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Brief Communication

Transcranial magnetic stimulation for posttraumatic stress disorder: an updated systematic review and meta-analysis

Estimulação magnética transcraniana para transtorno de estresse pós-traumático: revisão sistemática de literatura e metanálise

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Abstract

Introduction: Transcranial magnetic stimulation (TMS) is a promising non-pharmacological intervention for posttraumatic stress disorder (PTSD). However, randomized controlled trials (RCTs) and meta-analyses have reported mixed results.
Objective: To review articles that assess the efficacy of TMS in PTSD treatment.
Methods: A systematic review using MEDLINE and other databases to identify studies from the first RCT available up to September 2015. The primary outcome was based on PTSD scores (continuous variable). The main outcome was Hedges' g. We used a random-effects model using the statistical packages for meta-analysis available in Stata 13 for Mac OSX. Heterogeneity was evaluated with I^2 (> 35% for heterogeneity) and the χ^2 test ($p < 0.10$ for heterogeneity). Publication bias was evaluated using a funnel plot. Meta-regression was performed using the random-effects model.
Results: Five RCTs (n = 118) were included. Active TMS was significantly superior to sham TMS for PTSD symptoms (Hedges' g = 0.74; 95% confidence interval = 0.06-1.42). Heterogeneity was significant in our analysis (I^2 = 71.4% and p = 0.01 for the χ^2 test). The funnel plot shows that studies were evenly distributed, with just one study located marginally at the edge of the funnel and one study located out of the funnel. We found that exclusion of either study did not have a significant impact on the results. Meta-regression found no particular influence of any variable on the results.
Conclusion: Active TMS was superior to sham stimulation for amelioration of PTSD symptoms. Further RCTs with larger sample sizes are fundamental to clarify the precise impact of TMS in PTSD.
Keywords: Meta-analysis, posttraumatic stress disorder, transcranial magnetic stimulation, non-pharmacological therapies, systematic review.

Resumo

Introdução: A estimulação magnética transcraniana (EMT) é uma intervenção não farmacológica promissora no tratamento de transtorno de estresse pós-traumático (TEPT). No entanto, estudos controlados e metanálises apresentaram resultados conflitantes até o momento.
Objetivo: Revisar os artigos sobre a eficácia da EMT para o tratamento de TEPT.
Métodos: Conduzimos uma revisão sistemática da literatura no MEDLINE para identificar estudos controlados e randomizados publicados até setembro de 2015. O desfecho primeiro foi baseado nas escalas de gravidade de TEPT como variáreis contínuas. O desfecho principal foi o g de Hedges. Utilizamos o modelo de efeito randômico com as análises estatísticas para metanálise do Stata 13 para Mac OSX. A heterogeneidade foi avaliada com o I^2 (> 35% para heterogeneidade) e o teste do χ^2 ($p < 0,01$ para heterogeneidade). Viés de publicação foi avaliado utilizando-se o gráfico do funil. Realizamos metarregressões com modelo de efeito randômico.
Resultados: Cinco estudos foram incluídos. A EMT ativa foi superior ao placebo para o tratamento de TEPT (g de Hedges = 0,74; intervalo de confiança 95% = 0,06-1,42). A heterogeneidade entre os estudos foi significativa em nossa análise (I^2 = 71,4% e p = 0,01 para o teste do χ^2). O gráfico do funil nos mostrou estudos simetricamente distribuídos, com apenas um estudo localizado marginalmente ao gráfico e um estudo localizado fora do funil. Encontramos que a exclusão de cada estudo não alterou significativamente o resultado final. A metarregressão não mostrou influência de nenhuma variável no resultado.
Conclusões: A estimulação ativa de EMT foi superior à estimulação simulada para melhora dos sintomas de TEPT. Novos estudos randomizados e controlados por simulação são necessários para esclarecer com melhor precisão o impacto da EMT no TEPT.
Descritores: Metanálise, transtorno de estresse pós-traumático, estimulação magnética transcraniana, terapias não farmacológicas, revisão sistemática.

