Società Italiana di Psichiatria

Evidence based Psychiatric Care
Journal of the Italian Society of Psychiatry

Is Transcranial Magnetic Stimulation really safe? A systematic review and meta-analysis of its side effects

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Summary

Objective. The aim of the present meta-analysis was to investigate the safety of different Transcranical Magnetic Stimulation (TMS) protocols in pathological and healthy samples.

Methods. We used the following search words on Pubmed and Scopus, alone or in combination: TMS, side effects, secondary effects, adverse events (AEs). Comprehensive Meta-Analysis Software version 2 was used for data analysis.

Results. One-hundred and nine original papers were included in our quantitative synthesis, involving both healthy (N = 475) and pathological subjects (N = 4880). The pooled rate of dropouts due to side effects was 3.0%; subjects reporting at least one side effect were 13.7%. Headache, painful sensations, muscle twitching, ocular problems and discomfort were significantly related to active stimulation.

Conclusions. The results of our meta-analysis state that TMS is usually a safe technique, with mild and transient adverse events, that rarely provoke dropouts. Beside a complete assessment of the efficacy of TMS in different pathological conditions, it's also important to report in a clear and standardized way the occurrence of AEs.

Key words: Transcranical Magnetic Stimulation, dropout, adverse events, side effects, safety

Introduction

Transcranial Magnetic Stimulation (TMS) is a neuromodulation technique commonly used today to treat several clinical conditions, primarily neurological diseases, namely Parkinson's Disease (PD) [1], chronic pain [2], post-stroke recovery [3], essential tremor, Tourette's syndrome, amyotrophic lateral sclerosis, multiple sclerosis, epilepsy, Alzheimer's disease and tinnitus [4].

Regarding other clinical conditions, TMS has already been approved for the treatment of psychiatric pathologies, such as resistant depression [5-7]. Moreover, in the last decade, the interest for this treatment spread in several clinical trials, proving its efficacy in a large variety of conditions, such as Substance Use Disorder (SUD) [8], gambling [9], anxiety, obsessive compulsive disorder and schizophrenia [10].

TMS, based on Faraday's principle of electromagnetic induction [11], delivers magnetic stimuli through the scalp in conscious humans. There are many different types of TMS protocols: repetitive TMS (rTMS), used to induce

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How to cite this article: Sepede G, Miuli A, Spano MC, et al. Is Transcranial Magnetic Stimulation really safe? A systematic review and meta-analysis of its side effects. Evidence-based Psychiatric Care 2020;6:42-55. https://doi.org/10.36180/2421-4469-2020-09

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Conflict of interest
The Authors declare no conflict of interest.

changes in brain activity even after the stimulation period [12], single-pulse TMS (sTMS), used to explore brain functioning, and deep TMS (dTMS), which can modulate cortical excitability up to a maximum depth of 6 cm from the scalp, interfering, therefore, with deeper neural circuits [13]. The effect of TMS stimulation can be activating (Hz ≥ 10) or inhibiting (Hz ≤ 5) and it may vary according to the area stimulated and the coil type used [14-17].

Coils, which differ in shapes, are chosen in relation to their proprieties and the aim of the treatment. The most commonly used are: double coil (figure-8 coil), with a good efficiency and penetration (1.5-2.5 cm from the scalp), allowing to target a specific brain region [18], and Circular-shape coil, with good heat dissipation and stable head contact, but poor accuracy in stimulating a single area of the brain [19].

Even though TMS is usually safe and well tolerated, almost all the published articles report some collateral effects.

In order to confirm TMS safety, it is important to take into consideration the placebo and nocebo effects resulting from inactive forms of stimulations (usually called "sham") [20]. The neurobiological mechanism that causes the placebo effect has been widely studied in pharmacological treatments, but it still remains unclear. Several psychological factors, such as anxiety, suggestibility and patient's expectations, may contribute to this mechanism, and the biological response is mediated by the release of many neurotransmitters, such as endogenous opioids and dopamine. Those interactions activate different brain circuits, and, in particular, the prefrontal cortex seems to play a fundamental role [10,21-23]. With the reverse mechanism, adverse events could be recorded while using an inactive intervention, producing an effect called nocebo. Just as the placebo effect, the nocebo effect is caused by many psychological and neurobiological mechanisms and, in the specific, neurotransmitters seem to activate predominantly the limbic system [24]. In particular, a recent meta-analysis by Zis and colleagues [25] reports that the odds of dropping out, consequence of the side effects, do not differ between the sham and active treatment arms.

The aim of our meta-analysis is to analyze TMS studies, evaluate the adverse events and the rate of dropouts caused by collateral effects, involving not only clinical samples, but also healthy control groups. We also take into account several factors that may affect the tolerability, such as study design, publication year, protocols, stimulation intensity, coil type, target brain areas, acute treatment duration and clinical characteristics of the study samples.

Materials and methods

PubMed and Scopus were used as search engine to investigate the scientific literature about side effects of TMS on healthy subjects and pathological ones (affected by neurological, psychiatric or other disorders). The following words were used, alone or in combination, as query in the search engine: transcranial magnetic stimulation (TMS), side effects, secondary effects, Adverse Events (AEs).

The research, conducted on January 1st, 2019, yielded 635 records. After removing duplicate records, 331 potentially relevant abstracts were identified. Original articles (open label or double-blind trials, prospective or retrospective observational studies, case series and case reports) written in English, reporting number and type of AEs due to TMS, were included in the research. Instead, animal studies, in vitro experiments, reviews, commentaries and studies not specifying side effects of TMS were excluded from the research.

After screening each abstract, copies of potentially relevant articles were obtained. Afterwards, AM, GS, MCS and GSt independently reviewed the articles before discussing them with the other members of the group, overcoming any eventual disagreement on the selection of the studies. Sixty-eight records were excluded only by reading title and abstract. From the remaining 154 articles, 109 papers, that met our inclusion/exclusion criteria, were selected by reading the full text and were, therefore, included in the quantitative synthesis (Fig. 1).

Data extraction

The following data were reported for each study: article identification, year of publication, total number of participants, average age, study design (double blind randomized controlled trial (DB-RCT); single blind randomized controlled trial (SB-RCT); Open label; Retrospective studies; Case series/case reports), protocol arms (TMS, sham, other treatments), study duration, characteristics of participants based on the underlying pathology (psychiatric, neurological, healthy, other), machine type, coil, TMS protocol (rTMS, sTMS, dTMS, TBS, mixed, others), stimulation details (mean hertz, N impulses/session, resting motor threshold, target lobe). Data regarding the total number of dropouts, dropouts due to AEs, number of subjects reporting at least an AE, more commonly reported AEs (> 1%) were extracted.

The dropout rate and the AE rate, initially in all the studies and then in the studies comparing TMS to sham, were calculated using Excel.

