ORIGINAL ARTICLE

Repetitive Transcranial Magnetic Stimulation for Fibromyalgia: Systematic Review and Meta-Analysis

Leonardo M. Knijnik, MD*,†; Jairo A. Dussán-Sarria, MD*,‡,§; Joanna R. Rozisky, PhD*; Iraci L. S. Torres, PhD‡,¶; Andre R. Brunoni, MD, PhD**; Felipe Fregni, MD, PhD††; Wolnei Caumo, MD, PhD*,§,‡‡

*Laboratory of Pain and Neuromodulation, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre; †School of Medicine, Rio Grande do Sul Federal University (UFRGS), Porto Alegre; ‡Post-Graduate Program in Medical Sciences, School of Medicine, UFRGS, Porto Alegre; §Pain and Palliative Care Service at HCPA, UFRGS, Porto Alegre; ¶Pharmacology Department, Institute of Basic Health Sciences, UFRGS, Porto Alegre; **Service of Interdisciplinary Neuromodulation, Department and Institute of Psychiatry, University of São Paulo, São Paulo, Brazil; ††Spaulding Center of Neuromodulation, Department of Physical Medicine and Rehabilitation, Harvard Medical School, Boston, Massachusetts U.S.A.; ‡‡Department of Surgery, HCPA, UFRGS, Porto Alegre, Brazil

■ Abstract

Background: Fibromyalgia (FM) is a prevalent chronic pain syndrome with few effective therapeutic options available. Repetitive transcranial magnetic stimulation (rTMS) is an emerging therapeutic alternative for this condition; however, results have been mixed.

Objectives: To evaluate the efficacy of rTMS on FM, a comprehensive systematic review and meta-analysis were performed.

Methods: Relevant published, English and Portuguese language, randomized clinical trials (RCT) comparing rTMS (irrespective of the stimulation protocol) to sham stimulation for treating FM pain intensity, depression, and/or quality of life (QoL) were identified, considering only those with low risk for bias. Trials available until April 2014 were searched through MEDLINE, EMBASE, the Cochrane Library Databases, and other 26 relevant medical databases covering from every continent. The outcomes for pain, depression, and QoL assessed closest to the 30th day after rTMS treatment were extracted, and changes from baseline were calculated to compare the effects of rTMS vs. placebo.

Results: One hundred and sixty-three articles were screened, and five with moderate to high quality were included. rTMS improved QoL with a moderate effect size (Pooled SMD = −0.472 95%CI = −0.80 to −0.14); it showed a trend toward reducing pain intensity (SMD = −0.64 95% CI = −0.31 to 0.017), but did not change depressive symptoms.

Conclusion: In comparison with sham stimulation, rTMS demonstrated superior effect on the QoL of patients with FM 1 month after starting therapy. However, further studies are needed to determine optimal treatment protocols and to elucidate the mechanisms involved with this effect, which

does not seem to be mediated by changes in depression, but that may involve pain modulation. Level of evidence 1b. ∎

INTRODUCTION

Fibromyalgia is a chronic pain disorder with unknown etiology and incompletely known pathophysiology, generally considered as a central sensitization syndrome.[1] It is the most common cause of generalized musculoskeletal pain in women aged 20 to 55 years,[2] with an estimated prevalence of 2% [2,3] displaying a female preponderance.[4] In tertiary clinics, it is even more prevalent, with more than 40% of patients referred meeting the diagnostic criteria of the syndrome.[5]

Although widespread pain is central for the diagnosis,[6,7] other troublesome symptoms include fatigue, depressive mood, sleep disturbances, and cognitive decline, which coexist with Fibromyalgia (FM) in as much as 25% of the cases.[2] Thus, it is not surprising that patients have a substantial decrease in their quality of life (QoL) as well as functional limitations,[8–11] which is perhaps even greater than in other chronic pain syndromes such as osteoarthritis or rheumatoid arthritis.[12]

Despite the significant burden caused by fibromyalgia, current treatment strategies have modest effectiveness. Aerobic exercise impacts QoL and perhaps pain intensity[13,14]; multidisciplinary patient education decreases referrals and diagnostic testing[15,16]; and the approved pharmacological interventions (ie, tricyclic antidepressants, dual reuptake inhibitors, gabapentinoids[17–26]) provide clinically relevant improvements in less than half of patients (25% to 45%) with efficacy possibly decreasing over time.[18]

Noninvasive brain stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS) have emerged as a therapeutic alternative that has proved efficacy in other conditions such as depression.[27–30] rTMS is able to modulate cortical and deep brain areas through its electromagnetic field generated over the scalp,[31] either decreasing (when using low-frequency protocols) or increasing (via high frequency stimulation) cortical excitability.[30] Clinical and experimental evidence indicates that in patients with FM, rTMS may exert its effect through modulatory pain pathways such as the descending inhibitory pathways [32,33] and modulating social-affective regions of the brain such as the right temporal lobe.[34] Although there are randomized clinical trials of good quality suggesting favorable results, there is no consensus regarding the efficacy of rTMS on FM, neither on the optimal parameters of stimulation. Thus, we conducted a systematic review of the available literature searching for randomized clinical trials (RCT) comparing active to sham rTMS (irrespective of the stimulation protocols) to treat FM widespread pain, depression symptoms, and QoL, using meta-analytic methods to quantify (when possible) its effects 1 month after the intervention.