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Introduction

Posttraumatic stress disorder (PTSD) is a trauma and stress-related disorder, characterized by intrusive, avoidance and hyperarousal core symptoms that may result in significant social or occupational dysfunction. It is estimated that 7.8% of the United States population experience PTSD in their lifetime and it is estimated that it causes impaired ability to work that costs in excess of $3 billion per year in lost productivity in the United States.[1] There is no definitive pharmacotherapy for core PTSD symptoms. Although medications and psychotherapy have been shown to help reduce symptoms and treat comorbid anxiety and depressive symptoms, in one third of patients there is no improvement in symptoms.[2]

Brain mechanisms related to PTSD (such as, for instance, threatening processing and fear-inducing stimuli) have been traced to particular pathways related to the amygdala, the frontal lobe, and the hippocampus.[3] Working from the hypothesis that dysfunctional brain structures underlie PTSD symptoms, the use of transcranial magnetic stimulation (TMS) was proposed with the objective of modulating target areas. Several different protocols have emerged focusing on the left and right dorsolateral prefrontal cortex (DLPFC).[4] We hereby present a literature review and meta-analysis of the efficacy of active vs. sham TMS for treatment of PTSD. It is relevant to point out that a previous meta-analysis has already been published.[4] However, in the present study we aim to enlarge the pooled sample and improve the quality of data analysis.

Method

A systematic review and meta-analysis was conducted in accordance with the recommendations of the Cochrane group and the PRISMA guidelines.[5] Two authors (PS and APT) performed independent systematic reviews and data extraction, and any discrepancies were resolved by consensus.

Literature review

We reviewed the following references and databases:

a) MEDLINE and EMBASE databases 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; and (8) anxiety disorder. Boolean terms were used as follows: [(1) OR (2) OR (3) OR (4) OR (5)] AND [(6) OR (7) OR (8)]. We searched for work published up to September 30, 2015.

b) The references listed in articles found by a) above and review articles, particularly those included in the meta-analyses by Karsen et al.[4]

We also attempted to identify 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 articles retrieved were written in English); 2) describing randomized, sham-controlled trials; and 3) providing data (in the manuscript or upon request) needed to estimate the main outcomes, i.e., mean (standard deviation [SD]) values and response and remission rates. We excluded case reports and case series, uncontrolled trials and trials assessing conditions other than PTSD or interventions other than TMS.

Data extraction

The following variables were extracted according to a structured checklist developed by the authors in advance: 1) metadata (authorship, publication date, etc.); 2) demographics (sample size in each group, age, gender); 3) PTSD characteristics (baseline PTSD scores; use of medication; psychometric scales, interviews and checklists used for PTSD diagnosis and assessment of avoidance, hyperarousal and reexperiencing); 4) characteristics of the TMS technique (frequency; motor threshold; time period of stimulation; train; inter-train interval; number of sessions; side of brain); 5) research methods (randomization protocol; sham technique; blinding assessment; number of dropouts).

The primary outcome was based on PTSD scores (continuous variable). Although categorical variables might be more readily interpretable than continuous ones (despite the fact that the odds ratio is often misinterpreted as a risk ratio), our choice was based on the fact that the primary outcome of all studies included was based on continuous variables and so we considered that a continuous effect size would better synthesize the studies chosen for review.

For continuous outcomes, the meta-analysis was performed on endpoint PTSD scores. Since studies used more than one PTSD scale, we extracted data corresponding to the study's definitions of the primary outcome. When a study reported scores at more than one time-point, we used the scores corresponding to the longest time period prior to unblinding.

For studies in which three groups were compared, two separate datasets were compared in each of two different analyses. For example, in the study by Boggio et al.,[6] high frequency TMS for left and right DLPFC were compared with sham stimulation. We therefore compared active left DLPFC stimulation vs. sham stimulation in one analysis and we compared active right DLPFC stimulation with sham stimulation in another analysis. Likewise, in the study by Cohen et al.,[7] low frequency and high frequency stimulation of the right DLPFC were compared with sham stimulation. We therefore compared high frequency right DLPFC stimulation with sham stimulation in one analysis and in another analysis we compared low frequency right DLPFC stimulation with sham stimulation.

