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Original article

The effects of add-on non-invasive brain stimulation in fibromyalgia: a meta-analysis and meta-regression of randomized controlled trials

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Abstract

Objectives. The effects of non-invasive brain stimulation (NBS), including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (TDCS), in treating FM remain inconclusive. The aim of this study was to investigate present evidence of using NBS as an add-on treatment in treating FM.

Methods. We conducted a database search of the Medline, Embase, PsycINFO and Cochrane Library electronic databases, from inception to July 2015, to analyse randomized controlled trials of NBS in treating FM. A total of 16 studies were included in the current meta-analysis.

Results. The pooled mean effect sizes of the 16 included studies revealed significant favourable effects of NBS. The weighted mean effect size in reducing pain, depression, fatigue, sleep disturbance and tender points and improving general health/function were 0.667 (95% CI 0.446, 0.889), 0.322 (95% CI 0.140, 0.504), 0.511 (95% CI 0.247, 0.774), 0.682 (95% CI 0.350, 1.014), 0.867 (95% CI 0.310, 1.425) and 0.473 (95% CI 0.285, 0.661), respectively. rTMS stimulation yielded a greater effect size compared with that of TDCS (effect size 0.698 and 0.568, respectively; $P < 0.0001$). The primary motor cortex (M1) stimulation yielded a subtle greater effect size in pain reduction compared with that of the dorsolateral prefrontal cortex (effect size 0.709 and 0.693, respectively; $P < 0.0001$). No linear relationships were found between the effect sizes and treatment regimens and dose. Most of reported adverse effects were minor.

Conclusions. Both rTMS and TDCS may be feasible and safe modalities for treating FM. The general effects of rTMS and TDCS are compatible in FM patients. M1 stimulation may be better in pain reduction and the dorsolateral prefrontal cortex may be better in depression improvement.

Key words: fibromyalgia, non-invasive brain stimulation, transcranial direct current stimulation, repetitive transcranial magnetic stimulation, pain, depression, sleep, primary motor cortex, dorsolateral prefrontal cortex

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Rheumatology key messages

- Repetitive transcranial magnetic stimulation and transcranial direct current stimulation may be feasible add-on modalities in treating FM.
- Repetitive transcranial magnetic stimulation and transcranial direct current stimulation are generally compatible in treating FM.
- The sites of non-invasive brain stimulation may link to different effects on symptoms in treating FM.

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Introduction

The pathomechanism of FM is still unclear, however, it is considered to be associated with dysfunction of the CNS and dysregulation of the neurotransmitters resulting in exaggerated central sensitization to pain [1, 2]. FM patients usually suffer from a complex symptom spectrum in addition to pain, such as sleep problems, fatigue, cognition difficulty and depression [3, 4]. To facilitate assessments of the outcomes of treatment for FM, the core

symptom domains of pain, tenderness, sleep dysfunction, fatigue and global multidimensional function should be incorporated and reported in conducting randomized controlled trials of FM as recommended by OMERACT [4].

The treatments of FM remain challenging [5, 6]. Because the symptom profiles of FM patients vary, a multidisciplinary approach, including medications, education, exercise and cognitive behaviour therapy, is recommended to manage FM patients [7, 8]. It has been demonstrated that surgical implantation of electrodes in the brain to conduct deep brain stimulation can improve refractory chronic pain [9, 10]. Nevertheless, invasiveness and safety issues limit the clinical use of deep brain stimulation in pain patients. Two methods of non-invasive brain stimulation (NBS)—repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (TDCS)—have been developed. The adverse effects of NBS are generally considered to be minor and well tolerated [11–13], therefore studies have been conducted to explore the therapeutic applications of NBS in treating pathological conditions such as major depression, stroke, Parkinson disease, etc. [13, 14]. As a neuromodulation technique, both rTMS and TDCS have been reported to have positive effects in treating neuropathic pain [11, 12, 15–18]. However, previous meta-analysis investigated the effects of TDCS in treating clinical and experimental pain and found the level of evidence is still low [11]. In addition, a Cochrane review concluded the evidence was still insufficient to support the use of NBS in chronic pain treatment [19]. Nevertheless, this review focuses on pain as a main outcome measurement in chronic pain patients and included all patients with chronic pain. FM is a specific disease entity among chronic pain syndromes. The controversy regarding the potential effects of NBS in FM treatment should be further clarified with recent studies.