METHODS

Literature search

We searched the Medline/PubMed database, Cochrane Controlled Trials Register, Embase, a Brazilian Health Services Register (CAPES), PsychINFO, WHO database, INASP, local databases such as National Library of Australia, Index Medicus for the Eastern Mediterranean Region, IndMED, KoreaMed, LILACS, IMSEAR, Panteleimon, WPRIM, BIOSIS, Derwent Drug File, International Pharmaceutical Abstracts, BiblioMap, DoPHER, Global Health, ASSIA, C2-SPECTR, ERIC, Google Scholar, TripDatabase, Intute, Social Sciences Citation Index, scientific.thomson.com, isiwebofknowledge.com, and Scopus Elsevier, ProQuest. For Grey Literature research, we searched in Open-Single. We used the term (clinical trials) with keywords "rTMS", "transcranial magnetic stimulation" and "fibromyalgia", "Fibromyalgia/therapy"[Mesh] Transcranial magnetic stimulation, and "Fibromyalgia/therapy"[Mesh] rTMS, limiting to studies in humans in English or in Portuguese languages. The research process considered papers published until April 30, 2014. To reduce the probability of publication bias, we contacted the authors to request for similar studies that may have already been performed and for more information about those that were published as abstracts only.

Study selection and quality assessment

We included trials that met the following criteria: (1) involve human subjects only, (2) report original research, (3) used rTMS for treatment purposes, (4) were randomized, (5) included only patients with

fibromyalgia syndrome according to the 1990 or 2010 preliminary ACR criteria,[6,7] and (6) had outcomes addressing changes in pain intensity, in depression symptoms, and/or in QoL, irrespective of the scales used.

The study characteristics extracted were chosen according to the Cochrane Handbook of Systematic Reviews for Intervention Studies[35]: level of evidence and study design, study population inclusion and exclusion criteria, concomitant treatment use, type of intervention (high or low-frequency rTMS), sessions description, total number of sessions, follow-up time, total number of subjects per group (active/ sham, including proportions completing study), and study quality (assessed with the Jadad score).

Trials compared rTMS with a sham intervention. Two reviewers evaluated reports independently for eligibility without blinding to the names of the authors. The study outcomes had to include a numerical assessment for pain, the visual analog scale (VAS), the numerical pain scale, Likert scale for pain, or the Brief Pain Inventory (BPI). Examiner blinding was not necessary as long as the JADAD score was at least 3. Disagreements were resolved by consensus.

Outcome measures

The prespecified primary outcome was absolute pain intensity reported on recognized pain scales such as the VAS and the BPI on any time window. If more than 1 time point was reported, we extracted the one closest to 30 days from the last day of treatment. The first month after treatment was chosen because it was the most frequently reported outcome. If a trial report provided data on both mentioned scales, we recorded only data on the VAS. Secondary outcomes were depression scores using Hamilton Depression Rating Scale (HDRS) or Beck Depression Inventory (BDI) and QoL using Fibromyalgia Impact Questionnaire (FIQ).

Quality assessment

Two reviewers assessed independently the allocation concealment, blinding, and adequacy of analyses. We considered only allocation concealment adequate if the researchers did not know which group the next patient entering the study would be allocated to. Procedures considered predictable based on the generation of allocation were considered inadequate. The JADAD score was also used for bias assessment so that only trials

with a score of three or more were included. Disagreements were resolved by consensus.

Data collection

The reviewers independently used a systematic form to extract trial design, patients' characteristics, type of intervention, and outcome assessments for depression, QoL, and pain scores. In those trials in which pain scores were available only as graphs, it was used the WebPlot-Digitizer for data extraction, which provides a reasonable approximation of the scores.[36] Two independent reviewers extracted and cross-checked scores for pain, depression, and QoL.

Statistical analysis

Pain, depression, and QoL scores assessed closest to the 30th day after the last intervention session were subtracted from the baseline pain level in order to analyze the absolute change from baseline. The standardized mean difference (SMD) of the change in scores with its respective standard error (SE) using the Hedge's g method (which adjustment for small samples) was calculated for each treatment arm. Then, the changes from baseline were compared between the active and the sham arms. When the raw scores were not reported, the mean change from baseline was used. Quantifiable heterogeneity between studies was tested using the I^2 statistic, which is usually interpreted as no heterogeneity if equal to 0%, as low if 25% to 50%, and high if > 75%.[36] Then, a pooled SMD assuming a fixed-effects model was estimated. For studies with more than one treatment arm, changes from baseline were calculated for each arm independently. Small samples effects were analyzed using funnel plots with pseudo 95% confidence intervals. Data were analyzed using Stata Statistical Software: Release 12 (StataCorp LP., College Station, TX, USA). The present meta-analysis is reported according to the PRISMA guidelines.

