



REVIEW

Efficacy of transcranial magnetic stimulation in the treatment of Obsessive-compulsive disorder

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Abstract

Background: Obsessive-compulsive disorder (OCD) is a chronic and debilitating disease characterised by obsessions and compulsions that cause anxiety to the patient and his family. Its prevalence is around 2 to 3% in the general population, and despite being responsive to treatment, 40-60% of patients are not full responders and remain refractory. Therefore, new therapeutic options like transcranial magnetic stimulation (TMS) have been gaining interest recently due to their non-invasive nature and potentially promising results. However, there is not yet a consensus about its efficacy in this disease. The aim of this review is to assess the efficacy of TMS in the treatment of OCD, discussing some of the clinical trials available.

Methods: A search was made in MEDLINE, through Pubmed, using the query: "Obsessive-Compulsive Disorder"[Mesh] AND "Transcranial Magnetic Stimulation"[Mesh].

Results: Several demographic, clinical and technique-related variables of 16 clinical trials were analysed, along with their outcome. Most of the trials revealed promising results in three cortical areas: dorsolateral pre-frontal cortex, supplementary motor area and orbitofrontal cortex. However, their statistical power is affected by their small sample size and heterogeneity of parameters, which limits critical analysis and comparison of results. Depression was also identified as a possible confounding factor, which could predispose to positive results.

Conclusion: The distinct characteristics of the clinical trials make it impossible to generalise the effects of this technique in OCD. More robust studies, preferably without comorbid psychiatric disorders, are necessary to better evaluate the efficacy of this technique.

Keywords: Transcranial magnetic stimulation, Obsessive-compulsive disorder.

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Introduction

Obsessive-compulsive disorder (OCD) is a chronic and debilitating disease characterised by egodystonic obsessions and compulsions that cause anxiety to both the patient and his family [1]. Obsessions are persistent or disturbing thoughts, images or impulses, while compulsions are repetitive and ritualised behaviours that a person feels the need to perform. The most common examples of obsessions are worrying about germs, with involuntary acts of aggression, or with the need for symmetry or exactness. The most common compulsions are associated with the need to excessively wash hands, to organise or count objects, and to verify/repeat daily routines [2].

The prevalence of OCD in the general population is around 2 to 3%, and it affects both genders in an equal proportion. Moreover, the probability of occurrence of one major depressive episode during the lifetime of these patients is of 67% [1]. Despite that, OCD has a favourable response to treatment, with SSRIs and clomipramine being the most effective treatments, complemented by cognitive-behavioural therapy [1, 3]. However, even with these therapeutic options, 40 to 60% of patients don't fully respond to treatment and remain refractory [4]. Therefore, new treatment options, like transcranial magnetic stimulation (TMS), have been gaining more interest recently [5].

TMS is a technique that induces the formation of magnetic fields which, by alternating rapidly every millisecond, induce the formation of an electrical current in the cortex area below the coil. Consequently, depolarisation and hyperpolarisation of the axons of cortical neurons occurs [6]. When used repeatedly, such modulatory effect of cortical neural activity can persist beyond the period of stimulation, justifying the therapeutic use of repetitive transcranial magnetic stimulation (rTMS) [7]. However, despite its non-invasive nature and its potentially promising results, there isn't yet a general consensus about its efficacy in the treatment of OCD [8].

Some of the characteristics of this technique are important to mention, such as the frequency used (low (<1Hz) or high (>5H)) [7], its intensity and the coil type. Circular coils are known to stimulate large cortical areas with good penetration, but they sacrifice precision in guiding the stimulation towards the desired area; in contrast, coils with an "8" or "Double-D" shape, sometimes also known as "butterfly", offer high focality but reduced penetration [7, 9]. To evaluate the placebo effect, sham stimulation can consist in tilting the coil, placing it out of the patient's field of vision, or in using a sham coil [9].

The objective of this review is to evaluate the efficacy of TMS in the treatment of OCD, by providing a critical analysis of the randomised clinical trials performed to date.