Statistical analysis

A database was developed using Excel. The following variables were reported as outcomes of interest: total number of dropouts, dropouts due to AE, number of participants experiencing at least an AE during TMS. In case of studies with a placebo arm, a TMS *vs* sham comparison was also conducted. The meta-analysis was performed using Comprehensive Meta-Analysis Software version 2 [26], obtaining a pooled estimate (odds ratio) for each outcome of interest.

The random effects model was used as a conservative approach to account for different sources of variation among studies. Q statistics and I-squared index were used

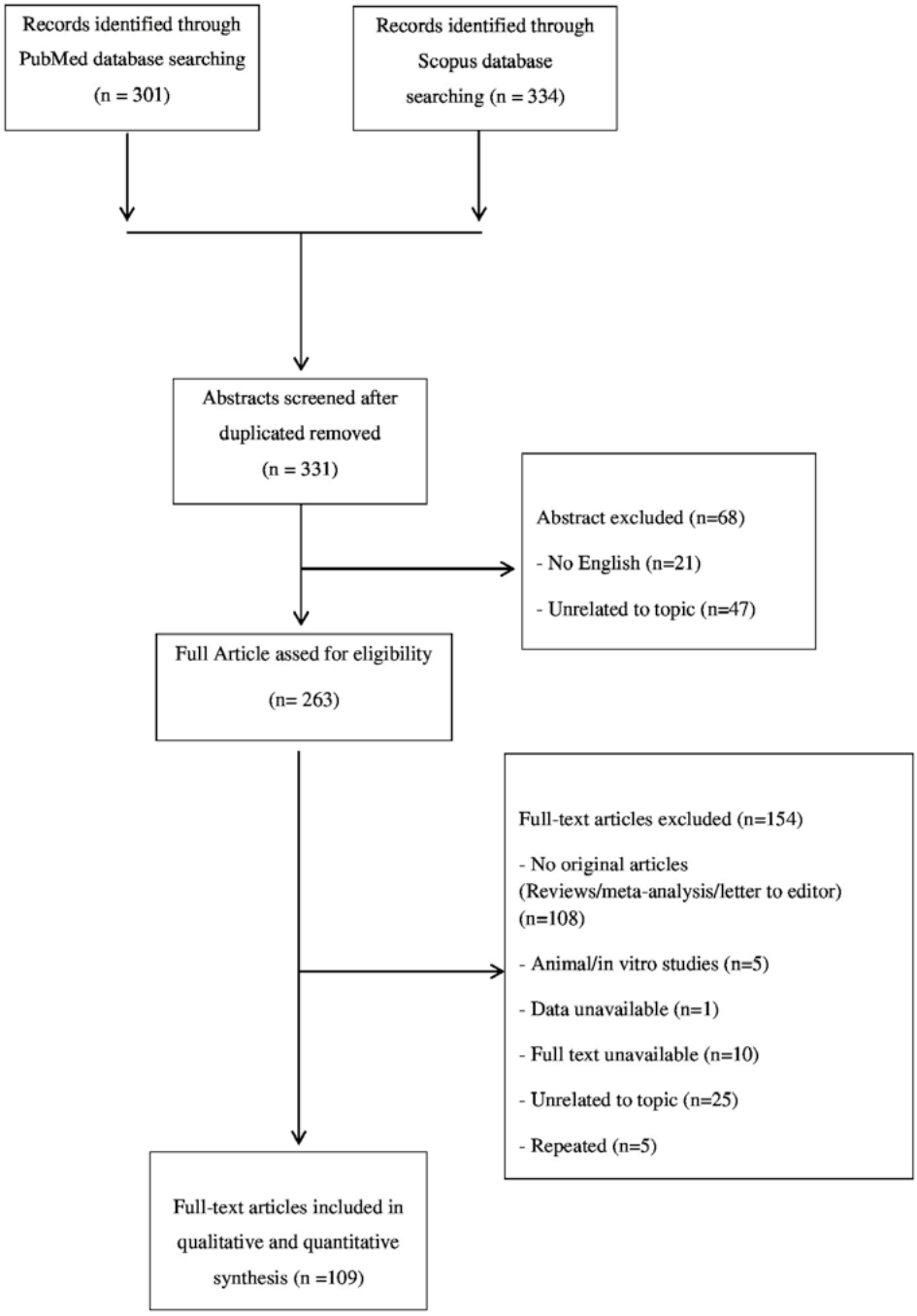

Figure 1.
Flow chart of the systematic review.

to assess heterogeneity among study point estimates. In case of heterogeneous results, a meta-analysis for each level of the categorical variables was performed to evaluate the influence of categorical moderators on study outcomes. The possibility of publication bias was examined applying Fail-safe method [27] and "Trim and fill" method [28].

Data availability

The Excel database, complete in all the extracted data, is available under request.

Results

A total of 110 experiments, reported in 109 articles, was considered: DB-RCTs (35), SB-RCTs (15), open label trials (39), retrospective studies (4) and case series/case reports (17). These articles were published between 1990 and 2018 and involved 5,355 subjects.

The primary diagnoses of the participants were the following:

1. psychiatric disorders (N = 2691): mood disorders (N = 2451); schizophrenic disorder (N = 27); SUD (N = 16); OCD (N = 33); other disorders (N = 164);

2. neurological disorders (N = 1004): PD (N = 237); stroke (N = 195), multiple sclerosis (N=106); chronic tension type headache (N=98), other neurological disorders (N = 368);
3. other conditions (N = 1,185);
4. healthy subjects (N = 475).

Dropout rates (Tab. I)

a. In all studies.
   Ninety-eight articles provide the required data to calculate the dropout rates that are included in the meta-analysis.
   The pooled dropout rate was 5.6% (95% CI = 4.0-8.0%), with a high heterogeneity (I^2 = 80.0%; Q = 485.2, p < 0.001). Taking into account the risk of publication bias, the adjusted rate was 10.6% (Trim and fill Adjusted value RFX, N studies trimmed right of mean = 36; Fail-safe Z = -30.0, p < 0.001; N missing = 23,180).
   Considering only DB-RCTs (N = 35), a pooled dropout rate of 5.4% (95% CI = 3.1-9.0%) was obtained, with a high heterogeneity (I^2 = 88.9%; Q = 307.3, p < 0.001) and an adjusted RFX value of 10.2% (Trim and fill: N studies trimmed right of mean = 13; Fail-safe Z = -22.0, p < 0.001; N missing = 4,361).
b. Due to side effects.
   Ninety-eight articles were included in the meta-analysis.
   The pooled dropout rate due to side effects was 3.0% (95% CI = 2.5-3.7%), with a low heterogeneity (I^2 = 0.0%; Q = 87.1, p = 0.75) (Trim and fill Adjusted value RFX = 3.7%, studies trimmed right of mean = 19; Fail-safe Z = -29.7, p < 0.001; N missing = 22,388;).
   Considering only the DB-RCTs (N = 35), a pooled dropout rate of 2.7% (95% CI = 2.0-3.7%) was obtained, with a low heterogeneity (I^2 = 5.8%; Q = 36.1, p = 0.37) (Fail-safe Z = -21.5, p < 0.001; N missing = 4169; Trim and fill Adjusted value RFX = 3.6%, N studies trimmed right of mean = 13).
   Regarding the sham *vs* stim comparison, the meta-analysis was possible only for 5 studies and the results were not significant: RFX pooled odds ratio= 1.04 (95% CI = 0.44-2.48), p = 0.93; with no heterogeneity (I^2 = 0.0%; Q = 1.5, p = 0.83) and a low risk of publication bias (Trim and fill Adjusted value RFX = 1.04, N studies trimmed right of mean = 0; Fail-safe Z = 0.01, p = 0.99; N missing = 0).