RESULTS

Initial search criteria identified 163 English language published studies, but after verifying criteria through titles and abstracts analysis, only 18 required full-text extraction for further evaluation. Of those, five trials met our inclusion criteria. All trials were published as full-text articles in international journals. Figure 1 shows the process of trial extraction and selection.
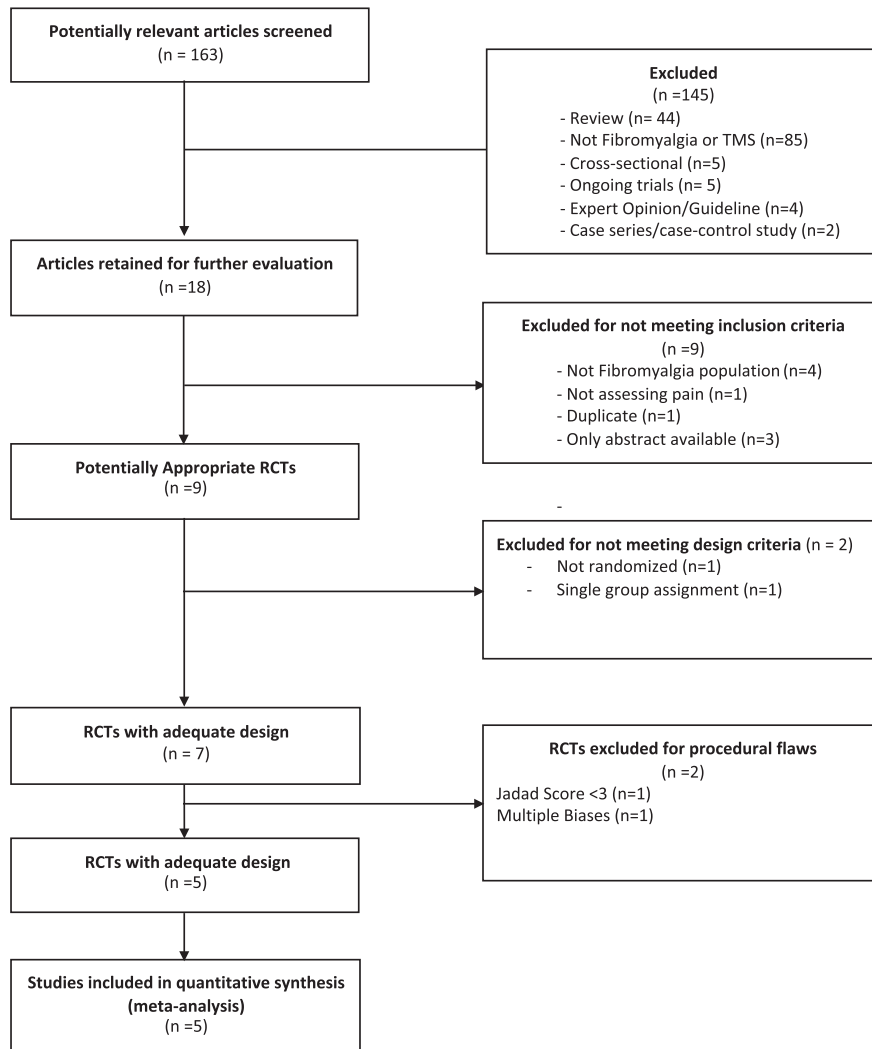
```
┌─────────────────────────────────┐
│ Potentially relevant articles   │
│ screened                        │
│ (n = 163)                       │
└─────────────────────────────────┘
                │                      ┌──────────────────────────────────────┐
                │                      │             Excluded                 │
                │                      │             (n =145)                 │
                ├─────────────────────▶│ - Review (n= 44)                     │
                │                      │ - Not Fibromyalgia or TMS (n=85)     │
                │                      │ - Cross-sectional (n=5)              │
                │                      │ - Ongoing trials (n= 5)              │
                │                      │ - Expert Opinion/Guideline (n=4)     │
                │                      │ - Case series/case-control study (n=2)│
                ▼                      └──────────────────────────────────────┘
┌─────────────────────────────────┐
│ Articles retained for further   │
│ evaluation                      │
│ (n =18)                         │
└─────────────────────────────────┘
                │                      ┌──────────────────────────────────────┐
                │                      │ Excluded for not meeting inclusion   │
                │                      │ criteria                             │
                │                      │ (n =9)                               │
                ├─────────────────────▶│ - Not Fibromyalgia population (n=4)  │
                │                      │ - Not assessing pain (n=1)           │
                │                      │ - Duplicate (n=1)                    │
                │                      │ - Only abstract available (n=3)      │
                ▼                      └──────────────────────────────────────┘
┌─────────────────────────────────┐
│ Potentially Appropriate RCTs    │
│ (n =9)                          │
└─────────────────────────────────┘
                │                      ┌──────────────────────────────────────┐
                │                      │ Excluded for not meeting design      │
                │                      │ criteria (n = 2)                     │
                ├─────────────────────▶│  -  Not randomized (n=1)             │
                │                      │  -  Single group assignment (n=1)    │
                │                      │                                      │
                ▼                      └──────────────────────────────────────┘
┌─────────────────────────────────┐    ┌──────────────────────────────────────┐
│ RCTs with adequate design       │    │ RCTs excluded for procedural flaws   │
│ (n = 7)                         ├───▶│ (n =2)                               │
│                                 │    │ Jadad Score <3 (n=1)                 │
└─────────────────────────────────┘    │ Multiple Biases (n=1)                │
                │                      └──────────────────────────────────────┘
                ▼
┌─────────────────────────────────┐
│ RCTs with adequate design       │
│ (n =5)                          │
└─────────────────────────────────┘
                │
                ▼
┌─────────────────────────────────┐
│ Studies included in quantitative│
│ synthesis                       │
│ (meta-analysis)                 │
│ (n =5)                          │
└─────────────────────────────────┘
```

Figure 1. The process of trial extraction and selection.

Table 1 shows the trials included in the meta-analysis. The total number of patients included was 143. All the trials compared rTMS with sham stimulation. Regarding pain outcomes, three trials used BPI,[37–39] one used the VAS,[40] and one used the "average pain intensity over the last 24 hours".[34] All trials used the FIQ as QoL outcome. Three trials used the BDI to assess depression,[34,37,40] one used the HDRS[38] and one used both.[39] The type of intervention varied slightly between the studies, four of them applied high frequency rTMS over the left M1,[34,37,39,40] while the other stimulated the DLPFC: one with high frequency over the left dorsolateral prefrontal cortex (DLPFC)[38] and other one with low frequency over the right DLPFC.[40] Table 2 shows the raw scores of each study.

Effects on pain

Although the rTMS stimulation-induced analgesia did not show a significant superiority to the sham-induced analgesia, a trend favoring the real stimulation effects was observed (SMD = −0.31; 95%CI = −0.64, 0.02; $P = 0.063$; $I^2 = 22.0\%$; Figure 2A).

Sensitivity analysis showed that excluding the only study arm using low-frequency rTMS did not change the direction of the result, but increased heterogeneity (SMD = −0.293 95%CI = −0.633 to 0.047, $P = 0.091$, $I^2 = 35.7\%$; Figure 2B). Furthermore, excluding the study with the smallest sample size (Lee SJ)[40] did not change the trend observed (SMD = −0.346 95%CI = −0.699 to 0.008, $P = 0.055$; $I^2 = 40.7\%$, $P = 0.167$). Funnel plots suggest low risk of publication bias and heterogeneity (Figure 2C).

