized clinical trials (RCTs).

Methods: Systematic review using MEDLINE from the first RCT available until January 2015. The main outcome was the Hedges' g for continuous scores for anxiety symptoms scales in a random-effects model. Heterogeneity was evaluated with the I2 and the χ^2 test. Publication bias was evaluated using the Begg's funnel plot. Meta-regression was performed using the random-effects model modified by Knapp and Hartung.

Results: We included 14 RCTs (n=395); most had small-to-modest sample sizes. Comparing active vs. sham TMS, active stimulation was not significantly superior for anxiety symptoms (Hedges' g = -0.02; 95% CI -0.24-0.20). The funnel plot showed that the risk of publication bias was low and between-study heterogeneity was not significantly (I2=12%). Meta-regression showed no particular influence of any variable on the results.

Conclusion: TMS active was not superior to sham stimulation for the amelioration of anxiety symptoms. Trials had homogeneous results, despite different protocols of stimulation used. Further RCTs with larger sample sizes are fundamentally needed to clarify the precise impact of TMS in anxiety symptoms.

Highlights

- We present a systematic review and meta-analysis on results of TMS for anxiety symptoms in anxiety disorders
- Four-teen studies (395 patients) were selected for the quantitative analysis
- We found that active TMS was not significantly superior to sham TMS in this dataset (Hedges' g = -0.02; 95% CI -0.24-0.20)
- Heterogeneity was not significant in our analysis (I2=12% and p=0.361 for the χ^2 test)
- Meta-regression showed no particular influence of any variable on the results
- The funnel plot displayed that studies were evenly distributed, with all studies within the limits deter-mined by the graphic except for one, indicating low bias

Keywords: Meta-analysis; Post-traumatic stress disorder; Obsessive-compulsive disorder; Anxiety disorders; Transcranial magnetic stimulation; Non-pharmacological therapies; Systematic review

Background

The anxiety disorders group is one of most prevalent set of psychiatric diagnoses. Specific phobia and social phobia are known as the most prevalent from the group (6-12% and up to 10%, respectively). Post-traumatic stress disorder comes in third position with a lifetime prevalence varying from 1% in Western Europe, to 10% in countries that have been exposed to long-term violence. The other anxiety disorders have a lower prevalence such as 2-5% for panic disorder 3-5% in generalized anxiety disorder and less than 3% for obsessive-compulsive disorder [1]. The combination of psychotherapy and pharmacotherapy are generally regarded as first line treatment. However, about 25% of patients respond poorly to treatment and show a high risk of chronicity [2]. The high prevalence and high risk for chronicity have contributed to an annual total societal cost of active anxiety disorders in the US over the decade of the 1990s estimated over $42 billion [3].

Neuroanatomical regions such as the amygdala, hippocampus,

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thalamus, and the dorsolateral prefrontal cortex (DLPFC) have been previously reported as involved in the network underlying anxiety symptoms [4]. It has been hypothesized that the right ventromedial frontal area, which is richly connected to lateral prefrontal areas and the amygdala, provides access to object recognition to the amygdala, which is responsible for fear-relevant information processing and its activation for fear or threat response both in animals and in humans [5]. However, the inhibitory control of the amygdala would be exerted by the lateral PFC in cognitive modulation of the emotional process [6]. Other frontal areas have been implicated in fear processing, such as the orbitofrontal cortex and the inferior frontal gyrus. Reduced cerebral blood flow in the right orbitofrontal cortex (OFC) was observed during an unexpected panic attack [7] and diminished activation in the inferior frontal gyrus (IFG) has been observed in patients with panic disorder during anticipated fear [8]. Obsessive-Compulsive Disorder patients' inability to suppress intrusive thoughts, impulses, or images and repetitive motor responses have been associated with excessive activity in orbitofronto-striatal regions, but also in medial and lateral frontal areas [e.g. supplementary motor area (SMA), anterior cingulate, DLPFC], and in parietal regions [9]. These lines of evidence suport the hypothesis that an insufficient activation of the PFC, resulting in reduced inhibition of the amygdala, would be associated with anxiety symptoms.