Materials and Methods

A search was conducted in MEDLINE, through Pubmed, using the query: "Obsessive-Compulsive Disorder"[Mesh] AND "Transcranial Magnetic Stimulation"[Mesh], between the months of September 2017 and March 2018.

73 articles were obtained. After reviewing the titles and abstracts, 21 studies were selected, while the other ones were excluded for not being relevant in the context of the topic under review. Out of these 21 studies, two were excluded for being case reports, and three were excluded for being observational studies, leading to 16 randomised clinical trials included in this review.

Results

Randomised Clinical Trials

In this review, 16 randomised clinical trials (RCTs) which assessed the effectiveness of TMS in the treatment of OCD were selected. These studies were divided into groups according to the area of the brain chosen to be the target of TMS:

- Dorsolateral Prefrontal Cortex (DLPFC): 9 studies
- Supplementary Motor Area (SMA): 5 studies
- Orbitofrontal Cortex (OFC): 2 studies

All these studies had the highest level of evidence (level I).

The primary outcome was defined as the assessment of the severity and type of obsessive-compulsive symptoms in the form of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Globally, these studies considered as responders those patients with a reduction of the Y-BOCS \geq 25%. The exception was the study performed by Ma et al. (2014), in which the criteria were a reduction in the Y-BOCS \geq 35% and a CGI (Clinical Global Impressions scale) score of 1 or 2 [10], and the studies performed by Sachdev et al. (2007) and Alonso et al. (2001), who considered as responders those with a reduction of the Y-BOCS $>$ 40% [11, 12]. Secondly, symptoms of depression and anxiety were also evaluated using the Hamilton Rating Scale for Depression (HAM-D), in the Hamilton Rating Scale for Anxiety (HAM-A) and in the Montgomery-Åsberg Depression Rating Scale (MADRS). All these scores were assessed, mainly, in the first, second and fourth weeks after the beginning of treatment.

Regarding blinding, it varied equally between single-blind and double-blind in the studies that focused their treatment on the DLPFC and OFC. However, all the trials who focused their stimulation in the SMA were double-blinded.

Randomisation of participants was generally made using software programs, closed envelopes, or by using chips of different colours. In this regard, Sarkhel et al. (2010) resorted to an alternated selection of patients, with the first patient chosen to be part of the experimental group, the second patient part of the control group, and so on [13].

Also, Ruffini et al. (2009) randomised patients using a 2:1 ratio (experimental group: control group) [14].

Lastly, all the RCTs maintained the patients' usual medication, without any change to the therapeutic dosages. All the participants were taking at least one SSRI/clomipramine, with the exception being the studies of Sachdev et al. (2007), in which four patients were unmedicated (1/10 in the experimental group, and 4/8 in the control group) [11]; of Alonso et al. (2001), in which five patients were unmedicated [12]; and in the study of Hawken et al. (2016), in which one patient of the experimental group was unmedicated as well [15]. Regarding benzodiazepines, some studies mentioned this pharmacological class in the usual medication of the patients, more specifically: Seo et al. (2016) (15/27 patients), Gomes et al. (2012) (14/22 patients), Hawken et al. (2016) (only in the cases of severe anxiety), Pelissolo et al. (2016) (22/36 patients), Ruffini et al. (2009) (18/23 patients) and Nauczyciel et al. (2014) (8/19 patients). In the remaining studies, the patients either did not take benzodiazepines, or they were not specified.

The most relevant characteristics of the sixteen clinical trials, as well as their results and conclusions, are presented in Tables 1, 2 and 3.

Discussion

The clinical trials included in this review targeted 3 different therapeutic targets in the brain (DLPFC, SMA and OFC), all of which are thought to be hyperactivated in OCD, and might be involved in its pathophysiology [16, 17].

Amongst the studies that targeted the Dorsolateral Prefrontal Cortex (DLPFC), three reported an inefficacy of the technique in the treatment of OCD: Sarkhel et al. (2010), Sachdev et al. (2007) and Alonso et al. (2001) [11-13].