Table 1. Characteristics of the Included Studies According to Published Year, Number of Patients, Inclusion and Exclusion Criteria, Treatment Protocol, Stimulation Site and Frequency, Pain-Related Outcome, JADAD Score, and Level of Evidence

Author	Year	N	Inclusion Criteria	Exclusion Criteria	Treatment Protocol	Stimulation Site	Stimulation Frequency	Pain-related Outcome	JADAD Score	GRADE Level of Evidence
Mhalla A	2011	40	1990 ACR criteria	Current Primary Psychiatric Condition or history of substance abuse; Rheumatic disease	5 daily sessions, then 3 sessions a week apart, 3 sessions a fortnight apart, and 3 sessions a month apart.	Left M1	10 Hz	BPI	4	B
Short EB	2011	20	1990 ACR criteria	Depression as main reason for functional impairment or study enrollment; Bipolar disorder; Schizophrenia; Epilepsy; stroke.	5 times per week during 2 weeks	Left DLPFC	10 Hz	BPI	4	B
Passard A	2007	30	1990 ACR criteria	Current Primary Psychiatric Condition or history of substance abuse; Rheumatic disease.	10 sessions for two consecutive weeks.	Left M1	10 Hz	BPI	5	B
Lee S	2012	15	1990 ACR criteria	Current Primary Psychiatric Condition Epilepsy; Rheumatic disease.	10 consecutive sessions	Right DLPFC or Left M1	1 Hz or 10 Hz	VAS	3	B
Boyer L	2014	38	1990 ACR criteria	Current Primary Psychiatric Condition; Rheumatic disease; Neurologic disorder.	14 sessions over 10 weeks	Left M1	10 Hz	Average pain intensity scale over the last 24 hours	5	B

DLPFC, dorsolateral prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation.

Effects on depression

The rTMS stimulation did not show a significant superiority to the sham-induced reduction in depression symptoms (SMD = −0.150; 95%CI = −0.473, 0.173; $P = 0.363$; $I^2 = 0.0\%$, $P = 0.987$).

Effects on quality of life

rTMS-induced significant improvement on the quality of life assessed by the FIQ (SMD = −0.472; 95% CI = −0.802, −0.141; $P = 0.005$; $I^2 = 0.0\%$, $P = 0.544$) of moderate size of the effect (Figure 3A). Sensitivity analysis (Figure 3B) showed that excluding the only study arm using low-frequency rTMS did not change the direction of the result, which remained significant (SMD = −0.450; 95%CI = −0.792, -0.109; $P = 0.010$; $I^2 = 0.0\%$, $P = 0.435$). A funnel plot

suggested low risk of publication bias and heterogeneity (Figure 3C).

DISCUSSION

The present systematic review quantitatively assessed the reported changes in pain, depressive symptoms, and QoL in patients with FM 30 days after receiving rTMS. The data support that rTMS improves with a moderate effect size the quality of life in FM patients and that this effect occurs independent of the changes in pain and depression symptoms, although the former showed a trend toward improvement but did not reach statistical significance.

Thorough research performed for the present report also revealed that there are few trials with rigorous methodological design addressing rTMS as a treatment

Table 2. Raw Scores for Pain, Depression, and QoL Extracted From Each Individual Study Arm

Author	Baseline Pain		Final Pain		Baseline Depression		Final Depression		Baseline QoL		Final QoL		Day of final evaluation
	rTMS	Sham	rTMS	Sham	rTMS	Sham	rTMS	Sham	rTMS	Sham	rTMS	Sham	
Mhalla A	BPI: 6.2 ± 1.4	6.5 ± 1.8	4.72 ± 1.03	6.63 ± 1.05	BDI: 9.6 ± 6.5	BDI: 10 ± 5.8	BDI: 9.2 ± 6.4	BDI: 9.3 ± 5.6	66.8 ± 12.5	67.2 ± 14.8	55.2 ± 15.2	67.5 ± 7.2	21
Short EB	BPI: 5.6 ± 1.85	5.34 ± 1.82	4.41 ± 1.95	5.37 ± 2.02	HDRS: 21.8 ± 7.79	HDRS: 17.6 ± 7.31	HDRS: 14.1 ± 9.42	HDRS: 16.4 ± 8.18	58.79 ± 11.93	54.38 ± 13.96	38.99 ± 19.44	47.93 ± 14.70	14
Passard A	BPI: 6.88 ± 1.24	6.56 ± 1.2	5.65 ± 1.85	6.3 ± 1.66	BDI: 10.2 ± 5.8	BDI: 8.6 ± 5.2	BDI: 8.3 ± 5.4	BDI: 8.5 ± 4	63.5 ± 10.8	61.3 ± 11.5	48.7 ± 10.4	62.2 ± 8.9	30
Lee SJ LF*	VAS: 7.24 ± 1.07	7.81 ± 1.31	4.75 ± 2.32	7.23 ± 2.53	BDI: 19.2 ± 4.4	BDI: 21.6 ± 5.5	BDI: 13.4 ± 6.2	BDI: 18.3 ± 5.8	67.2 ± 11.1	59.3 ± 23.4	45.1 ± 13.8	53.7 ± 27.3	30
Lee SJ HF†	VAS: 7.0 ± 0.85	7.81 ± 1.31	7.35 ± 1.06	7.23 ± 2.53	BDI: 25.5 ± 6.4	BDI: 21.6 ± 5.5	BDI: 22.3 ± 2.8	BDI: 18.3 ± 5.8	60.4 ± 21.1	59.3 ± 23.4	58.5 ± 9.2	53.7 ± 27.3	30
Boyer L	Average daily pain: 6.5 ± 1.6	6.5 ± 2.0	0.1 ± 1.8 (mean change from baseline)	4.7 ± 33.1 (mean change from baseline)	BDI: 9.1 ± 5.9	11.7 ± 8.1	−1.3 ± 2.7 (mean change from baseline)	−0.5 ± 4.0 (mean change from baseline)	60.0 ± 11.6	64.1 ± 11.6	0.3 ± 18.2 (mean change from baseline)	1.3 ± 9.5 (mean change from baseline)	15