Based on the neurobiological findings, the use of transcranial magnetic stimulation (TMS) has been proposed as an adjunct therapy for modulating areas associated with anxiety symptoms. TMS is a safe, non-invasive treatment that uses electromagnetic fields to modulate cortical areas activity; in practice, a high-intensity current passes through a magnetic coil placed on the scalp, and this generates a time-varying pulsed magnetic field that penetrates the cranium approximately 2-cm from the scalp surface to cortical tissue. The neurobiological consequences of TMS depend upon the parameters of the magnetic field. Low-frequency TMS (~1 Hz) is generally thought to produce inhibitory effects, while high-frequency TMS (≥ 5 Hz) is excitatory to underlying neural tissue [10]. Recently, intermittent theta-burst stimulation (iTBS) has been investigated and shown to have excitatory effects on cortex, while continuous theta-burst stimulation led to inhibitory effects [11]. Another protocol proposed was a personalized rTMS set at the individual's intrinsic frequency of alpha activity in electroencephalography, known as αEEG-guided transcranial magnetic stimulation (αTMS) to treat patients with schizophrenia [12] or with major depression [13]. Different protocols have emerged focusing on left and right DLPFC, the SMA and OFC. In the present study, we present a systematic review and meta-analysis on results of TMS for anxiety symptoms in anxiety disorders.

Methods

A systematic review and meta-analysis according to the recommendations of the Cochrane group and to the PRISMA guidelines was conducted [14]. Two authors (APT and PS) performed independent systematic reviews and data extraction, and any discrepancy was resolved by consensus.

Literature review

We reviewed the following references and databases:

(a) MEDLINE database using the key words: (1)"transcranial stimulation"; (2)"TMS"; (3) "transcranial magnetic stimulation"; (4) "non-invasive brain stimulation"; (5) "NIBS"; (6) "Post-traumatic Stress Disorder"; (7) "PTSD"; (8) "Anxiety Disorder"; (9) "Obsessive-Compulsive Disorder"; (10) "Panic Disorder"; (11) "Agoraphobia"; (12) "Social Phobia"; (13) "Phobia", (14) "Specific Phobia"; (15) "Generalized Anxiety Disorder". The Boolean terms were imputed: [(1) OR (2) OR (3) OR (4) OR (5)] AND [(6) OR (7) OR (8) OR (9) OR (10) OR (11) OR (12) OR (13) OR (14) OR (15)]. We searched for publications listed in MEDLINE up to January 30, 2015.

(b) Study references in retrieved articles and reviews, particularly those included in the meta-analyses by Karsen et al. [15] and Berlim et al. [16].

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

Eligibility criteria

We adopted the following inclusion criteria: (1) manuscript written in English, Spanish or Portuguese (in fact all retrieved articles were written in English); (2) randomized, sham-controlled trials; (3) provided data (on the manuscript or upon request) for the estimation of the main outcomes, i.e., mean (SD) values and response and remission rates. We excluded case reports and series of cases, non-controlled trials and trials assessing conditions other than PTSD, OCD, Social Phobia, Specific Phobia, Agoraphobia, GAD or interventions other than TMS.

Data extraction

The following variables were extracted according to a structured checklist previously elaborated by the authors: (1) metadata (i.e., authorship, publication date, etc.); (2) demographics (i.e., sample size in each group, age, gender); (3) Disorder characteristics (baseline anxiety scores; use of medication; psychometric scales, interviews and checklists used for diagnosis and assessment anxiety and depressive symptoms); (4) characteristics of the TMS technique (i.e., frequency; motor threshold; time period of stimulation; train; intertrain interval; number of sessions; cortical target stimulated; side of brain); (5) research methods (i.e., randomization protocol; sham technique; blinding assessment).