The study by Isserles et al.[8] requires further explanation, since patients were randomly allocated into three treatment groups, combining deep transcranial magnetic stimulation (DTMS) and brief exposure of script-driven imagery of the traumatic event. The groups were configured as follows: in group a) EXP-STIM, patients were given DTMS after script-driven imagery of the traumatic experience immediately followed by script-driven imagery of a neutral event; in group b) NOEXP-STIM, patients were given DTMS after script-driven imagery of a positive experience immediately followed by script-driven imagery of a neutral event; and in group c) EXP-SHAM patients were given sham-DTMS after script-driven imagery of the traumatic experience immediately followed by script-driven imagery of a neutral event. Even though all groups received some kind of treatment, we considered group c) to be the sham group since TMS was not applied. In a crossover study conducted by Osuch et al.,[9] patients underwent active or sham TMS combined with exposure therapy.

Quality assessment

We assessed the methodological quality of each trial by assessing the following: 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 available in Stata 13 for Mac OSX. For the main outcome (PTSD scores) we initially calculated the standardized mean difference and the pooled SD of each comparison. This procedure is convenient when handling different scales (such as PTSD scales) since it standardizes the effect sizes across all studies based on the SD of each study. For the study by Boggio et al.,[6] PTSD scale scores were assessed by graphic evaluation. For the study by Osuch et al.,[9] data were provided by the authors. Hedges' g was used as the measure of effect size, which is appropriate for studies with small sample sizes. The pooled effect size was weighted by the inverse variance method and measured using the random-effects model. Studies that failed to provide crucial data such as SD or scale assessment were excluded from the final analysis.

Quantitative assessment of heterogeneity and bias

Heterogeneity was evaluated with the I^2 statistic (> 35% for heterogeneity) and the χ^2 test ($p < 0.10$ for heterogeneity). Publication bias was evaluated using a 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 the studies are distributed asymmetrically and/or fall outside the funnel). A sensitivity analysis was also performed, assessing the impact of each study on the overall results by excluding one study at a time.

Meta-regression

Meta-regression was performed using the random-effects model as modified by Knapp & Hartung,[10] using only one variable at a time.

Results

Overview

Our systematic review yielded 54 studies after duplicates were removed. Of these, 49 articles did not meet the eligibility criteria. Five studies[6-9,11] (n = 118 patients) were selected for the quantitative analysis. Mean age was 51.5 (SD = 2.5) years and 44% of the participants were women. No washout of drugs was performed. Demographics and stimulation protocols are summarized in Table 1.

The 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 did not provoke scalp sensation; 3) the coil was held at 90° vertical over the stimulated head area (no significant magnetic field was evoked, just the auditory artifact); 4) the coil 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.

Table 1 - Overview of demographics and stimulation parameters

	Sham group		Active group		TMS parameters				
Article	**n**	**Age**	**n**	**Age**	**TMS Site**	**F (Hz)**	**No. of Sessions**	**PPS**	**MT (%)**
Boggio et al.[6]	10	45.9	10	47.1	L-DLPFC	20	10	1600	80
Boggio et al.[6]	10	45.9	10	40.7	R-DLPFC	20	10	1600	80
Watts et al.[11]	10	57.8	10	54	R-DLPFC	1	10	400	90
Isserles et al.[8]*	9	40.4	8	40.5	Bilateral	20	12	1680	120
Isserles et al.[8]*	9	40.4	9	49	Bilateral	20	12	1680	120
Cohen et al.[7]	6	42.8	8	40.8	R-DLPFC	1	10	100	80
Cohen et al.[7]	6	42.8	10	41.8	R-DLPFC	10	10	400	80
Osuch et al.[9]	9	41.4	9	41.4	R-DLPFC	1	20	1800	100

* Deep transcranial magnetic stimulation.
F = frequency; L-DLPFC = left dorsolateral prefrontal cortex; MT = motor threshold; PPS = pulses per session; R-DLPFC = right dorsolateral prefrontal cortex; TMS = transcranial magnetic stimulation.

Primary outcome

We calculated the effect size for the endpoint. We found that active TMS was significantly superior to sham TMS (Hedges' g = 0.74; 95%CI 0.06-1.42) (Figure 1).