Some aspects of these trials can contribute towards a reduced statistical power. For instance, Sarkhel et al. (2010) did not use a pure randomisation method, instead choosing to alternately select the patients [13]. The latter is a method that can make the researcher aware of which group the next patient will be in, and that can have an effect in the researcher's decisions. Alonso et al. (2001) used a circular coil, which has the problem of reducing the precision in targeting the desired area of the brain [7, 9, 12]. Sachdev et al. (2007) reported a very similar response rate between the experimental group and control group (30% and 25%, respectively), which can perhaps indicate the presence of a placebo effect [11].

Moreover, neither Sarkhel et al. (2010) or Alonso et al. (2001) showed any reduction in the Y-BOCS of patients submitted to TMS in the follow-up period, but since such reduction was accompanied by a similar reduction in the MADRS scale, the researchers formulated the hypothesis that OCD symptoms could have improved secondarily to depression, and theorised a cause-effect relationship between the two pathologies [11, 13].

The notion that depression might be a confounding factor is frequently debated in these trials and, in fact,

it's in accord with the previous statement that OCD and depression are frequently related to one another [1, 10, 11, 13]. For instance, Overbeek et al. (2002) suggested that OCD with comorbid depression might be associated with more negative therapeutic results [18], which might partially explain the observed inefficacy of TMS in these studies. An alternative association was also suggested by Marazziti et al. (2008), who implied that a stabilisation of OCD might bring a beneficial effect to depression [19]. This last hypothesis is supported by some of the studies included in this review, more specifically Ma et al. (2014) and Mantovani et al. (2010), which observed a reduction in the HAM-D scores only after having observed a reduction in the Y-BOCS scores [10, 20]. Despite the lack of understanding regarding the exact nature of the relationship between OCD and depression, there is an agreement that depression is an important factor that must be assessed in patients with OCD. Despite this notion, some studies in this review did not assess depression: Shayganfard et al. (2016) [6], Jahangard et al. (2016) [21], Haghghi et al. (2015) [22] and Elbeh et al. (2016) [23]. As a result, it is difficult to know the impact that depression could have had in these trials' results.

Regarding the frequency of stimulation, there was a preferential use of high-frequency TMS in the studies that targeted the DLPFC (6/9 studies), in comparison to the studies that targeted the SMA (5/5 studies) or the OFC (2/2 studies), all of which used low-frequency TMS. Considering that low-frequency TMS has inhibitory effects, reducing cortical excitability, and that high-frequency TMS has excitatory effects, increasing cortical excitability [7, 24], a preferential use of low-frequency TMS might have been expected, due to the aforementioned hyperactivity in certain cerebral areas in OCD. In fact, only one study compared simultaneously high-frequency and low-frequency TMS (Elbeh et al. (2016)), and that study suggested that low-frequency TMS might cause long-term effects, since the reduction in Y-BOCS was maintained in the 3-months follow-up period, while high-frequency TMS might cause short-term effects, since such reduction was only maintained for two weeks in the high-frequency group [23]. It is worth noting that it is difficult to generalise the results of just one study. Moreover, in the studies that targeted the DLPFC, both low-frequency and high-frequency were associated with both an efficacy and inefficacy of TMS, which makes any generalisation more difficult.

There are also some studies, amongst those that targeted the DLPFC, that are worth mentioning.

Ma et al. (2014) conducted a study that used α EEG-guided TMS, a technique that had previously been used to treat schizophrenia and that showed promising results in these patients [25]. In fact, OCD is associated with changes in the EEG, such as a reduction in the alpha frequency in the frontotemporal region [26]. α EEG-guided TMS allows researchers to adjust the TMS frequency to the patient's intrinsic α frequency, which helps to individualise treatment

Table 1. Results of the studies that focused on the dorsolateral prefrontal cortex (DLPFC).