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

For continuous outcomes, the meta-analysis was performed on endpoint anxiety scores. Since many studies employed more than one anxiety scale, we extracted data from the Hamilton Anxiety Rating Scale (HAMA) as the first option, followed by State-Trait Anxiety Inventory (STAI) and Beck Anxiety Inventory (BAI) as second and third options respectively when HAMA data were not presented. When a study reported scores at more than one time-point, we used the scores corresponding to the first time period after the last session of TMS intervention prior to unblinding.

In studies in which three intervention groups were studied, two separate datasets were considered for two different analyses. In the study of Boggio et al. [17] high frequency TMS for left and right DLPFC were compared with sham stimulation. We compared active left DLPFC stimulation vs. sham stimulation in our first analysis. In our second analysis, we compared active right DLPFC stimulation with sham stimulation. In the study of Cohen et al. [18] the authors

compared low frequency and high frequency stimulation of the right DLPFC with sham stimulation. We compared high frequency right DLPFC stimulation vs. sham stimulation in the primary meta-analysis. In our second analysis, we compared low frequency right DLPFC stimulation with sham stimulation.

Quality assessment

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

Quantitative analysis

Main outcomes: All analyses were performed using the statistical packages for meta-analysis of Stata 13 for Mac OSX. For the main outcome (anxiety scores), we initially calculated the standardized mean difference and the pooled standard deviation of each comparison. This procedure is convenient when handling different scales (such as anxiety scales) since it standardizes the effect sizes across all studies based on the standard deviation of each study. In the study by Boggio et al. [17] anxiety scales scores were assessed by graphic evaluation. In the study by Sachdev et al. [19] and Sarkhel et al. [20] data was provided by the authors. The study conducted by Ruffini et al. [21] was excluded from our meta-analyses due to crucial missing data despite multiple requests to receive this information. In all other studies data was reported in the articles. The main outcome reported was HAMA in all studies but two Watts et al. [22] and Sachdev et al. [19]; in those studies the STAI was employed. The Hedges' g was used as the measure of effect size, which is appropriate for studies of small sample sizes. The pooled effect size was weighted by the inverse variance method and measured using the random-effects model.

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

Meta-regression: Meta-regression was performed using the random-effects model modified by Knapp and Hartung [23], using only one variable at a time.

Subgroup analyses: We evaluated the results of TMS on anxiety symptoms separately for OCD, PTSD and Panic Disorder separately. The Hedges' g was used as the measure of effect size, which is appropriate for studies of small sample sizes. The pooled effect size was weighted by the inverse variance method and measured using the random-effects model.

Qualitative analysis

We used patient's dropouts as most severe outcome for safety evaluation we compared result between sham and active groups. A categorical analysis was used for Odds Ratio assessment between groups.

Results

Overview

Our systematic review yielded 170 studies. Among them, 156 articles did not match eligibility criteria (Figure 1). Fourteen studies [18] (395 patients) were selected for the quantitative analysis. Across all subjects, the mean age was 35.94 (SD=7.1) years and 41.5% of participants were women. No main treatment drug washout was performed. Demographics and stimulation protocols are displayed in Table 1.

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

Primary outcome

We calculated the effect size for endpoint. We found that active TMS was not significantly superior to sham TMS in this dataset (Hedges' g = -0.02; 95% CI -0.24 – 0.20) (Figure 2).

Quantitative assessment of heterogeneity and bias

Heterogeneity was not significant in our analysis (I^2=12% and p=0.361 for the χ^2 test). The funnel plot displays that studies were evenly distributed, with no study located out of the funnel (Figure 3). We found that the exclusion of each study did not have a significant impact on the results, with resulting effect sizes close to the overall effect size (Figure 4). Therefore, no particular study could be driving the results of our analysis.

Meta-regression

Meta-regression showed no particular influence of any variable on the results (Table 2). No study used Deep TMS or a crossover design. Medication washout was not performed.