BDI, beck depression inventory; BPI, brief pain inventory; HDRS, Hamilton depression rating scale; VAS, visual analog scale; QoL, Quality of Life; rTMS, repetitive transcranial magnetic stimulation.
*Low-frequency arm of Lee study.
†High-frequency arm of Lee study.

strategy for FM. The large number of initially found articles (163), compared to the low number of clinical trials, suggests that the research of rTMS as a therapeutic tool in FM is still in phase II and the clinical benefits are promising. The quality of the trials included was acceptable, and all of them achieved JADAD scores superior to 3. Perhaps, the good methodological quality of these trials together with the effect size achieved with the rTMS allowed detecting its effect on the FM QoL even with the relatively restricted sample size of 143 patients. On the other hand, the stringent criteria excluding male patients with FM and those with major depression or with psychiatric illnesses significantly reduce the external validity and, thus, clinical applicability of rTMS on the FM population.

The mechanisms underlying rTMS effects are not completely understood. It acts through an electromagnetic field created by the 8-coil over the patient's scalp, generating a superficial cortical current capable of changing neuron activity even in brain regions distant from the stimulation site.[32,33,41–46] As pain processing and negative affect during experimental pain might be processed independently and are not modulated by depressive symptoms or catastrophizing,[47] it is plausible to hypothesize that rTMS-induced improvement in QoL might also be the result of modulation of neuronal circuits not directly related to pain processing. However, we cannot exclude the possibility that the sample size included in our meta-analysis was too small or that either the follow-up or treatment period was too short. Indeed, the analgesic effects caused by rTMS may require longer periods to take effect, possibly because rTMS may not act directly on pain sensory pathways, but instead may alter emotional processing—and increase QoL—secondarily decreasing pain intensity. Accordingly, catastrophizing has been demonstrated to precede changes in pain scores in patients with FM.[48] The right temporal lobe may be the brain region implicated in this phenomenon.[34] Also, it has been shown to be involved in the modulation of emotion during pain sensation [49] and is intricately connected to the limbic system,[50] supporting the view that rTMS could alter affective pain processing.