Study name	Sample size	Average age	Major Depression	Disease duration	Baseline Y-BOCS	Treatment duration	N° of sessions	Follow-up	Frequency	Coil type	Placebo strategy	Results	Response rate
Shayganfard et al. (2016) ^{(6),a}	10 (E.G.:5; C.G.:5)	33.50 years	No	NR ^d	33.80	2 weeks	10	No	High (20Hz)	Double Air Film	Tilted	Y-BOCS: reduction at 2 nd week (11.2 e 8 points) in each group after real TMS. <u>TMS is effective in OCD.</u>	NR
Jahangard et al. (2016) ^{(21),a}	10 (E.G.:5; C.G.:5)	33.10 years	No	NR	31.00	2 weeks	10	No	High (20Hz)	Double Air Film	Tilted	Y-BOCS: reduction at 2 nd week (9.8 e 8.4 points) in each group after real TMS. <u>TMS is effective in OCD.</u>	NR
Seo et al. (2016) ⁽³⁰⁾	27 (E.G.:14; C.G.:13)	35.45 years	Yes (22 patients)	NR	33.25	3 weeks	15	No	Low (1Hz)	Figure of Eight	Sham	Y-BOCS: reduction at 3 rd week. HAM-D: reduction at 2 nd week. HAM-A: unchanged. <u>TMS is effective in OCD and depression, without affecting anxiety.</u>	E.G.:50% C.G.:23.1%
Elbeh et al. (2016) a ⁽²³⁾	45 (E.G.:15/15 C.G.:15)	27.07 years	No	18.7 months	25.63	2 weeks	10	3 months	Low (1Hz) and High (10Hz)	Figure of Eight	Tilted	Y-BOCS: <i>Low-frequency</i> : reduction at 2 nd week (12 points) and at the 3 months follow-up (11 points). <i>High-frequency</i> : reduction at 2 nd week (6.8 points). HAM-A: <i>Low-frequency</i> : reduction at 2 nd week and at the 3 months follow-up. <i>High-frequency</i> : reduction at 2 nd week. <u>Low-frequency TMS is effective in OCD at short and long-term. High-frequency TMS is effective in OCD at short-term.</u>	NR
Haghighi et al. (2015) ^{(22),a}	21 (E.G.:10; C.G.:11)	35.86 years	No	NR	30.25	2 weeks	10	No	High (20Hz)	Double Air Film	Tilted	Y-BOCS: reduction at 2 nd week in each group after real TMS. <u>TMS is effective in OCD.</u>	E.G.:60% e 73% C.G.:0%
Ma et al. (2014) ⁽¹⁰⁾	46 (E.G.:25; C.G.:21)	28.49 years	No	12.43 years	24.44	2 weeks	10	1 week	High (8-12Hz)	Circular	Sham	Y-BOCS: reduction at 2 nd week and at the 1-week follow-up. HAM-D: reduction at the 1-week follow-up. HAM-A: reduction at 2 nd week and at the 1-week follow-up. <u>TMS is effective in OCD, and belatedly in depression.</u>	E.G.:90% (2 nd week)/60% (follow-up) C.G.:0%
Sarkhel et al. (2010) ^{(13),cB}	42 (E.G.:21; C.G.:21)	30.67 years	No	7.05 years	24.65	2 weeks	10	2 weeks	High (10Hz)	Figure of Eight	Tilted	Y-BOCS: unchanged. HAM-D: reduction at 2 nd week and at the 4-week follow-up. <u>TMS is not effective in OCD, but effective in depression.</u>	NR
Sachdev et al. (2007) ⁽¹¹⁾	18 (E.G.:10; C.G.:8)	32.65 years	No	12.45 years	24.85	2 weeks	10	2 weeks	High (10Hz)	Figure of Eight	Sham	Y-BOCS: reduction at the 4-week follow-up. MADRS: reduction at the 4-week follow-up. <u>TMS isn't effective in OCD, due to depression's confounding factor.</u>	E.G.:30% C.G.:25%
Alonso et al. (2001) ⁽¹²⁾	18 (E.G.:10; C.G.:8)	34.17 years	No	NR	24.72	6 weeks	18	10 weeks	Low (1Hz)	Circular	Tilted	Y-BOCS: unchanged. HAM-D: unchanged. <u>TMS is not effective in OCD.</u>	E.G.:20% C.G.:12.5%

^acrossover study; ^bE.G.: experimental group; ^cC.G.: control group; ^dNR: not referred.