Subgroup analyses

We calculated the effect size for endpoint. We found that active

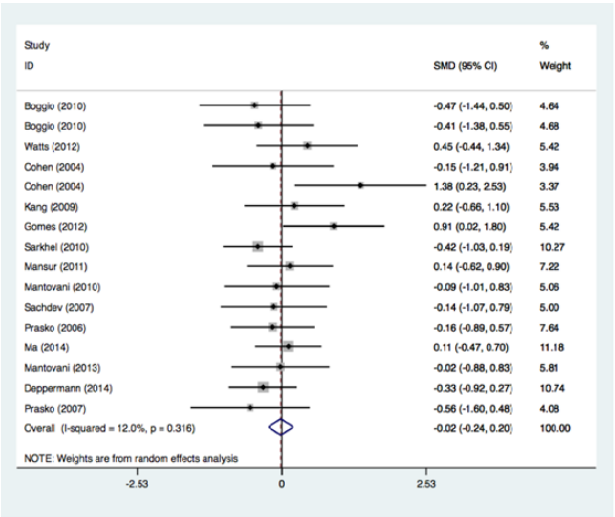

Figure 1: Study simple size ranged from 15 to 50 subjects (average 13.17 SD=5.39).

Study	Diagnosis	Active TMS			Sham TMS			TMS Parameters				
		n	Fem (n)	Age (yrs)	n	Fem (n)	Age (yrs)	Brain Cortex Region	F (Hz)	N of Pulses	MT (%)	Blinding Strategy
Boggio et al. [17]	PTSD	10	6	40.7	10	8	45.9	R-DLPFC	20	16000	80	1
Boggio et al. [17]	PTSD	10	5	47.1	10	8	45.9	L-DLPFC	20	16000	80	1
Watts et al. [22]	PTSD	10	1	54	10	1	57.8	R-DLPFC	1	4000	90	2
Cohen et al. [18]	PTSD	10	1	40.8	8	2	42.8	R-DLPFC	1	1000	80	3
Cohen et al. [18]	PTSD	10	3	41.8	8	2	42.8	R-DLPFC	10	4000	80	3
Prasko et al.	OCD	18	5	28.9	12	7	33.4	L-DLPFC	1	18000	110	3
Sachdev et al.	OCD	10	3	29.5	8	5	35.8	L-DLPFC	10	15000		2
Kang et al.	OCD	10	2	28.6	10	1	26.2	R-DLPFC + SMA	1	12000	110	4
Mantovani et al.	OCD	11	4	39.7	10	3	39.4	SMA	1	24000	100	1
Sarkhel et al.	OCD	21	11	29.3	21	8	31.9	R-DLPFC	10	-	110	4
Mansur et al.	OCD	15	6	42.1	15	8	39.3	R-DLPFC	10	60000	110	2
Gomes et al.	OCD	12	8	35.5	10	5	37.5	SMA	1	12000	100	1
Prasko et al.	PD	7	6	33.7	8	5	33.8	R-DLPFC	1	18000	110	3
Ma et al.	OCD	27	8	27.1	23	8	29.8	BILATERAL DLPFC	-	6480- 8720	80	2
Mantovani et al.	PD	12	5	40.2	13	8	39.8	R-DLPFC	1	36000	110	1
Depperman et al.	PD	22	13	37.6	22	14	36.3	L-DLPFC	-	900	80	4

Table 1: Study sample size ranged from 15 to 50 subjects (average 13.17 SD=5.39).

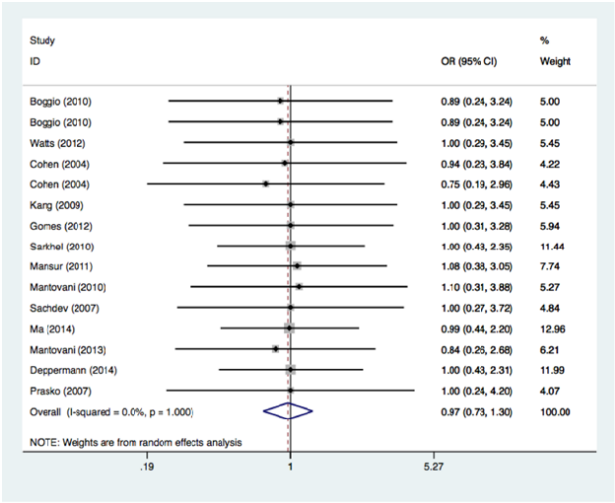

Figure 2: Effective size for endpoint.