Participants reporting at least one side effect (Tab. II)

a. In all studies.
   Seventy-four articles were included in the meta-analysis.
   The pooled rate of participants reporting at least one side effect was 13.7% (95% CI = 9.6-19.2%), with a high heterogeneity (I^2 = 88.1%; Q = 614.5, p < 0.001) and Trim and fill Adjusted value RFX = 25.1% (studies trimmed right of mean = 20; Fail-safe Z = -16.2, p < 0.001; N missing = 4,997)
   In order to analyze in detail, the possible reasons for the high heterogeneity registered, the following

Table I. Drop out: meta-analysis results.

Outcome	N studies	Pooled effect size (95% CI)	Q for heterogeneity	Fail safe Z for publication bias (p, N missing)	Trim and Fill adjusted values RFX for publication bias
Total dropout rates in all studies	N = 98	Pooled dropout rates = 5.6% (4.0-8.0%)	I^2 = 80.0% Q = 485.2 (p < 0.001)	Z = -30.0 (p < 0.001; N missing = 23180)	Adjusted values=10.6% N studies trimmed right of mean N = 36
Dropout rate due to side effect	N = 98	Pooled dropout rates = 3.0% (2.5-3.7%)	I^2 = 0.0% Q = 87.1 (p = 0.75)	Z = -29.7 (p < 0.001; N missing = 22388)	Adjusted values = 3.7% N studies trimmed right of mean N = 19
Dropout rates due to side effects in DBRCTs	N = 35	Pooled dropout rates = 2.7% (2.0-3.7%)	I^2 = 5.8% Q = 36.1 (p = 0.37)	Z = -21.5 (p < 0.001; N missing = 4169)	Adjusted values = 3.6% N studies trimmed right of mean N = 13
Dropout rates due to side effects in psychiatric sample	N = 46	Pooled dropout rates = 3.1% (2.1-4.6%)	I^2 = 38.4% Q = 73.0 (p = 0.005)	Z = -21.8 (p < 0.001; N missing = 5660)	Adjusted values = 4.8% N studies trimmed right of mean N = 14
Dropout due to side effect sham *vs* active comparison	N = 5	RFX pooled Odds Ratio = 1.04 (0.44-2.48) p = 0.93	I^2 = 0.0% Q = 1.5 (p = 0.83)	Z = -0.01 (p = 0.99; N missing = 0)	Adjusted values = 1.04 N studies trimmed right of mean N = 0
Dropout due to side effect in psychiatric sample sham *vs* active comparison	N = 3	RFX pooled Odds Ratio = 1.41 (0.50-3.93) p = 0.51	I^2 = 0.0% Q = 0.28 (p = 0.87)	Z = 0.70 (p = 0.49; N missing = 0)	Adjusted values = 1.41 N studies trimmed right of mean N = 0

CI: Confidence Interval; DBRCTs: Double Blind Randomized Controlled Trials; RFX: Random-Effects.

Table II. Subjects reporting at least one side effect: meta-analysis results.

Outcome	N studies	Pooled effect size (95% CI)	Q for heterogeneity	Fail safe Z for publication bias (p, N missing)	Trim and Fill adjusted values RFX for publication bias
Subjects reporting at least one side effect	N = 74	Pooled rates = 13.7% (9.62-19.2%)	I^2 = 88.1% Q = 614.5 (p < 0.001)	Z = -16.2 (p < 0.001; N missing = 4,997)	Adjusted values = 25.1 N studies trimmed right of mean N = 20
• Year of publication 2018-2014	N = 29	Pooled rates = 15.6% (9.0-25.6%)	I^2 = 90.0% Q = 279.7 (p < 0.001)	Z = -8.1 (p < 0.001; N missing = 471)	Adjusted values = 32.0% N studies trimmed right of mean N = 9
• Year of publication previously 2013	N = 45	Pooled rates = 13.5% (9.0-19.7%)	I^2 = 76.9% Q = 190.2 (p < 0.001)	Z = -14.3 (p < 0.001; N missing = 2,342)	Adjusted values = 23.3% N studies trimmed right of mean N = 13
• Psychiatric sample	N = 34	Pooled rates = 12.6% (7.2-21.1%)	I^2 = 90.4% Q = 343.2 (p < 0.001)	Z = -11.5 (p < 0.001; N missing = 1,147)	Adjusted values = 23.1% N studies trimmed right of mean N = 9
• Neurological sample	N = 19	Pooled rates = 9.4% (3.5-22.5%)	I^2 = 84.2% Q = 114.1 (p < 0.001)	Z = -7.9 (p < 0.001; N missing = 288)	Adjusted values = 17.6% N studies trimmed right of mean N = 5
• Healthy subjects sample	N = 14	Pooled rates = 17.7% (6.3-40.9%)	I^2 = 82.5% Q = 74.5 (p < 0.001)	Z = -4.7 (p < 0.001; N missing = 67)	Adjusted values = 23.9% N studies trimmed right of mean N = 2
• Other sample	N = 5	Pooled rates = 24.9% (11.5-44.8%)	I^2 = 89.1% Q = 36.8 (p < 0.001)	Z = -7.2 (p < 0.001; N missing = 68)	Adjusted values = 28.3% N studies trimmed right of mean N = 1
• DBRCT	N = 24	Pooled rates = 14.0% (8.1-23.2%)	I^2 = 91.9% Q = 285.8 (p < 0.001)	Z = -10.9 (p < 0.001; N missing = 718)	Adjusted values = 25.0% N studies trimmed right of mean N = 8
• Other designs	N = 50	Pooled rates = 13.5% (8.3-21.4%)	I^2 = 82.1% Q = 273.8 (p < 0.001)	Z = -12.2 (p < 0.001; N missing = 1,884)	Adjusted values = 24.8% N studies trimmed right of mean N = 12
• 1 single stimulation during acute treatment	N = 14	Pooled rates = 12.2% (4.0-31.5%)	I^2 = 74.7% Q = 51.4 (p < 0.001)	Z = -6.24 (p < 0.001; N missing = 128)	Adjusted values = 22.4% N studies trimmed right of mean N = 3
• ≤ 2 weeks of acute treatment	N = 39	Pooled rates = 12.4% (8.0%-18.8%)	I^2 = 81.8% Q = 209.1 (p < 0.001)	Z = -13.58 (p < 0.001; N missing = 1,834)	Adjusted values = 27.0% N studies trimmed right of mean N = 16
• > 2 weeks of acute treatment	N = 21	Pooled rates = 19.3% (9.6-34.9%)	I^2 = 93.0% Q = 287.8 (p < 0.001)	Z = -6.85 (p < 0.001; N missing = 236)	Adjusted values = 31.7% N studies trimmed right of mean N = 4
• Age of participant < 18 years	N = 1	Point estimate = 55.5% (25.1-82.3%)	N/A	N/A	N/A