We included trials with different modalities of stimulation, such as stimulation of M1, DLPFC, and different stimulation protocols. Four studies [34,37,39,40] stimulated the left M1 and two stimulated the DLPFC, although in different hemispheres.[38,40] As the objective of the meta-analysis was to assess the effects of rTMS on pain, depression, and QoL, we included all
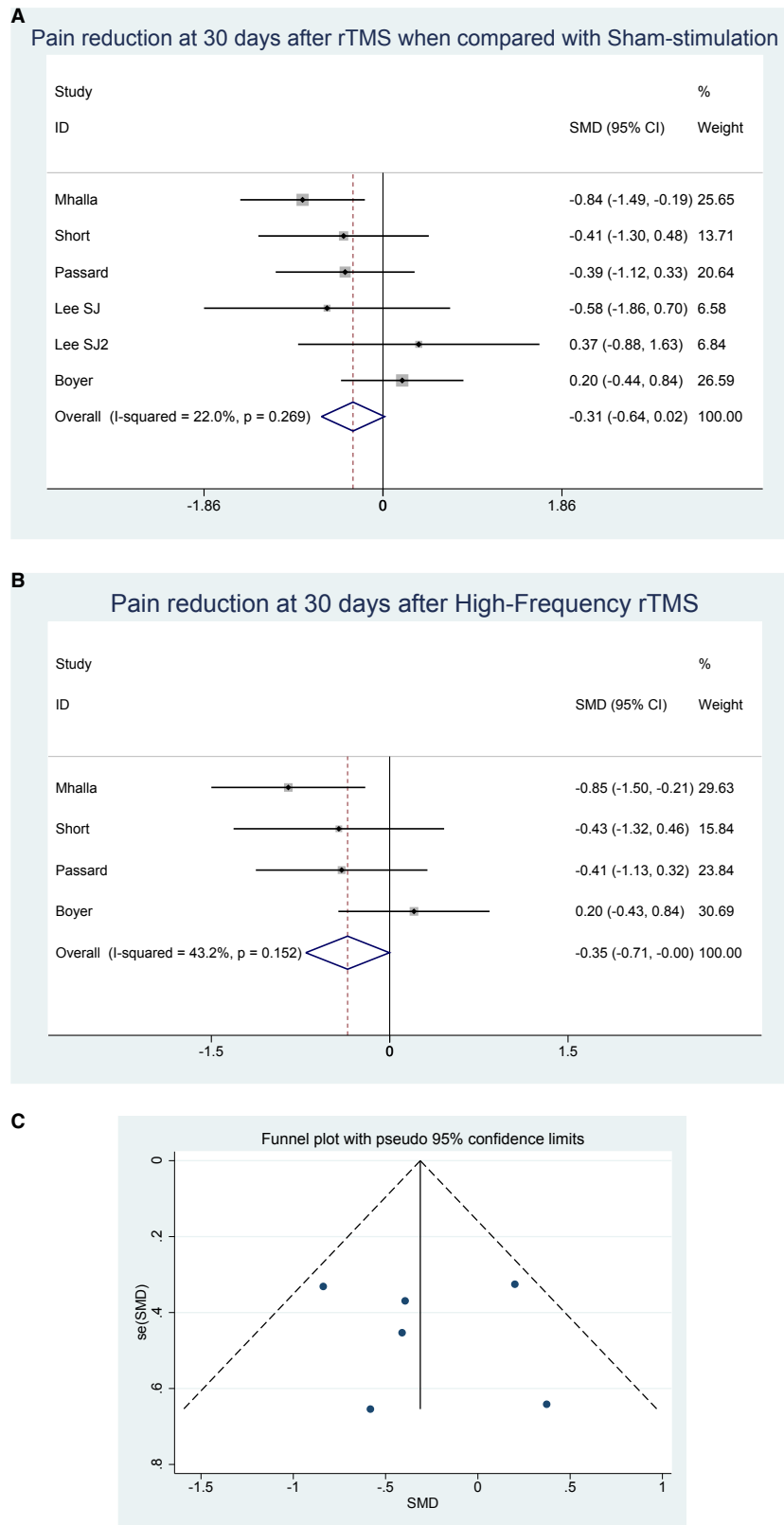
Figure 2. Pain reduction at 30 days after repetitive transcranial magnetic stimulation (rTMS) when compared with sham stimulation. Forest plots are presented for analysis with all the studies (A) and sensitivity analysis including only data from studies that used high frequency rTMS (B). Funnel plot supports low risk of publication bias (C).
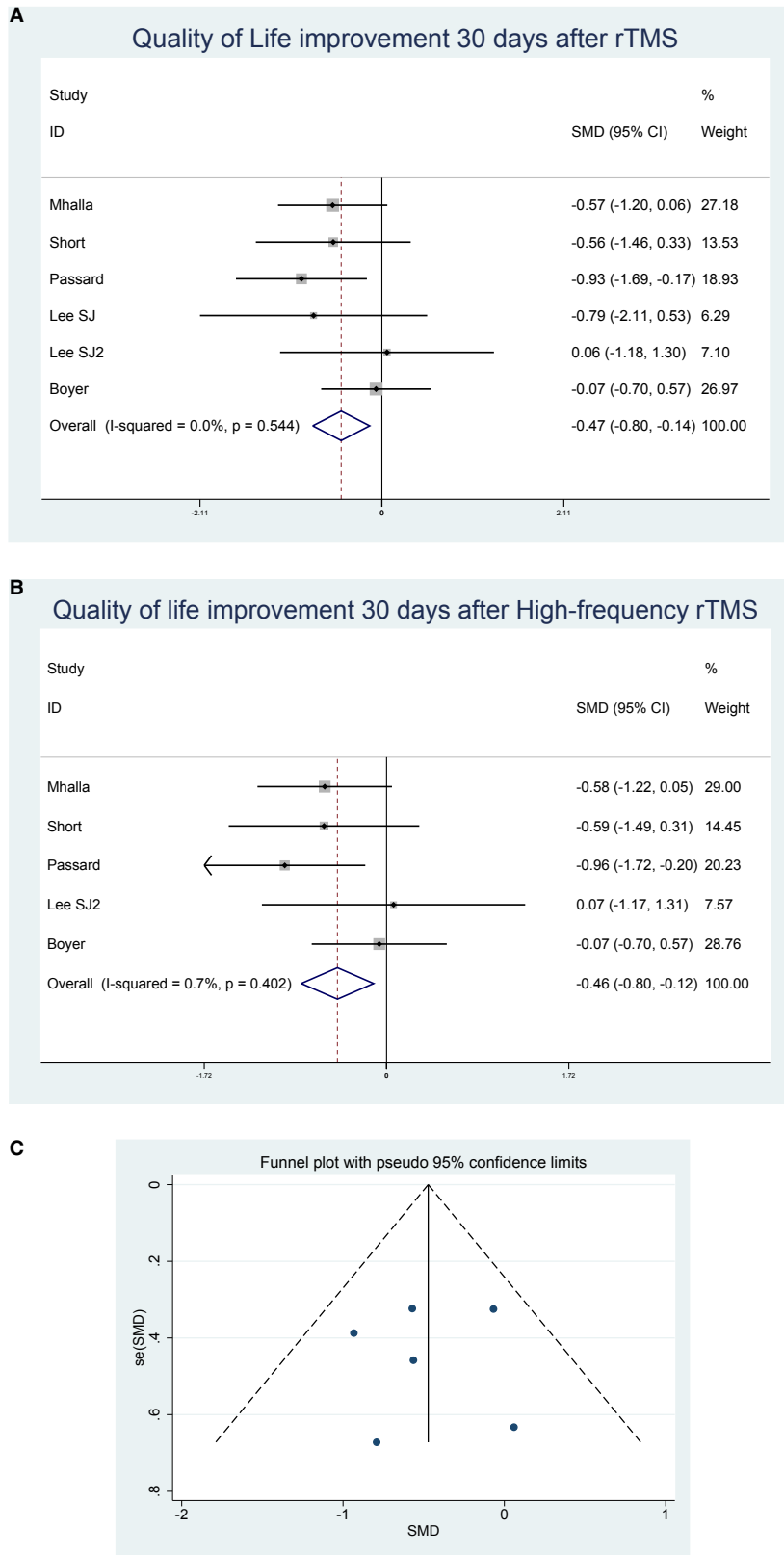
A

B

C

Figure 3. Quality of Life improvement 30 days after repetitive transcranial magnetic stimulation (rTMS) when compared with sham stimulation. Forest plots are presented for analysis with all the studies (A) and sensitivity analysis including only data from studies that used high frequency rTMS (B). Funnel plot supports low risk of publication bias (C).