In the present study, we conducted a meta-analysis to investigate the add-on effects of NBS in treating FM and compared the effects between two main methods of NBS, i.e. rTMS and TDCS. The stimulation sites of NBS are critical to elicit clinical effects. Therefore, we compared the effects between the primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC), two of the most common stimulation sites of NBS, in FM patients. We further conducted a dose–response analysis of NBS in treating FM with a meta-regression. These data are essential and critical to determine the clinical application and optimize the treatment of NBS in treating FM.

Methods

Eligibility criteria

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, which provides detailed guidelines on the reporting items that should be included in systematic reviews and meta-analyses [20]. We included prospective randomized controlled trials (RCTs) that examined the effects of NBS (e.g. TDCS and rTMS) on patients with FM to decrease FM-related symptoms (i.e.

pain, anxiety, depression, fatigue and poor sleep) and improve general health and function.

Search

One of the authors (T.W.Y.) conducted a database search of the Medline, Embase, PsycINFO and Cochrane Library electronic databases, from inception to July 2015, using both keywords and MeSH of FM OR chronic widespread pain combined with transcranial direct current stimulation OR transcranial magnetic stimulation OR non-invasive cortical stimulation. Also, retrieved articles were restricted to human subjects and publication type was limited to RCTs or clinical trials while searching the databases of Embase and PsycINFO. A hand search of the bibliographies of relevant articles was also carried out.

Study selection

We selected articles that fulfilled the following criteria: the study was described as an RCT or a clinical trial, the study design enabled the evaluation of the sole or additive benefit of non-invasive cortical stimulation therapy by using at least one appropriate control condition, there was at least one measurement of pain condition both before treatment and after at least one treatment and the presented data were sufficient to calculate the effect size [mean (S.D.), F or t statistics] for the pain scale. Studies including only one session of NBS were excluded because we considered that the effect of a single session was too short to have clinical applications.

Data collection process

Two reviewers (W.H.H. and J.H.K.) independently extracted data from all included studies after excluding 125 duplications from titles and abstracts. The data extracted corresponded with that in the above description and Fig. 1. Disagreements between reviewers were resolved through the third author (T.Y.W). Information was extracted from each identified trial on the number of participants, treatments compared, follow-up period, primary and secondary outcome measures, percentages of female participants, average ages of participants and average disease duration of participants. The assessment of risk of bias was performed using Cochrane Collaboration's tool for assessing the risk of bias [21].

Data analysis

Quantitative data were entered into Comprehensive Meta-Analysis software, version 2.0 (Biostat, Englewood, NJ, USA). Individual effect sizes for each domain that were assessed in more than one study were calculated using pre- and post-treatment differences. The standard mean difference was calculated using mean (S.D.) or standard error (S.E.) and n at baseline and the endpoint mean or post-baseline (S.D. or S.E.) and n for change from baseline. All the analyses were performed using the inverse variance random effects model, because this model is more conservative and less biased due to small-study effects compared with the fixed effects model [22, 23]. A sensitivity analysis was also performed by removing the study

Fɪɢ. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram
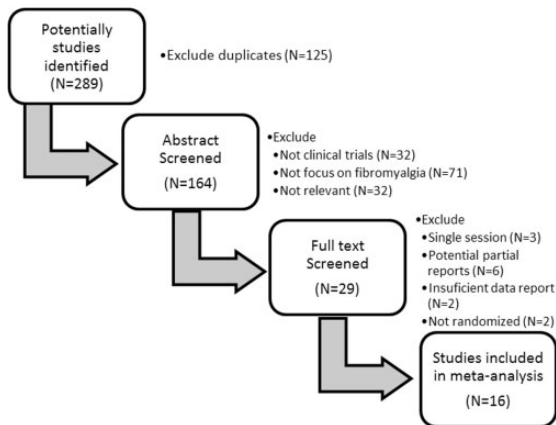
with the largest effect size to determine its contribution to the overall effect size in the current meta-analysis.