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Table II *(follows)*. Subjects reporting at least one side effect: meta-analysis results.

Outcome	N studies	Pooled effect size (95% CI)	Q for heterogeneity	Fail safe Z for publication bias (p, N missing)	Trim and Fill adjusted values RFX for publication bias
• Age of participant 18-65 years	N = 58	Pooled rates = 14.2% (9.5-20.7%)	I^2 = 88.9% Q = 513.1 (p < 0.001)	Z = -14.41 (p < 0.001; N missing = 3,080)	Adjusted values = 24.6% N studies trimmed right of mean N = 15
• Age of participant > 65 years	N = 7	Pooled rates = 12.4% (2.8-40.8%)	I^2 = 79.1% Q = 28.7 (p < 0.001)	Z = -4.24 (p < 0.001; N missing = 26)	Adjusted values = 18.2% N studies trimmed right of mean N = 1
• rTMS	N = 61	Pooled rates = 12.2% (8.2-17.9%)	I^2 = 88.6% Q = 526.2 (p < 0.001)	Z = -15.59 (p < 0.001; N missing = 3,801)	Adjusted values = 22.9% N studies trimmed right of mean N = 18
• rTMS < 5Hz	N = 17	Pooled rates = 8.7% (4.5-16.7%)	I^2 = 70.3% Q = 53.9 (p < 0.001)	Z = -10.38 (p < 0.001; N missing = 460)	Adjusted values = 20.7% N studies trimmed right of mean N = 8
• rTMS = 5Hz	N = 2	Pooled rates = 5.5% (0.3-55.9%)	I^2 = 66.9% Q = 3.02 (p = 008)	N/A	N/A
• rTMS > 5Hz	N = 41	Pooled rates = 14.9% (9.12-23.5%)	I^2 = 90.8% Q = 434.2 (p < 0.001)	Z = -11.26 (p < 0.001; N missing = 1,313)	Adjusted values = 26.9% N studies trimmed right of mean N = 11
• rTMS not specified Hz	N = 1	Point estimate = 27.7% (0.2-32.2%)	N/A	N/A	N/A
• rTMS N impulses ≤ 1,000	N = 9	Pooled rates = 15.1% (4.7-38.9%)	I^2 = 76.0% Q = 33.2 (p < 0.001)	Z = -4.87 (p < 0.001; N missing = 47)	Adjusted values = 26.4% N studies trimmed right of mean N = 2
• rTMS N impulses 1,001-2,000	N = 28	Pooled rates = 14.7% (8.4-24.6%)	I^2 = 92.5% Q = 362.6 (p < 0.001)	Z = -11.38 (p < 0.001; N missing = 917)	Adjusted values = 27.7% N studies trimmed right of mean N = 9
• rTMS N impulses 2,001-3,000	N = 3	Pooled rates = 13.7% (0.8-75.7%)	I^2 = 82.44% Q = 11.4 (p = 0.003)	Z = -2.15 (p = 0.031; N missing = 1)	Adjusted values = 13.7% N studies trimmed right of mean N = 0
• rTMS N impulses > 3,000	N = 7	Pooled rates = 18.3% (8.4-49.8%)	I^2 = 82.5% Q = 34.3 (p < 0.001)	Z = -3.17 (p = 0.001; N missing = 12)	Adjusted values = 18.3% N studies trimmed right of mean N = 0
• rTMS N impulses not specified	N = 6	Pooled rates = 4.2% (0.5-27.1%)	I^2 = 83.1% Q = 29.5 (p < 0.001)	Z = -3.17 (p = 0.001; N missing = 12)	Adjusted values = 8.6% N studies trimmed right of mean N = 2
• dTMS	N = 4	Pooled rates = 21.0% (5.8%-53.7%)	I2 = 88.4% Q = 25.8 (p < 0.001)	Z = - 4.32 (p < 0.001; N missing = 16)	Adjusted values = 21.0% N studies trimmed right of mean N = 0

(continues)

Table II *(follows)*. Subjects reporting at least one side effect: meta-analysis results.