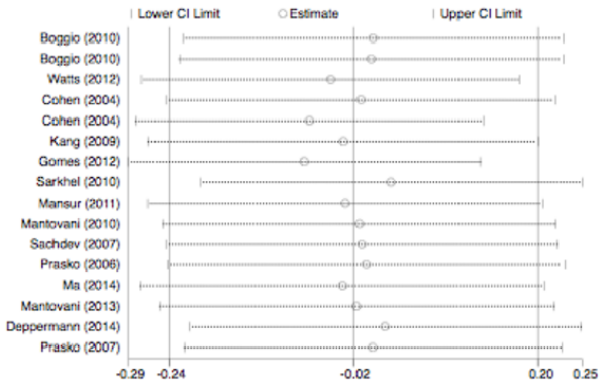

Figure 3: Quantitative assessment of heterogeneity and bias.

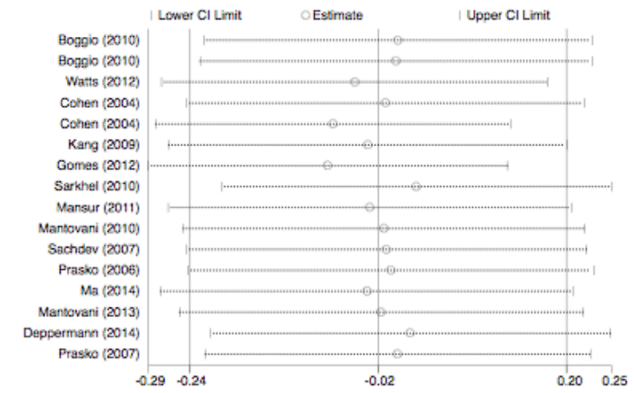

Figure 4: Quantitative assessment of heterogeneity and bias overall effect size.

TMS was not significantly superior to sham TMS when OCD (Hedges' g = 0.02; 95% CI -0.24 – 0.29, N=233 subjects in 8 studies), PTSD (Hedges' g = 0.13; 95% CI -0.51 – 0.76, N=78 subjects in 3 studies) and PD (Hedges' g = 0.29; 95% CI -0.73 – 0.15, N=84 subjects in 3 studies) were evaluated separately.

Safety evaluation

A categorical analysis of safety using dropout as most severe possible outcome was performed. No difference between groups was observed (Figure 5). Evaluation of most common side effects was not possible due to lack of detailed data provided in the papers (Figure 6).

Discussion

In this systematic review that included 14 randomized clinical trials [18] (n= 395), we found that active TMS was not significantly superior to sham TMS for the treatment of anxiety symptoms in PTSD, OCD and Panic Disorder (Hedges' g = -0.02; 95% CI -0.24 – 0.20). This result was apparent in our main analysis that used a continuous effect size measure. The funnel plot assessment showed that the risk of publication bias was also low and between-study heterogeneity was not significant (I^2=12%).

Metaregression	p value	Metaregression	p value
Diagnosis (OCD/PD/PTSD)	0.264	Side of Stimulation	0.543
Age Sham	0.98	Frequency	0.395
Age Active	0.496	Number of Sessions	0.699
Duration of Illness Sham	0.135	Duration of Sessions	0.819
Duration of Illness Active	0.135	Number of Weeks of Stimulation	0.513
Baseline Anxiety Score Sham	0.943	Pulses per Session	0.941
Baseline Anxiety Score Active	0.98	Motor Threshold	0.879
Anxiety Scale	0.583	Blinding	0.298
Baseline Depression Score Sham	0.103	iTBS	0.335
Baseline Depression Score Active	0.299	Alpha Guided TMS	0.676
Depression Scale	0.538	Left DLPFC Stimulation or Right DLPFC Inhibition	0.296
Cortex Area	0.222		

Table 2: Meta regression.