Table 2. Results of the studies that focused on the supplementary motor area (SMA).

Study name	Sample size	Average age	Major Depression	Disease duration	Baseline Y-BOCS	Treatment duration	N° of sessions	Follow-up	Frequency	Coil type	Placebo strategy	Results	Response rate
Pelissolo et al. (2016) ⁽²⁸⁾	36 (E.G. ^a :20; C.G. ^b :16)	40.7 years	Yes (75% of patients)	21.9 years	29.40	4 weeks	20	12 weeks	Low (1Hz)	Figure of Eight	Sham	Y-BOCS: unchanged. HAM-D: unchanged. <u>TMS is not effective in neither OCD nor depression.</u>	E.G.:10.5% C.G.:20%
Hawken et al. (2016) ⁽¹⁵⁾	22 (E.G.:10; C.G.:12)	33.5 years	No	12.5 years	28.00	6 weeks	25	6 weeks	Low (1Hz)	Figure of Eight	Tilted	Y-BOCS: reduction at 6 th week and at the 6-week follow-up. HAM-D: reduction at 6 th week. No follow-up data. <u>TMS is effective in OCD and depression.</u>	E.G.:80% C.G.:8%
Pallanti et al. (2016) ⁽³¹⁾	50 (E.G.:25; A.G.:25)	33.46 years	Yes (4 patients)	NR ^c	30.80	3 weeks	15	No	Low (1Hz)	Figure of Eight	Without	Y-BOCS: reduction at 3 rd week. HAM-D: reduction at 3 rd week. HAM-A: reduction at 3 rd week. <u>TMS is more effective in OCD than antipsychotics. antipsicóticos.</u>	E.G.:68% A.G. ^d :24%
Gomes et al. (2012) ⁽²⁹⁾	22 (E.G.:12; C.G.:10)	36.5 years	Yes (17 patients)	18.25 years	34.10	2 weeks	10	14 weeks	Low (1Hz)	Figure of Eight	Sham	Y-BOCS: reduction at 2 nd week and at the 14-week follow-up. HAM-D: unchanged. HAM-A: reduction at 2 nd week <u>TMS is effective in OCD.</u>	G.E.:42% G.C.:12%
Mantovani et al. (2010) ⁽²⁰⁾	18 (E.G.:9; C.G.:9)	39.55 years	Yes (10 patients)	22.25 years	26.35	4 weeks	20	3 months	Low (1Hz)	Figure of Eight	Sham	Y-BOCS: reduction at 4 th week and at the 3-month follow-up. HAM-D: reduction at the 3-month follow-up. HAM-A: reduction at the 3-month follow-up. <u>TMS is effective in OCD.</u>	E.G.:67% C.G.:22%

^aE.G.: experimental group. ^bC.G.: control group. ^cNR: not referred. ^dA.G.: antipsychotics group.

Table 3. Results of the studies that focused on the orbitofrontal cortex (OFC).

Study name	Sample size	Average age	Major Depression	Disease duration	Baseline Y-BOCS	Treatment duration	N° of sessions	Follow-up	Frequency	Coil type	Placebo strategy	Results	Response rate
Nauczyciel et al. (2014) ^{(27),a}	19 (E.G. ^b :10; C.G. ^c :9)	39 years	Yes (6 patients)	NR ^d	32.00	1 week	10	No	Low (1Hz)	Butterfly double-cone coil	Sham	Y-BOCS: reduction at 1 st week in the experimental and control groups (6 e 2 points), normalising 1 month after (1 e 0 points). HAM-D: unchanged. <u>TMS is effective in OCD at short-term.</u>	NR
Ruffini et al. (2009) ⁽¹⁴⁾	23 (E.G.:16; C.G.:7)	40.8 years	No	NR	32.00	3 weeks	15	3 months	Low (1Hz)	Figure of Eight	Tilted	Y-BOCS: reduction since the 3 rd week to the 10 th week. HAM-D: unchanged. HAM-A: unchanged. <u>TMS is effective in OCD at short-term.</u>	E.G.:75% C.G.:14.3%

^acrossover study; ^bE.G.: experimental group; ^cC.G.: control group; ^dNR: not referred.