Outcome	N studies	Pooled effect size (95% CI)	Q for heterogeneity	Fail safe Z for publication bias (p, N missing)	Trim and Fill adjusted values RFX for publication bias
• dTMS > 5Hz	N = 4	Pooled rates = 21.0% (5.8-53.7%)	I^2 = 88.4% Q = 25.8 (p < 0.001)	Z = -4.32 (p < 0.001; N missing = 16)	Adjusted values = 21.0% N studies trimmed right of mean N = 0
• dTMS N impulses ≤ 1,000	N = 1	Point estimate = 52.1% (38.2-65.7%)	N/A	N/A	N/A
• dTMS N impulses 1,001-2,000	N = 2	Pooled rates = 23.9% (7.5-54.8%)	I^2 = 65.1% Q = 2.9 (p = 0.09)	N/A	N/A
• dTMS N impulses 2,001-3,000	N = 1	Point estimate = 0.6% (0.04-8.9%)	N/A	N/A	N/A
• sTMS	N = 1	Event rate = 97.6% (71.3-99.8%)	N/A	N/A	N/A
• TBS	N = 2	Pooled rates = 2.8% (3.6-16.2%)	I^2 = 0.0% Q = 0.32 (p = 0.57)	N/A	N/A
• Mixed protocol	N = 2	Pooled rates = 43.4% (5.2-91.4%)	I^2 = 80.9% Q = 5.2 (p = 0.02)	N/A	N/A
• Other protocols	N = 1	Point estimate = 96.4% (61.6-99.7%)	N/A	N/A	N/A
• Not specified protocol	N = 3	Pooled rates = 3.5% (0.3-33.5%)	I^2 = 79.2% Q = 9.6 (p < 0.01)	Z = -5.3 (p < 0.001; N missing = 19)	Adjusted values = 3.5% N studies trimmed right of mean N = 0
• RMT < 100%	N = 24	Pooled rates = 13.2% (7.0-23.5%)	I^2 = 80.1% Q = 115.9 (p < 0.001)	Z = -8.56 (p < 0.001; N missing = 435)	Adjusted values = 31.1% N studies trimmed right of mean N = 10
• RMT = 100%	N = 11	Pooled rates = 18.5% (8.3-36.3%)	I^2 = 68.9% Q = 32.1 (p < 0.001)	Z = -5.29 (p < 0.001; N missing = 70)	Adjusted values = 26.0% N studies trimmed right of mean N = 3
• RMT > 100%	N = 31	Pooled rates = 12.5% (7.1-21.0%)	I^2 = 92.8% Q = 417.3 (p < 0.001)	Z = -12.35 (p < 0.001; N missing = 1,195)	Adjusted values = 25.0% N studies trimmed right of mean N = 9
• RMT not specified	N = 8	Pooled rates = 13.6% (2.3-23.5%)	I^2 = 79.0% Q = 33.4 (p < 0.001)	Z = -4.04 (p < 0.001; N missing = 27)	Adjusted values = 13.6% N studies trimmed right of mean N = 0
• Frontal lobe	N = 28	Pooled rates = 10.8% (4.6-23.3%)	I^2 = 81.9% Q = 148.8 (p < 0.001)	Z = -8.84 (p < 0.001; N missing = 542)	Adjusted values = 21.3% N studies trimmed right of mean N = 7
• Prefrontal lobe	N = 36	Pooled rates = 12.9% (7.7%-20.9%)	I2 = 89.9% Q = 347.2 (p < 0.001)	Z = -11.7 (p < 0.001; N missing = 1264)	Adjusted values = 25.1% N studies trimmed right of mean N = 11

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Table II *(follows)*. Subjects reporting at least one side effect: meta-analysis results.

Outcome	N studies	Pooled effect size (95% CI)	Q for heterogeneity	Fail safe Z for publication bias (p, N missing)	Trim and Fill adjusted values RFX for publication bias
• Temporal lobe	N = 6	Pooled rates = 15.1% (7.0-29.5%)	I^2 = 83.2% Q = 29.9 (p < 0.001)	Z = -9.11 (p < 0.001; N missing = 124)	Adjusted values = 19.5% N studies trimmed right of mean N = 2
• Parietal lobe	N = 1	Pooled rates = 65.0% (52.6-75.8%)	N/A	N/A	N/A
• Others lobe	N = 3	Pooled rates = 31.6% (10.2-95.3%)	I^2 = 87.8% Q = 16.46 (p < 0.001)	Z = -1.24 (p = 0.21; N missing = 0)	Adjusted values = 31.6% N studies trimmed right of mean N = 0
• Eight shape coil	N = 41	Pooled rates = 12.2% (7.5-19.2%)	I^2 = 90.2% Q = 406.8 (p < 0.001)	Z = -13.06 (p < 0.001; N missing = 1,779)	Adjusted values = 24.1% N studies trimmed right of mean N = 14
• Circular coil	N = 9	Pooled rates = 5.4% (0.8-27.4%)	I^2 = 83.8% Q = 49.37 (p < 0.001)	Z = -6.64 (p < 0.001; N missing = 95)	Adjusted values = 11.4% N studies trimmed right of mean N = 2
• H shape coil	N = 6	Pooled rates = 32.4% (11.5-63.8%)	I^2 = 89.2% Q = 46.5 (p < 0.001)	Z = -2.86 (p = 0004; N missing = 7)	Adjusted values = 44.6% N studies trimmed right of mean N = 1
• Double cone coil	N = 6	Pooled rates = 19.0% (2.6-66.8%)	I^2 = 90.0% Q = 49.6 (p < 0.001)	Z = -3.68 (p < 0.001; N missing = 16)	Adjusted values = 19.0% N studies trimmed right of mean N = 0
• Others different coil	N = 2	Pooled rates = 1.32% (0.18-8.8%)	I^2 = 0.0% Q = 0.35 (p = 0.55)	N/A	N/A
• Not specified coil	N = 10	Pooled rates = 22.9% (11.6-40.1%)	I^2 = 58.3% Q = 21.7 (p = 0.001)	Z = -4.41 (p < 0.001; N missing = 41)	Adjusted values = 25.9% N studies trimmed right of mean N = 1
Subjects reporting at least one side effect sham *vs* active comparison	N = 10	RFX pooled Odds Ratio = 1.95 (0.93-4.13) p = 0.08	I^2 = 36.3% Q = 14.1 (p = 0.12)	Z = 2.57 (p = 0.01; N missing = 8)	Adjusted values = 1.95 N studies trimmed right of mean N = 0

CI: Confidence Interval; DBRCTs: Double Blind Randomized Controlled Trials; RFX: Random-Effects; rTMS: repetitive Transcranial Magnetic Stimulation; TBS: Theta Burst Stimulation; dTMS: deep Transcranial Magnetic Stimulation; sTMS: single Transcranial Magnetic Stimulation; RMT: Resting Motor Threshold; N/A: not applicable.

moderators were considered: year of publication, sample type, design, acute treatment duration, age of participants, protocol (Hz, N impulses), RMT, target brain lobes, coil type.

b. Sham *vs* active stimulation comparisons (N = 10) (Fig. 2).

The meta-analysis results showed only a statistical trend favoring active stimulation: RFX pooled odds ratio = 1.95 (95% CI = 0.93-4.13%), p=0.08; with a low heterogeneity (I^2 = 36.3%; Q = 14.1, p = 0.12) and a low risk of publication bias (Fail-safe Z = 2.57, p = 0.01; N missing = 8; Trim and fill Adjusted value RFX = 1.95, N studies trimmed right of mean = 0).