Heterogeneity

To establish whether the results of the studies were consistent, we investigated between-study heterogeneity by evaluating Cochran Q and I^2 statistics, which indicate the evidence and proportion of variability across studies that are not explained by chance alone. Q statistics of $\geqslant 0.1$ and I^2 values <50% reflect homogeneity across studies according to the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [23]. Visual examination of a forest plot was performed to confirm heterogeneity.

Publication bias

Potential publication bias was examined using the fail-safe N, which provides an estimate for the number of unpublished studies with a non-significant intervention effect required to reduce the overall estimation of effect size to a non-significant level (P > 0.05). The Begg rank correlation test and Egger intercept test were also adopted to test the publication bias, with P > 0.05 indicating significant publication bias. A funnel plot was used to examine the publication bias, and the trim and fill method was used to test and adjust for possible bias in the overall effect size by considering the effect sizes from the estimated number of missing studies.

Moderator effect

Subgroup analyses were conducted by dividing the studies into groups according to the mode of stimulation and the location of electrode placement. To explore the possible reasons for the observed heterogeneity, moderator analyses were performed. A mixed effect model was used to compare differences among the effect sizes in the comparisons of stimulation mode and electrode location. In order to explore the optimal treatment regimens for FM, meta-regression analyses were used to examine the moderator effects for three continuous variables of weekly sessions, total sessions and total treatment days.

Results

Search results

Our literature search uncovered 289 articles, 29 of which were potential candidates for inclusion in the meta-analysis. Thirteen of the 29 remaining studies were excluded because they were not randomized trials, were signal-session trials, did not provide sufficient data to compute an effect size or had selective reporting. The remaining 16 studies were included in the current meta-analysis [24–39]. Two of the aforementioned studies that reported different outcomes of NBS were combined due to duplications using the same subjects [29, 35]. This process is illustrated in Fig. 1.

Study characteristics

Table 1 summarizes the characteristics of the 16 included studies in which different cortical stimulations were used for improving the eight core symptoms of FM (three studies with two interventions in each). The study sample sizes ranged from 15 to 77, with a total of 572 randomized subjects. Of the sampled patients, 81.6% were women. The majority of the studies (11 studies) were conducted with TMS stimulation, while the 5 more recent studies used TDCS. Two of the studies contained three arms to compare the effects of different electrode placements of TMS [33] and TDCS [29, 35]. The intervals of treatment ranged from 5 days to 22 weeks, while the total stimulation doses varied from 12 000 to 45 000 pulses in TMS and 100–242 min in TDCS. The most frequently used measure of pain was the visual analogue scale. The methodological quality of the included studies according to the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 is reported in Table 2.

Quantitative data synthesis

Overall effect

The overall effect sizes compared with sham stimulation for each FM symptom domain are summarized in Table 3 and Figure 2. Three studies consisted of three arms [29, 33, 35], and two of these were considered as a serial study with the same participants and authors [29, 35]. All included studies showed no significant differences in baseline covariates and used only two-sample independent *t*-test or one-way analysis of variance to test the differences in mean changed scores. Therefore the pooled mean effect sizes of the 16 selected studies revealed a significant effect in all the symptom domains except for cognition. The weighted mean effect size in reducing pain, depression, fatigue, sleep disturbance and tender points and improving general health/function were 0.667 (95% CI 0.446, 0.889), 0.322 (95% CI 0.140, 0.504), 0.511 (95% CI 0.247, 0.774), 0.682 (95% CI 0.350, 1.014), 0.867 (95% CI 0.310, 1.425) and 0.473 (95% CI 0.285, 0.661), respectively. By calculating the statistics I^2 and Cochran Q of the