[10]. Such treatment individualisation might be partially responsible for the observed efficacy of TMS in OCD and for the late improvement in the depressive symptoms in this trial, which improved only in the first week of follow-up. Ma et al. (2014) also used a circular coil (similarly to Alonso et al. (2001)) which, as mentioned previously, reduces the precision in targeting the desired area of the brain, despite offering greater penetration [7, 9]. In the end, such observations might suggest that α EEG-guided TMS might be a promising choice in the future, although more clinical trials are needed to prove its efficacy in OCD [10].

Haghighi et al. (2015), Jahangard et al. (2016) and Shayganfard et al. (2016) were performed by the same researchers in the same location (Hamadan, Iran) and in close dates (2014/2014, 2014 and 2015, respectively) [6, 21, 22]; as a result, a sampling bias might be present, as we do not know if the same patient might have been included in one or more of these studies. In fact, the demographic data of these trials seem to suggest that, as there seems to be a significant similarity between the sampling characteristics of these studies (regarding average age of patients, baseline Y-BOCS and lack of major depression). Other limitations of these trials that might reduce their statistical power are the small sample sizes (Jahangard et al. (2016) and Shayganfard et al. (2016) had 10 patients each), the fact that depression was not assessed—unlike most studies—and, finally, the presence of a crossover design. In this type of design, patients change from experimental group to control group and vice-versa, which increases the chance that they realise the difference between a real coil and a tilted/sham coil and, as a result, blinding could be affected. The same disadvantage associated with a crossover design holds true for the study conducted by Nauczyciel et al (2014) [27].

Regarding the studies that targeted the Supplementary Motor Area (SMA), Pelissolo et al. (2016) was the only one that reported an inefficacy of TMS in the treatment of OCD, with no reduction of either obsessive-compulsive or depressive symptoms. Moreover, this study seems to be robust and with high statistical power, due to its considerable sample size of 36 patients (in comparison with the average sample size), a duration of treatment of four weeks (which is higher than the average) and, also, due to its use of a MRI-based neuronavigation system to target precisely the SMA [28]. Therefore, despite the high statistical power of the study performed by Pelissolo et al. (2016), it is important to mention that the remaining four studies that targeted the SMA reached a different conclusion, specifically that TMS might be effective in treating OCD.

Approaching each one of these studies individually, we have the following: Mantovani et al. (2010), after the expected four weeks of treatment, offered four more weeks of TMS to every patient in the trial (independently of the group that they belonged to previously), except to those who did not show a reduction in the Y-BOCS $\geq 25\%$ (labelled as responders). As a result, since responders were excluded

after the initial four weeks of treatment, any result that was obtained past four weeks, including during the follow-up, might be biased to produce positive results. Long-term conclusions are, therefore, difficult to assess in this study [20].

Gomes et al. (2012) reported a reduction in OCD symptoms regardless of depressive symptoms, contrary to what previous studies had shown; besides that, after the three-month follow-up period, HAM-A scores increased to those close to baseline, without a similar increase in Y-BOCS [29]. Considering that OCD and anxiety have a close relationship with one another, these findings seem to be incongruent [1, 29]. This dissociation between OCD and anxiety was something that was also observed in the study performed by Seo et al. (2016), who observed a reduction of the Y-BOCS scores without a similar reduction in HAM-A scores [30].

Regarding Pallanti et al. (2016), one particularity of his study was the absence of a control group. Instead, the researchers compared the efficacy of TMS with the efficacy of antipsychotic drugs (complemented with a SSRI/clomipramine), with risperidone being the most used antipsychotic (in 84% of patients) [31]. However, it is worth mentioning that the lack of a control group does not invalidate the presence of a placebo effect. In fact, due to the absence of a sham or tilted coil, the placebo effect might be present in the TMS group, as patients can have the notion that this technique is new or innovative, thus predisposing them to more positive results [32]. In the end, the results suggested that TMS might be better than antipsychotics in treating OCD, as a last-line treatment [31].