Event rate and sham vs active stimulation comparisons in more common side effects (Tab. III)

We considered as common side effects those affecting 1-10% of the population [29]. The pooled rate was first calculated and then compared sham *vs* active stimulation. The pooled rate of the following common side effects was

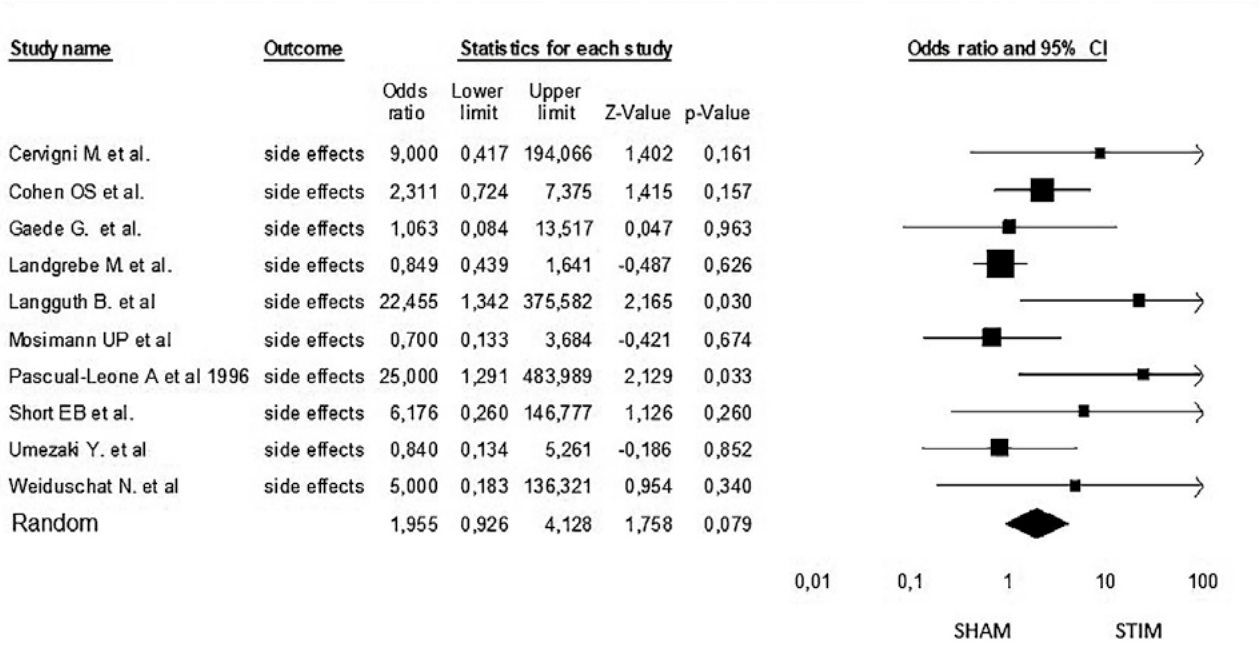

Figure 2.
Meta analysis.

calculated: headache (9.4%; 95% CI = 6.7-13.2%), painful sensations (3.9%; 95% CI = 2.5-6.0%), discomfort (3.5%; 95% CI = 2.5-5.0%), dizziness (3.4%; 95% CI = 2.6-4.4%), fatigue (3.2%; 95% CI = 2.4-4.2%), insomnia (3.2%; 95% CI = 2.4-4.3%), gastrointestinal adverse events (3.0%; 95% CI = 2.1-4.1%), muscle twitching (2.9%; 95% CI = 2.0-4.1%), ear problems (2.9%; 95% CI = 2.2-4.0%), ocular problems (2.7%; 95% CI = 2.0-3.7%), vegetative alterations (2.2%; 95% CI = 1.3-3.7%).

Sham *vs* active stimulation comparisons were significant (favoring active stimulation) for the following side effects:

a. headache (N studies = 22). RFX pooled odds ratio = 1.83 (95% CI = 1.13-2.96), p = 0.013; considering only DBRCTs, the meta-analysis was possible for 15 studies and the results remained significant: RFX pooled odds ratio = 2.03 (95% CI = 1.12-3.69), p = 0.02;
b. painful sensations (N studies = 9): RFX pooled odds ratio = 5.41 (95% CI = 2.07-14.13), p < 0.001; when considering only DBRCT (N studies = 7) RFX pooled odds ratio was 5.79 (95% CI = 2.07-16.12), p < 0.001;
c. discomfort (N studies = 9): RFX pooled odds ratio = 2.64 (95% CI = 1.63-6.02), p = 0.02; for what regard the DBRCTs, the meta-analysis was possible for seven studies and the results were still significant: RFX pooled odds ratio = 2.71 (95% CI = 1.0-7.40), p = 0.05;
d. muscle twitching (N studies = 6, all DBRCTs): RFX pooled odds ratio = 7.67 (95% CI = 1.29-45.70), p = 0.025;
e. ocular problems (N studies = 6): RFX pooled odds ratio = 3.78 (95% CI = 1.52-9.36), p = 0.004; in the five DBRCTs, the meta-analysis showed an RFX pooled odds ratio = 3.63 (95% CI = 1.41-9.38), p = 0.007.

Discussion

Our meta-analysis includes double blind and single blind RCTs, open label trials, retrospective studies and case series/case reports about TMS treatment reporting side effects. Our results confirm that TMS is a safe neuromodulation technique for both healthy and pathological subjects, that is in line with the results from previous systematic reviews and meta-analytic studies [25,30].

Knowing that the number of dropouts caused by adverse events is one of the most important parameters considered to measure the safety of a therapy, our results pointed out a very low rate of withdrawal as a consequence of side effects (3.0%). The rate remained low even after separately considering DB-RCTs alone (2.7%) and psychiatric samples (3.1%). Some of the studies considered in our meta-analysis used a sham *vs* active protocol, but, at the end, no significant differences between these two protocols were found.

A pooled rate of 13.7% was found by performing an analysis that considered the percentage of subjects experiencing at least one side effect. Due to the high heterogeneity of these results, several moderators were considered, and an even lower rate of side effects resulted from those rTMS protocols with Hz < 5 (8.7%) and those using a circular coil (5.4%). These findings suggest that using less penetrative coil and low frequency may be a good strategy to reduce adverse effects. However, studies

Table III. More common side effects: meta-analysis results.