TABLE 1 Characteristics of included randomized controlled studies

Reference	Group	Enrolled/completed	Diagnostic criteria	Age, years, mean (s.d.)	Disease duration, months, mean (s.d.)	Combined treatment	Detail of interventions	Outcome measure	Follow-up	Adverse event
rTMS										
Avery et al. [27] (USA)	Sham	11/11	ACR 1990	52.09 (10.02)	15.64 (6.9)	Medications/psychotherapy	10 Hz, 120% RMT, 3000 pulses/session; 15 sessions/4 weeks	BIRS, BURS, PI-NRS, McGill PQ-SF, BPI-SF, SF-36, MFI/HDR-17/ VAS/BDI	1 w, 1 m, 3 m	Headaches, pain at site of stimulation, increased muscle aches, insomnia, nausea abdominal pain
	HF TMS	8/7		54.86 (7.65)	11 (4.26)					
Yagci et al. [24] (Turkey)	Sham	14/13	ACR 1990	43 (7.63)	54.92 (30)	Medications	1 Hz, 90% RMT, 1200 pulses/session; 10 sessions/2 weeks	VAS/BDI/FIQ	1 m, 3 m	Not mentioned
	LF rTMS	14/12		45.25 (9.33)	53 (29.15)					
Tekin et al. [28] (Turkey)	Sham	25/4	Not mentioned	46.5 (8.36)	159.96 (80)	No analgesic use	10 Hz, 100% RMT, 1500 pulses/session; 10 sessions/2 weeks	VAS/MADRS/WHOQOL-BREF	1 w, 2 w	Not mentioned
	rTMS	27/27		42.4 (7.63)	129.72 (75.72)					
Maestu et al. [32] (Spain)	Sham	28/26	ACR 1990	40.7 (6.7)	Not mentioned	Not mentioned	8 Hz, 20min; 8 sessions/8 weeks	Pain threshold/VAS	1 w, 4 w, 8 w	Not mentioned
	LF rTMS (low intensity)	28/28		40.7 (6.7)	Not mentioned					
Lee et al. 2012 [33] (Korea)	Sham	8/5	ACR 1990/ACR 2010	51.3 (6.2)	44.7 (11)	Medications	1 Hz, 110% RMT, 1600 pulses/session; 10 sessions/2 weeks	TPs/K-FIQ/VAS/BDI	2 w, 1 m	No major AEs
	LF rTMS	7/5		45.6 (9.6)	47.2 (20.1)		10 Hz, 80% RMT, 2000 pulses/session; 10 sessions/2 weeks			
	HF rTMS	7/5		53 (4.2)	57.1 (6.4)					
Baudic et al. [39] (France)	Sham	18/18	ACR 1990	49.7 (10.4)	140.4 (122)	Medications	10 Hz, 80% RMT, 1500 pulses/session; 14 sessions/21 weeks	Average pain intensity, BPI/HADS/MOS-SF-12/AVLT/SDMT/Trail/SCWT	3 w, 11 w	Not mentioned
	rTMS	20/20		51.8 (11.6)	156 (154.8)					
Short et al. [25] (USA)	Sham	10/10	ACR 1990	51.67 (18.19)	121.2 (154)	Medications	10 Hz, 120% RMT, 4000 pulses/session; 10 sessions/2 weeks	BPI/HDRS/FIQ	1 w, 2 w, 3 w, 4 w	Not mentioned
	rTMS	10/10		54.2 (8.28)	145.2 (93)					
Mhalla et al. [26] (France)	Sham	20/13	ACR 1990	49.6 (10)	169.2 (143)	Medications	10 Hz, 80% RMT, 1500 pulses/session; 14 sessions/21 weeks	BPI, McGill PQ/FIQ/HADS-21/BDI-13	5 d, 3 w, 9 w, 25 w	Head, dizziness
	HF rTMS	20/17		51.8 (11.6)	156 (154.8)					
Carretero et al. [37] (Spain)	Sham	12/12	ACR 1990	54.9 (4.9)	Not mentioned	Medications	1 Hz, 110% RMT, 1200 pulses/session; 20 sessions/4 weeks	Zachrisson FibroFatigue Scale, Likert Pain Scale/HDRS-17, CGI	2 w, 4 w,8 w	Neck pain, headache, worsening of depression, dizziness, tiredness
	LF rTMS	14/14		47.5 (5.7)	Not mentioned					
Passard et al. [31] (France)	Sham	15/13	ACR 1990	55.3 (8.9)	130.8 (103)	Medications	10 Hz, 80% RMT, 2000 pulses/session; 10 sessions/2 weeks	BPI (average pain intensity), McGill PQ/BPI, FIQ/HDR-17, BDI, HADS-14	1 d, 15 d, 30 d, 60 d	Headaches, nausea, tinnitus, dizziness
	rTMS	15/13		52.6 (7.9)	97.2 (94.8)					
Boyer et al. [38] (France)	Sham	19/13	ACR 2010	49.1 (10.6)	43.2 (46)	Medications	10 Hz, 90% RMT, 2000 pulses/session; 14 sessions/10 weeks	Tender points, average daily pain, pressure pain threshold/FIQ, SF-36(PCS), SF-36(MCS)/BDI, HADS	2 w, 11 w	Intercurrent medical conditions, headache
	HF rTMS	19/16		47.7 (10.4)	44.4 (54)					
TDCS										
Fagerlund et al. [36] (Norway)	Sham	25/24	ACR 1990	48.7 (10.56)	222 (138)	Medications	8 s fade-in, 30s current, 5 s fade-out 2 mA/35 cm², 20 min/session, 5 sessions/week	NRS/FIQ, HADS, SCL-90, SF-36 version 2	30 d	Skin redness, tingling, sleepiness
	Anodal tDCS	25/24		49.04 (8.63)	212.76 (90.48)					
Hargrove et al. [34] (USA)	Sham	45/39	ACR 1990	54 (3.0)	130.8 (15.6)	Medications	0.3 mA/cm², 11 min/session, 22 sessions/11 week	TePs, PPT/FIQ(VAS), BDI-II, SCL-90, Sleep VAS	11 w	Short-lived headache, eye movement/flutter during treatment, increased perception of restlessness
	tDCS	45/38		51.3 (3.4)	126 (18.0)					
Riberto et al. [30] (Brazil)	Sham	12/12	ACR 1990	Not mentioned	Not mentioned	Multidisciplinary rehabilitation	2 mA/35 cm², 20 min/session; 10 sessions/10 weeks	VAS/FIQ, SF-36/HAQ/BDI, HAM	4 m	No AEs
	Anodal tDCS	11/11		Not mentioned	Not mentioned					
Roizenblatt et al [29] (Brazil/USA)	Sham	10/10	ACR 1990	50.8 (10.2)	97.2 (90)	Medications	M1 stimulation was turned off after 30s 2 mA/35cm², 20 min/session, 5 sessions/5 days	VAS, TePs/BDI, MMSE, Tiredness/Sleep Structure	21 d	Not mentioned
	Anodal M1	11/11		54.8 (9.3)	120 (93.6)					
	Anodal DLPFC	11/11		54.2 (7.4)	100.8 (111.6)		2 mA/35 cm², 20 min/session, 5 sessions/5 day			