Lastly, Hawken et al. (2016) conducted a study that included two different populations with similar characteristics (differing only in the duration of the disease). However, the follow-up period only included patients from one of the two initial populations (15/22 patients), which can compromise the long-term conclusions of this study [15].

Overall, in the studies that targeted the SMA, there seems to be a direct relationship between the duration of treatment or number of sessions and the response to treatment, with a higher duration being associated with higher response rates. Therefore, from the lowest to the highest duration of treatment, Gomes et al. (2012) resorted to 10 sessions in 2 weeks of treatment, Pallanti et al. (2016) resorted to 15 sessions in 3 weeks of treatment, Mantovani et al. (2010) resorted to 20 sessions in 4 weeks of treatment and Hawken et al. (2016) resorted to 25 sessions in 6 weeks of treatment, obtaining response rates of, respectively, 42%, 68%, 67% and 80% [15, 20, 29, 31].

Lastly, the studies that targeted the SMA also revealed a higher prevalence of concomitant major depression (in 4/5 studies) which, as referred previously, might be a reason that can distort the positive results that were obtained.

Concerning the two studies that targeted the Orbitofrontal Cortex (OFC), both reached the same conclusion: that TMS has a temporary effect in reducing OCD symptoms, since such reduction was no longer observed after a few

weeks [14, 27]. Moreover, both studies also suggested that the technique's effect over OCD is independent from its effect over depression, since there were no changes in HAM-D in either study, with Ruffini et al. (2009) suggesting that such effect is also independent from TMS's effect over anxiety, since HAM-A scores were also unaffected.[14, 27]. In fact, these claims are supported by Nauczyciel et al. (2014), who performed a PET scan in both groups, after the end of the study. What he observed was a reduction in glucose metabolism in OFC only in the group which was subject to TMS, which can suggest a direct cause-effect relationship between applying TMS and a reduction in obsessive-compulsive symptoms, via a reduction of OFC's metabolism [27].

However, the generalisation of these conclusions should take into consideration that only two studies who targeted the OFC were included in this review, as no other study that targeted the OFC was found. Such lack of studies could perhaps be explained due to the deeper location of the orbitofrontal cortex which, in practice, can make targeting it a difficult task. In fact, this is what prompted Nauczyciel et al. (2014) to resort to a butterfly double-cone coil, whose design allows TMS to reach greater depths [27, 33]. On the other hand, the presence of a high heterogeneity in these two studies (regarding the presence of major depression, treatment duration, number of sessions, presence of follow-up, coil type and placebo strategy), perhaps more noticeable than in the other trials, could also diminish their statistical power and compromise their conclusions.

Limitations of this review include the reduced sample size across all studies (average 318 of 27.5 participants per study, with $n=427$) and the heterogeneity of the demographic, 319 clinical and therapeutic variables, which are presented in Tables 1, 2 and 3.

Amongst the demographical variables, the reduced sample size, as mentioned above, is particularly notorious in the studies of Shayganfard et al. (2016) and Jahangard et al. (2016), who included only 10 patients each [6, 21]. Regarding the clinical variables, the presence of major depression was most noticeable in the studies that targeted the SMA (4/5 studies), in comparison to the studies that targeted the DLPFC (1/9 studies). Information regarding the average duration of the disease was also missing in 7/16 studies and, furthermore, amongst the studies that assessed it, Elbeh et al. (2016) presented an average disease duration much lower than the rest (18.7 months, in comparison to the average of 12.2 years) [23], which can predispose to more favourable responses to treatment. Finally, regarding the treatment parameters, the duration of treatment and number of sessions were higher in the studies that targeted the SMA, which might predispose to better results since a longer duration of stimulation induces effects that persist for longer [7]. On the other hand, not all studies presented a follow-up period, which limits the assessment of long-term results. Coil type and placebo strategy varied greatly amongst the RCTs, therefore making it difficult to evaluate its impact in this review.