Quantitative assessment of heterogeneity and bias

Heterogeneity was significant in our analysis (I^2 = 71.4% and p = 0.01 for the χ^2 test). The funnel plot shows that studies were evenly distributed, with just one study located marginally at the edge of the funnel and one study located out of the funnel. We found that exclusion of each of these studies in turn did not have a significant impact on the results, with resulting effect sizes close to the overall effect size. Therefore, no single study in particular was driving the results of our analysis.

Meta-regression

The following variables were assessed: baseline depression severity scores, session duration, whether a crossover study, use of brief exposure, frequency, number of sessions, duration of sessions, number of pulses per session, total number of pulses, motor threshold, type of blinding, whether deep TMS was used, number of days of stimulation, side of brain stimulation, and subject's age. Meta-regression showed no particular influence of any variable on the results.

Discussion

In this systematic review of five randomized clinical trials (n = 118), we found that active TMS was significantly superior to sham TMS for treatment of core PTSD symptoms. Our results are in line with those of a previous meta-analysis.[4] However, we were able to enlarge the pooled sample over that of the previous review by 59% with the inclusion of two further trials. We also improved the quality of data analysis. The previous investigation did not analyze heterogeneity or publication bias and did not conduct meta-regression to detect the influence of variables or exclude each study one by one in the meta-analysis to evaluate their impact on the final result. The funnel plot assessment conducted in the present study showed that the risk of publication bias was also low, further strengthening our results. Importantly, we found that between-study heterogeneity was high. New clinical trials with uniform intervention protocols could clarify results in future analyses.

Another characteristic of our meta-analysis is that we analyzed separately two datasets for each of three studies, Boggio et al.,[6] Cohen et al.[7] and Isserles et al.[8] This is because they used a triple-arm design. Indeed, using this approach we were able to increase the sample size and narrow the confidence interval further.

Our meta-regressions did not identify clinical and/or methodological predictors of TMS responsiveness. In our meta-analysis we included intervention protocols that either stimulated or inhibited left or right DLPFC. Meta-regressions were performed in order to identify the possibility of different results if protocols were evaluated separately. None of the protocols (stimulation of the left DLPFC; stimulation of the left DLPFC and inhibition of right DLPFC; stimulation of right DLPFC; inhibition of right DLPFC; bilateral DTMS) were identified as predictive of TMS non-responsiveness. Moreover, in order to verify the influence of each study on the overall effect, subgroup analysis was performed using the metaninf command in Stata. No single study influenced the overall effect by itself.

The neurobiological hypothesis for the efficacy of TMS in PTSD treatment is based on dysfunctions of brain regions so far associated with processing threatening and fear-inducing stimuli, including the amygdala, the frontal lobe, and the hippocampus. The ventral prefrontal areas are richly connected to lateral prefrontal areas and amygdala. The right ventromedial frontal area provides access to