Outcome	N studies	Pooled effect size (95% CI)	Q for heterogeneity	Fail safe Z for publication bias (p, N missing)	Trim and Fill adjusted values RFX for publication bias
Headache	N < 86	Pooled rates < 9.4% (6.7-13.2%)	I^2 = 89.6% Q = 814.2 (p < 0.001)	Z < -25.6 (p < 0.001; N missing = 4613)	Adjusted values = 16.4% N studies trimmed right of mean N = 25
Subjects reporting headache sham *vs* active comparison	N = 22	RFX pooled Odds Ratio < 1.83 (1.13-2.96) p = 0.013	I^2 = 36.3% Q = 14.1 (p = 0.125)	Z < 3.29 (p < 0.001; N missing = 41)	Adjusted values = 1.83 N studies trimmed right of mean N = 0
Subjects reporting headache only in DBRCT sham *vs* active comparison	N = 15	RFX pooled Odds Ratio < 2.03 (1.12-3.69) p = 0.02	I^2 = 24.0% Q = 14.1 (p = 0.05)	Z < 3.33 (p < 0.001; N missing = 29)	Adjusted values = 2.03 N studies trimmed right of mean N = 0
Discomfort	N < 86	Pooled rates < 3.5% (2.5-5.0%)	I^2 = 70.9% Q = 291.7 (p < 0.001)	Z < -27.27 (p < 0.001; N missing = 6,558)	Adjusted values = 7.3% N studies trimmed right of mean N = 31
Subjects reporting discomfort sham *vs* active comparison	N = 9	RFX pooled Odds Ratio = 2.64 (1.63-6.02) p = 0.02	I^2 = 18.1% Q = 9.8 (p = 0.28)	Z < 2.29 (p = 0.021; N missing = 4)	Adjusted values = 3.61 N studies trimmed right of mean N = 2
Subjects reporting discomfort only in DBRCT sham *vs* active comparison	N = 7	RFX pooled Odds Ratio < 2.71 (1.0-7.40) p = 0.05	I^2 = 32.7% Q = 8.9 (p = 0.18)	Z < 2.26 (p = 0.023; N missing = 3)	Adjusted values = 4.24 N studies trimmed right of mean N = 2
Painful sensations	N < 87	Pooled rates < 3.9% (2.5-6.0%)	I^2 = 80.6% Q = 444.4 (p < 0.001)	Z < -24.97 (p < 0.001; N missing = 4037)	Adjusted values = 8.6% N studies trimmed right of mean N = 31
Subjects reporting painful sensations sham *vs* active comparison	N = 9	RFX pooled Odds Ratio < 5.41 (2.07-14.13) p < 0.001	I^2 = 40.2% Q = 13.4 (p = 0.1)	Z < 5.07 (p < 0.001; N missing = 52)	Adjusted values = 5.41 N studies trimmed right of mean N = 0
Subjects reporting painful sensations only in DBRCT sham *vs* active comparison	N = 8	RFX pooled Odds Ratio < 5.79 (2.07-16.12) p < 0.001	I^2 = 44.0% Q = 12.5 (p = 0.084)	Z < 5.23 (p < 0.001; N missing = 49)	Adjusted values = 5.79 N studies trimmed right of mean N = 0
Vegetative alteration	N < 88	Pooled rates < 2.2% (1.3-3.7%)	I^2 = 80.2% Q = 438.9 (p < 0.001)	Z < -25.57 (p < 0.001; N missing = 4,891)	Adjusted values = 2.2% N studies trimmed right of mean N = 0
Subjects reporting vegetative alteration sham *vs* active comparison	N = 2	RFX pooled Odds Ratio < 0.65 (0.12-3.35) p = 0.61	I^2 = 0.0% Q = 0.55 (p = 0.45)	N/A	N/A
Muscle twitching	N < 86	Pooled rates < 2.9% (2.0% - 4.1%)	I2 = 61.7% Q = 222.2 (p < 0.001)	Z < -26.57 (p < 0.001; N missing = 5720)	Adjusted values = 6.1% N studies trimmed right of mean N = 33

(continues)

Table III *(follows)*. More common side effects: meta-analysis results.

Outcome	N studies	Pooled effect size (95% CI)	Q for heterogeneity	Fail safe Z for publication bias (p, N missing)	Trim and Fill adjusted values RFX for publication bias
Subjects reporting muscle twitching sham *vs* active comparison (all DBRCT)	N = 6	RFX pooled Odds Ratio < 4.53 (1.32-15.58) p = 0.016	I^2 = 59.3% Q = 12.3 (p = 0.031)	Z < 4.01 (p < 0.001; N missing = 20)	Adjusted values = 4.53 N studies trimmed right of mean N = 0
Subjects reporting muscle twitching using an eight-shaped coil only in DBRCT sham *vs* active comparison	N = 3	RFX pooled Odds Ratio < 7.67 (1.29-45.70) p = 0.025	I^2 = 56.2% Q = 4.57 (p = 0.1)	Z < 3.51 (p < 0.001; N missing = 7)	Adjusted values = 7.67 N studies trimmed right of mean N = 0
Subjects reporting muscle twitching using a H-shaped coil only in DBRCT sham *vs* active comparison	N = 1	RFX pooled Odds Ratio < 5.60 (0.26-118.11) p = 0.26	N/A	N/A	N/A
Subjects reporting muscle twitching using a double cone coil only in DBRCT sham *vs* active comparison	N = 1	RFX pooled Odds Ratio < 0.097 (0.005-1.85) p = 0.12	N/A	N/A	N/A
Subjects reporting muscle twitching using a NS coil only in DBRCT sham *vs* active comparison	N = 1	RFX pooled Odds Ratio < 7.92 (3.0-20.9) p < 0.001	N/A	N/A	N/A
Subjects reporting muscle twitching using RMT > 100% only in DBRCT sham *vs* active comparison	N = 5	RFX pooled Odds Ratio < 3.1 (0.88-10.86) p = 0.075	I2 = 54.0% Q = 8.7 (p = 0.07)	Z < 2.92 (p = 0.003; N missing = 7)	Adjusted values = 3.1 N studies trimmed right of mean N = 0
Subjects reporting muscle twitching using RMT < 100% only in DBRCT sham *vs* active comparison	N = 1	RFX pooled Odds Ratio < 38.33 (4.39-334.39) p < 0.001	N/A	N/A	N/A
Dizziness	N < 87	Pooled rates < 3.4% (2.6- 4.4%)	I^2 = 22.8% Q = 111.5 (p = 0.03)	Z < -28.07 (p < 0.001; N missing = 7760)	Adjusted values = 6.8% N studies trimmed right of mean N = 39
Subjects reporting dizziness sham *vs* active comparison	N = 6	RFX pooled Odds Ratio < 0.73 (0.30-1.78) p = 0.49	I^2 = 0.0% Q = 4.7 (p = 0.45)	Z < -0.54 (p = 0.58; N missing = 0)	Adjusted values = 0.86 N studies trimmed right of mean N = 2
Subjects reporting dizziness only DBRCT sham *vs* active comparison	N = 5	RFX pooled Odds Ratio < 0.84 (0.30-2.39) p = 0.74	I^2 = 8.5% Q = 4.4 (p = 0.35)	Z < -0.24 (p = 0.81; N missing = 0)	Adjusted values = 0.92 N studies trimmed right of mean N = 1
Fatigue	N < 87	Pooled rates < 3.2% (2.4% - 4.2%)	I^2 = 21.4% Q = 109.4 (p = 0.04)	Z < -27.74 (p < 0.001; N missing = 7347)	Adjusted values = 6.6% N studies trimmed right of mean N = 39
Subjects reporting fatigue sham *vs* active comparison	N = 4	RFX pooled Odds Ratio < 2.62 (0.58-11.83) p = 0.21	I^2 = 0.0% Q = 0.7 (p = 0.87)	Z < -1.28 (p = 0.2; N missing = 0)	Adjusted values = 2.62 N studies trimmed right of mean N = 0

(continues)

Table III *(follows)*. More common side effects: meta-analysis results.