modalities of stimulation despite their potential differences. Our analysis considered the time point closest to 30 days after the last day of stimulation, which provides evidence for lasting effects of rTMS, even though it is not known whether those changes would persist beyond this time point. Unfortunately, the lack of uniformity in the reported protocols forbids us from assessing longer follow-up periods. The closest assessment to 30th day after rTMS stimulation was chosen because it was the time point most often reported in the trials and encompasses clinical relevance. A quantitative assessment of differences in outcomes between the areas of stimulation was limited due to the small number of patients. Furthermore, although there is always some chance of publication bias, this possibility is unlikely as shown in the funnel plot. Nevertheless, it should be acknowledged that there might be other clinical trials using rTMS for FM, as we detected reports published only as abstract posters but that could not be retrieved in the full text, because some authors did not respond to our requests (Figure 1). The number of patients included in the meta-analysis is low, and our findings are based on trials results from publicly available literature instead of individual-patient data, which would have proved stronger evidence. Another aspect that should be considered is that the included studies used different scales to address depression (ie, BDI and HDRS). Although we calculated standardized mean differences from baseline to minimize this effect, the scales assess different aspects of depression, which could account for the negative result, or because they may lack sensitivity to detect small changes in depressive symptoms.[51] For instance, BDI is a self-rated based scale, whereas HDRS is scored based on clinical interview. Theoretically, HDRS should be preferred over BDI, particularly for patients with FM who tend to catastrophize their symptoms. Furthermore, the lack of significant effects of mood might also be explained because most of the studies included in the present meta-analysis used protocols stimulating M1, which has no clear relationship with mood modulation. Additionally, the trials excluded patients with depressive disorder, and the baseline depression scores in the included studies were generally low, which represents an obstacle to detect significant but small changes in depression scores.

Our results differ from those found other authors.[52] These discrepancies can be attributed to differences in the trials included, because we excluded two trials included by other authors [53,54] due to their low-quality

(ie, Jadad score of less than three or multiple possible biases found), and we included a new recently reported trial.[34] Additionally, we provided a quantitative approach (meta-analysis) and evaluated the change in depression and QoL scores.

Future researches are needed to elucidate the potential difference in clinical effects according to area of stimulation (M1 vs. DLPFC) and treatment protocols (number of days, duration of each stimulation, frequency). Additionally, despite our significant result, further larger RCTs are needed to confirm rTMS clinical capacities in a clinical, more near to "real world" settings, such as in FM patients with concurrent psychiatric disorders. For example, future works may consider studying the stimulation of both M1 and DLPFC according to the presence of concurrent depression, as high frequency DLPFC rTMS is well studied as a treatment for unipolar depression.

CONCLUSION

In comparison with sham stimulation, rTMS demonstrated superior effect on the quality of life of patients with fibromyalgia 1 month after starting therapy. However, further studies are needed to determine optimal treatment protocols and to elucidate mechanisms involved with this effect, which does not seem to be accompanied by changes in depression, but that may involve pain modulation.

REFERENCES

1. Lautenbacher S, Rollman GB. Possible deficiencies of pain modulation in fibromyalgia. *Clin J Pain*. 1997;13: 189–196.

2. Goldenberg DL. Fibromyalgia syndrome. An emerging but controversial condition. *JAMA*. 1987;257:2782.

3. Weir PT, Harlan GA, No FL, et al. The incidence of fibromyalgia and its associated comorbidities: a population-based retrospective cohort study based on International Classification of Diseases, 9th Revision codes. *Clin Rheumatol*. 2006;12:124.

4. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum*. 2008;58:26–35.

5. Brill S, Ablin JN, Goor-Aryeh I, Hyat K, Slefer A, Buskila D. Prevalence of fibromyalgia syndrome in patients referred to a tertiary pain clinic. *J Investig Med*. 2012;60: 685–688.

6. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria

for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)*. 2010;62:600.

7. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. *Arthritis Rheum*. 1990;33:160–172.

8. Al-Allaf AW. Work disability and health system utilization in patients with fibromyalgia syndrome. *J Clin Rheumatol*. 2007;13:199–201.

9. Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L. An internet survey of 2,596 people with Fibromyalgia. *BMC Musculoskelet Disord*. 2007;8:27.

10. Verbunt JA, Pernot DH, Smeets RJ. Disability and quality of life in patients with fibromyalgia. *Health Qual Life Outcomes*. 2008;6:8.

11. Kurtze N, Gundersen KT, Svebak S. Quality of life, functional disability and lifestyle among subgroups of fibromyalgia patients: the significance of anxiety and depression. *Br J Med Psychol*. 1999;72(Pt 4):471–484.

12. Hoffman DL, Dukes EM. The health status burden of people with fibromyalgia: a review of studies that assessed health status with the SF-36 or the SF-12. *Int J Clin Pract*. 2008;62:115–126.

13. Busch AJ, Schachter CL, Overend TJ, et al. Exercise for fibromyalgia: a systematic review. *J Rheumatol*. 2008;35:1130.

14. Thomas EN, Blotman F. Aerobic exercise in fibromyalgia: a practical review. *Rheumatol Int*. 2010;30: 1143–1150.

15. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA*. 2004;292:2388.

16. Pfeiffer A, Thompson JM, Nelson A, et al. Effects of a 1.5-day multidisciplinary outpatient treatment program for fibromyalgia: a pilot study. *Am J Phys Med Rehabil*. 2003;82:186.

17. Carette S, McCain GA, Bell DA, Fam AG. Evaluation of amitriptyline in primary fibrositis. A double-blind, placebo-controlled study. *Arthritis Rheum*. 1986;29:655.

18. Tofferi JK, Jackson JL, O'Malley PG. Treatment of fibromyalgia with cyclobenzaprine: a meta-analysis. *Arthritis Rheum*. 2004;51:9.

19. Arnold LM, Keck PE Jr, Welge JA. Antidepressant treatment of fibromyalgia. A meta-analysis and review. *Psychosomatics*. 2000;41:104.

20. Mease PJ, Clauw DJ, Gendreau RM. The efficacy and safety of milnacipran for treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. *J Rheumatol*. 2009;36:398.

21. Arnold LM, Lu Y, Crofford LJ, et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis Rheum*. 2004;50:2974.

22. Russell IJ, Mease PJ, Smith TR, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. *Pain*. 2008;136:432.

23. Tzellos TG, Toulis KA, Goulis DG. Gabapentin and pregabalin in the treatment of fibromyalgia: a systematic review and a meta-analysis. *J Clin Pharm Ther*. 2010;35: 639–656.