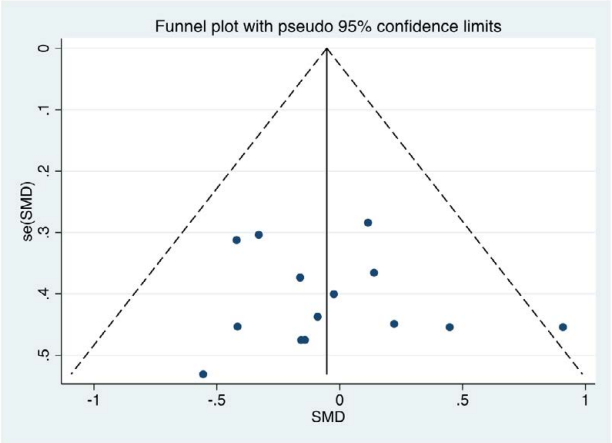

Figure 5: Safety Evaluation.

Meta-regression did not identify clinical and/or methodological predictors for TMS non-responsiveness. However, we included intervention protocols that either stimulated or inhibited left or right DLPFC, two studies focused on the inhibition of the Supplementary Motor Area, one study inhibited DLPFC bilaterally. Meta-regressions were performed in order to identify the possibility of different results if protocols were evaluated separately. No treatment protocol (stimulation of the left DLPFC ; stimulation of the left DLPFC and inhibition of right DLPFC; stimulation of right DLPFC; inhibition of right DLPFC; bilateral deep magnetic inhibition; SMA inhibition) was identified as predictor to TMS non-responsiveness. Different diagnosis (OCD, PTSD and Anxiety Disorder) were not predictors to TMS non-responsiveness as well. Moreover, as to verify the influence of each study on the overall effect, we used the "metaninf" Stata tool. No study individually influenced the overall effect. A key limitation of the present report is the small number of evaluable sham controlled RCTs in anxiety disorders (14 of 170 potential publications). Another limitation is that all studies employed TMS as an adjunct to other treatments, so the incremental advantage of active over sham may have been obscured by the effects of the underlying primary treatment.

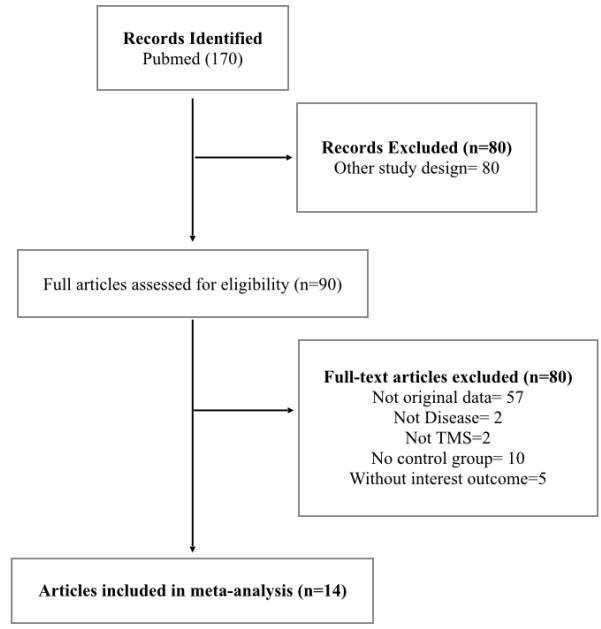

Figure 6: Categorical analysis.

Conclusion

Based upon this meta-analysis of published double-blind randomized controlled trials, we found that active TMS is not clinically or statistically superior to sham TMS in the treatment of anxiety symptoms in OCD, PTSD and PD. Notwithstanding, the number of trials published to date was relatively small, so further phase III studies assessing broader samples are fundamentally needed to clarify the potential impact of TMS in the treatment of anxiety symptoms in daily clinical practice.

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