Outcome	N studies	Pooled effect size (95% CI)	Q for heterogeneity	Fail safe Z for publication bias (p, N missing)	Trim and Fill adjusted values RFX for publication bias
Subjects reporting fatigue only DBRCT sham *vs* active comparison	N = 2	RFX pooled Odds Ratio < 0.84 (0.30-2.39) p = 0.51	I^2 = 0.0% Q = 0.51 (p = 0.47)	N/A	N/A
Insomnia	N < 87	Pooled rates < 3.2% (2.4-4.3%)	I^2 = 28.8% Q = 120.8 (p = 0.007)	Z < -27.77 (p < 0.001; N missing = 7381)	Adjusted values = 6.5% N studies trimmed right of mean N = 37
Subjects reporting insomnia sham *vs* active comparison	N = 2	RFX pooled Odds Ratio < 0.74 (0.15-3.43) p = 0.70	I^2 = 0.0% Q = 0.63 (p = 0.42)	N/A	N/A
Ear problem	N < 87	Pooled rates < 2.9% (2.2-4.0%)	I^2 = 39.9% Q = 143.2 (p < 0.001)	Z < -27.13 (p < 0.001; N missing = 6585)	Adjusted values = 6.4% N studies trimmed right of mean N = 36
Subjects reporting ear problem sham *vs* active comparison	N = 6	RFX pooled Odds Ratio < 0.75 (0.34-1.62) p = 0.46	I^2 = 0.0% Q = 2.33 (p = 0.80)	Z < -1.04 (p = 0.3; N missing = 0)	Adjusted values = 0.91 N studies trimmed right of mean N = 2
Subjects reporting ear problem only DBRCT sham *vs* active comparison	N = 5	RFX pooled Odds Ratio < 0.70 (0.32-1.56) p = 0.38	I^2 = 0.0% Q = 1.9 (p = 0.75)	Z < -1.32 (p = 0.18; N missing = 0)	Adjusted values = 0.90 N studies trimmed right of mean N = 3
Ocular problem	N < 87	Pooled rates < 2.7% (2.0-3.7%)	I^2 = 42.2% Q = 148.7 (p < 0.001)	Z < -27.54 (p < 0.001; N missing = 7084)	Adjusted values = 7.5% N studies trimmed right of mean N = 42
Subjects reporting ocular problem sham *vs* active comparison	N = 6	RFX pooled Odds Ratio < 3.78 (1.52-9.36) p = 0.004	I^2 = 0.0% Q = 2.56 (p = 0.76)	Z < 2.76 (p = 0.005; N missing = 6)	Adjusted values = 3.78 N studies trimmed right of mean N = 0
Subjects reporting ocular problem only DBRCT sham *vs* active comparison	N = 5	RFX pooled Odds Ratio < 3.63 (1.41-9.38) p = 0.007	I^2 = 0.0% Q = 2.5 (p = 0.64)	Z < 2.53 (p = 0.011; N missing = 4)	Adjusted values = 3.63 N studies trimmed right of mean N = 0
Gastrointestinal problem	N < 87	Pooled rates < 3.0 % (2.1-4.1%)	I^2 = 62.7% Q = 230.3 (p < 0.001)	Z < -28.54 (p < 0.001; N missing = 8371)	Adjusted values = 5.9% N studies trimmed right of mean N = 34
Subjects reporting ocular problem sham *vs* active comparison (all DBRCT)	N = 6	RFX pooled Odds Ratio < 1.32 (0.42-4.21) p = 0.62	I^2 = 41.0% Q = 8.39 (p = 0.13)	Z < 0.58 (p = 0.56; N missing = 0)	Adjusted values = 1.32 N studies trimmed right of mean N = 0

CI: Confidence Interval; DBRCT: Double Blind Randomized Controlled Trial; RFX: Random-Effects; N/A: not applicable.

comparing the safety of different coils and frequencies are still not available [31].

For what regards the sham-controlled treatment, we reported only a statistical trend for the role of active TMS in the development of side effects.

The pooled rate was first calculated considering the most common side effects (affecting 1-10% of the population) [29], and then it was compared sham *vs* active stimulation.

As a result, we found that active TMS was more likely to elicit headache, painful sensations, muscle twitching, ocular problems, discomfort, including all the studies and the DB-RCTs alone. Headache was reported in about 10% of the

subjects, in line with other literature findings [32]. TMS can modulate regional blood flow [33] and these vascular changes are considered a possible explanation for TMS-related headache [34]. Another way to explain the link between TMS and headache is the activation of nerves and muscles in the proximity of the stimulation coil, thus resulting in painful sensations [35]. For what regards the muscle twitching, there is a well- known mechanism of activation due to the action of TMS on the motor cortex [36] or directly on the facial muscles [37]. When considering the ocular side effects, i.e. blurred vision, phosphenes, photophobia, they occurred four-times more frequently in active TMS, with respect to sham. The effects of TMS on visual cortex and linked areas have been thoroughly investigated [38,39], but the neurobiological mechanisms explaining ophthalmic side effects are not yet completely understood. The subjective sensation of discomfort and pain related to active TMS, may be explained with the contraction of muscle of scalp, head and neck [40] or due to a wrong body posture during the stimulation. A statistical trend was observed for vegetative alterations, whereas no significant active *vs* sham effect was observed for insomnia, ear problems, dizziness, fatigue and gastrointestinal adverse events.

All the above mentioned side effects related to TMS were usually mild and transient, in agreement with other meta-analyses, reviews and consensus papers [25,41,42], also in fragile populations such as elderly [43] and children [35].

Conclusions

In line with previous publications, the results of our meta-analysis confirm that TMS is a safe technique with usually mild and transient adverse events rarely provoking dropouts. In conclusion, the use of TMS as an add-on treatment could be a promising clinical strategy in psychiatric and somatic conditions. Future studies should carefully report methods and measurements for monitoring the safety of the study, in order to assess the number of adverse effects and their severity.

Limits of the study

One of the most important limits is the unavailability of the exact number of AEs in several papers. RCTs, open label studies and case reports were considered in our meta-analysis in order to take into account all the studies describing the occurrence of AEs during TMS. The number of studies with both active TMS and sham arms was low, thus it was not always possible to compare them. Furthermore, due to the possible confounding effect given by the heterogenic way of describing the collateral effects, the papers were collected in clusters.

Acknowledgments

We thank Dr. Fabiola Sarchione for her precious help in the selection of the studies, Dr. Marco Lorusso for his good suggestions, and Claudia Cappello for kindly editing the language.

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