24. Vitton O, Gendreau M, Gendreau J, Kranzler J, Rao SG. A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. *Hum Psychopharmacol*. 2004;19(Suppl. 1):S27.

25. Branco JC, Zachrisson O, Perrot S, Mainguy Y. A European multicenter randomized double-blind placebo-controlled monotherapy clinical trial of milnacipran in treatment of fibromyalgia. *J Rheumatol*. 2010;37:851–859.

26. Wiffen PJ, Derry S, Moore RA. Antiepileptic drugs for neuropathic pain and fibromyalgia – an overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2013;11: CD010567.

27. Schutter DJ. Quantitative review of the efficacy of slow-frequency magnetic brain stimulation in major depressive disorder. *Psychol Med*. 2010;40:1789.

28. Berlim MT, Van den Eynde F, Jeff Daskalakis Z. Clinically meaningful efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (rTMS) for treating primary major depression: a meta-analysis of randomized, double-blind and sham-controlled trials. *Neuropsychopharmacology*. 2013;38:543.

29. Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. *Psychol Med*. 2009;39:65.

30. Rosa MA, Lisanby SH. Somatic treatments for mood disorders. *Neuropsychopharmacology*. 2012;37:102–116.

31. George MS, Post RM. Daily left prefrontal repetitive transcranial magnetic stimulation for acute treatment of medication-resistant depression. *Am J Psychiatry*. 2011; 168:356–364.

32. Yoo WK, You SH, Ko MH, et al. High frequency rTMS modulation of the sensorimotor networks: behavioral changes and fMRI correlates. *NeuroImage*. 2008;39: 1886–1895.

33. Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J. Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. *Eur J Neurosci*. 2004;19:1950–1962.

34. Boyer L, Dousset A, Roussel P, et al. rTMS in fibromyalgia: a randomized trial evaluating QoL and its brain metabolic substrate. *Neurology*. 2014;82:1231–1238.

35. Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2 [updated September 2009]. The Cochrane Collaboration; 2009. Available from www.cochrane-handbook.org (Accessed June 24, 2014).

36. Rohatgi A. *WebPlotDigitizer* (Version 3.2) [software].Available from arohatgi.info/WebPlotDigitizer (Accessed May 15, 2014).

37. Mhalla A, Baudic S, Ciampi de Andrade D, et al. Long-term maintenance of the analgesic effects of transcranial

magnetic stimulation in fibromyalgia. *Pain*. 2011;152: 1478–1485.

38. Short EB, Borckardt JJ, Anderson BS, et al. Ten sessions of adjunctive left prefrontal rTMS significantly reduces fibromyalgia pain: a randomized, controlled pilot study. *Pain*. 2011;152:2477–2484.

39. Passard A, Attal N, Benadhira R, et al. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. *Brain*. 2007;130:2661–2670.

40. Lee SJ, Kim DY, Chun MH, Kim YG. The effect of repetitive transcranial magnetic stimulation on fibromyalgia: a randomized sham-controlled trial with 1-mo follow-up. *Am J Phys Med Rehabil*. 2012;91:1077–1085.

41. Kito S, Fujita K, Koga Y. Regional cerebral blood flow changes after low-frequency transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in treatment-resistant depression. *Neuropsychobiology*. 2008;58:29.

42. Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *J Neurosci*. 2001;21:RC157.

43. Fregni F, Ono CR, Santos CM, et al. Effects of antidepressant treatment with rTMS and fluoxetine on brain perfusion in PD. *Neurology*. 2006;66:1629.

44. Nadeau SE, McCoy KJ, Crucian GP, et al. Cerebral blood flow changes in depressed patients after treatment with repetitive transcranial magnetic stimulation: evidence of individual variability. *Neuropsychiatry Neuropsychol Behav Neurol*. 2002;15:159.

45. Speer AM, Kimbrell TA, Wassermann EM, et al. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. *Biol Psychiatry*. 2000;48:1133.

46. Fitzgerald PB, Sritharan A, Daskalakis ZJ, et al. A functional magnetic resonance imaging study of the effects of low frequency right prefrontal transcranial magnetic stimulation in depression. *J Clin Psychopharmacol*. 2007;27:488.

47. Jensen KB, Petzke F, Carville S, et al. Anxiety and depressive symptoms in fibromyalgia are related to poor perception of health but not to pain sensitivity or cerebral processing of pain. *Arthritis Rheum*. 2010;62:3488–3495.

48. Campbell CM, McCauley L, Bounds SC, et al. Changes in pain catastrophizing predict later changes in fibromyalgia clinical and experimental pain report: cross-lagged panel analyses of dispositional and situational catastrophizing. *Arthritis Res Ther*. 2012;14:R231.

49. Peyron R, Garcia-Larrea L, Gregoire MC, et al. Haemodynamic brain responses to acute pain in humans: sensory and attentional networks. *Brain*. 1999;122(Pt 9):1765–1780.

50. Kleinhans NM, Richards T, Sterling L, et al. Abnormal functional connectivity in autism spectrum disorders during face processing. *Brain*. 2008;131:1000–1012.

51. Schneibel R, Brakemeier EL, Wilbertz G, Dykierek P, Zobel I, Schramm E. Sensitivity to detect change and the correlation of clinical factors with the Hamilton Depression Rating Scale and the Beck Depression Inventory in depressed inpatients. *Psychiatry Res*. 2012;198:62–67.

52. Marlow NM, Bonilha HS, Short EB. Efficacy of transcranial direct current stimulation and repetitive transcranial magnetic stimulation for treating fibromyalgia syndrome: a systematic review. *Pain Pract*. 2013;13:131–145.

53. Carretero B, Martín MJ, Juan A, et al. Low-frequency transcranial magnetic stimulation in patients with fibromyalgia and major depression. *Pain Med*. 2009;10:748–753.

54. Sampson SM, Rome JD, Rummans T. Slow-frequency rTMS reduces fibromyalgia pain. *Pain Med*. 2006;7:115–118.