A third limitation of this review is the absence of an ideal sham condition. While tilting the coil can promote blinding by placing it outside the patient's field of vision, the blinding of the operator is not guaranteed; on the other hand, using a sham coil can theoretically guarantee double-blindness, as long as the operator is unaware that the coil is fake [9]. Moreover, a tilted coil can preserve the scalp sensation associated with an active coil, while a sham coil can preserve the auditory sensation present in a real stimulation; both factors can be arguments towards a greater resemblance to an active coil, and for the assurance of blinding [8, 34]. Lastly, tilting the coil can also be associated with biological effects that may influence results [9].

Fourthly, only patients who had treatment-refractory OCD were included in all the clinical trials, thus making it unable to assess whether the results would have stayed the same in the absence of such resistance.

A fifth limitation of this review is that patients were taking medication (mainly SSRI/clomipramine) alongside TMS, a pattern which was observed in all studies. In particular, patients were also taking benzodiazepines in 6/16 studies, and the importance of this pharmacological class is its inhibitory effect on cerebral excitability [20, 35]. In fact, by reducing cerebral excitability, benzodiazepines might increase the intensity of TMS necessary to create the same effect in the absence of benzodiazepines. This logic is what motivated Mantovani et al. (2010) to prohibit patients from taking benzodiazepines during the duration of his study [20]. Lastly, and as mentioned before, the presence of comorbid depression in some of the studies is also another important limitation that must be mentioned.

The main reported side effects were headaches or localised scalp pain that disappeared shortly after the end of TMS, with no major side effect being observed. Hawken et al. (2016) and Ruffini et al. (2009) did not report, however, any information portraying the presence or absence of side effects [14, 15]. In fact, globally, TMS has very few complications, with headache or scalp pain/discomfort being the most common ones, although there is also a low convulsive risk associated with TMS [36]. Such risk, despite being low, can be slightly higher when the technique is applied with high-frequency over the DLPFC [31]. Therefore, the results obtained in this review support the idea that TMS is a technique that offers a high degree of safety.

Lastly, it is important to mention two large meta-analysis that focused on the same topic as this review, the ones conducted by Berlim et al. (2013) and Zhou et al. (2017), which included, respectively, 10 and 20 randomised clinical trials.

Berlim et al. (2013) deducted that high-frequency TMS over the DLPFC was not effective. However, when applied over the SMA or OFC, the technique seemed to reduce obsessive-compulsive symptoms. Overall, the response rate in the experimental groups was of 35%, in comparison to 13% in the control groups. It was also suggested that, when compared to other treatment options for treatment-resist-

ant OCD, such as antipsychotics, TMS offered the same level of efficacy [5].

In turn, Zhou et al. (2017) suggested that TMS applied over the DLPFC produces more evident results than when applied over the SMA or OFC, which differs completely from the results of Berlim et al. (2013). Moreover, it was also suggested some of the technique's parameters that seemed to make it more effective: an intensity of 100% of the RMT and a tilted coil as placebo strategy, with high and low frequency proven to be equally effective [8].

Conclusion

The high heterogeneity of the clinical trials and the incongruence of results make it difficult to establish, at this moment, any conclusion about the efficacy of transcranial magnetic stimulation in the treatment of obsessive-compulsive disorder.

Is it, therefore, necessary to conduct further studies on this topic, with more statistical power and larger sample sizes (n=427, in this review), and offer a more uniformity of sample variables and stimulation parameters, as well as a longer duration of treatment, number of sessions and longer follow-up periods. In particular, clinical trials without co-morbid psychiatric disorders such as depression, and without a treatment-resistant pattern of the disease, would contribute to a more precise assessment of this technique's efficacy in OCD.

Abbreviations

CGI: Clinical Global Impressions scale; DLPFC: Dorsolateral Prefrontal Cortex; HAM-A: Hamilton Rating Scale for Anxiety; HAM-D: Hamilton Rating Scale for Depression; MADRS: Montgomery-Åsberg Depression Rating Scale; OCD: Obsessive-compulsive disorder; OFC: Orbitofrontal Cortex; RCT: Randomised clinical trial; rTMS: repetitive transcranial magnetic stimulation; SMA: Supplementary Motor Area; TMS: Transcranial magnetic stimulation

Competing interests

The authors declare that there are no conflicts of interests.

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