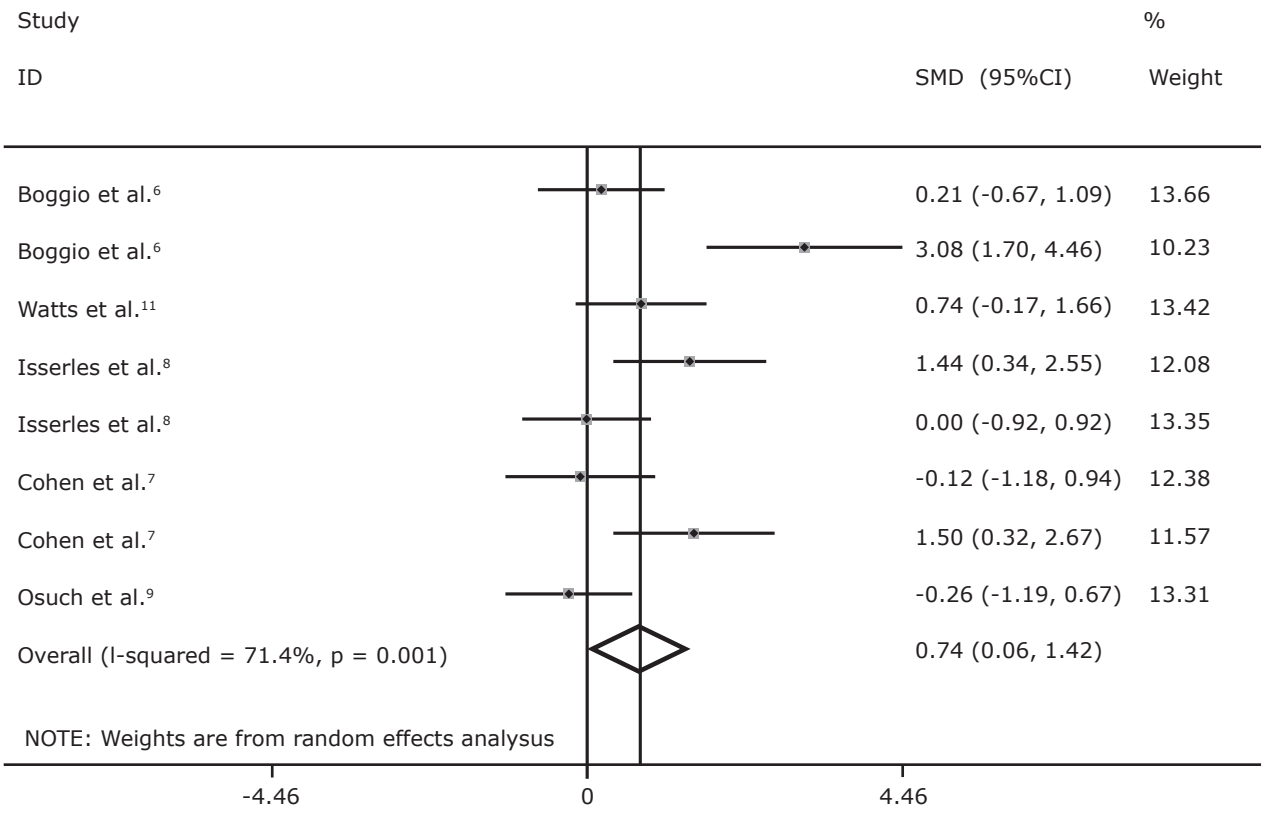

Figure 1 - Forest plot of effect sizes (Hedges' g). The forest plot was used to graphically illustrate the relative strength of treatment effects for each study reviewed. The vertical line represents the overall effect. 95%CI = 95% confidence interval; SMD = standardized mean difference.

object-recognition systems to the amygdala, where the fear or threat response is mediated.[12] Electroencephalographic (EEG) studies have shown alpha power decreases in the right hemisphere in PTSD patients compared to control groups while they are exposed to trauma-related pictures.[13] These findings have been corroborated by single photon emission computed tomography (SPECT) studies that have shown cerebral blood flow to the right hemisphere is increased in PTSD patients when they hear trauma-related sounds.[3] Morey et al.,[14] compared trauma-related stimuli during a visual working-memory task in combat veterans without PTSD and combat veterans with PTSD. These authors showed greater activation in the right ventrolateral prefrontal cortex (VLPFC) compared to the control group, suggesting that PTSD patients may require more effort to ignore emotionally distracting stimuli. The increased activation in the VLPFC was associated with decrease in the dorsolateral prefrontal cortex and with increased activation of the amygdala. The interpretation was that amygdala activation signaled the emotional distraction, which was inhibited by the VLPFC, taking attention away from tasks, as indicated by activation of the DLPFC. Modulating the DLPFC using TMS was proposed to assess its efficacy in PTSD treatment, since it is a safe, non-invasive treatment that uses an electromagnetic field to modulate the activity of cortical areas based on a high-intensity current through a magnetic coil placed on the scalp, generating a time-varying pulsed magnetic field that penetrates the cranium approximately 2-cm from the scalp surface to cortical tissue. Low-frequency TMS (1 Hz) is inhibitory, and high-frequency TMS (frequency above 10 Hz) is excitatory to underlying neural tissue.

In the present systematic review and meta-analysis we found that active TMS was clinically and statistically superior to sham TMS for treatment of PTSD. Notwithstanding, given the relatively small number of trials published to date and the heterogeneity of those studies, further phase III studies assessing broader samples are fundamental for clarifying the potential impact of TMS for treatment of PTSD in daily clinical practice.

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