(continued)

TABLE 1 Continued

Reference	Group	Enrolled/completed	Diagnostic criteria	Age, years, mean (s.d.)	Disease duration, months, mean (s.d.)	Combined treatment	Detail of interventions	Outcome measure	Follow-up	Adverse event
Fregni et al. [35] (Brazil/USA)	Sham	10/10	ACR 1990	50.8 (10.2)	97.2 (90)	Medications	M1 stimulation was turned off after 30 s	VAS, CGI, PGA, TePs/FIQ, SF-36, BDI, MMSE	5 d, 4 w	Not mentioned
	Anodal M1	11/10		54.8 (9.3)	120 (93.6)		2 mA/35 cm², 20 min/session, 5 session/5 days			
	Anodal DLPFC	11/11		54.2 (7.4)	100.8 (111.6)		2 mA/35 cm², 20 min/session, 5 session/5 days			

BIRS: Gracely Box Intensity Scale; BURS: Gracely Box Unpleasantness Rating Scales; PI-NRS: Pain Intensity Numerical Rating Scale; McGill PQ-SF: McGill Pain Questionnaire-Short Form; BPI-SF: Brief Pain Inventory-Short Form; SF-36: 36-item Short Form Health Survey; MFI: Multidimensional Fatigue Inventory; HDR-17: 17-item Hamilton Depression Rating Scale; VAS: visual analogue scale; BDI: Beck Depression Inventory; FIQ: Fibromyalgia Impact Questionnaire; MADRS: Montgomery Asberg Rating Scale; WHOQOL-BREF: World Health Quality of Life-BREF; TPs: tender points; K-FIQ: Korean version of the Fibromyalgia Impact Questionnaire; HADS: Hospital Anxiety and Depression Scale; MOS-SF-12: Medical Outcomes Study Short Form 12 items; SCWT: Stroop Colour Word Test; CGIS: Clinical Global Impression Scale; SF-36(PCS): SF-36 Physical Composite Scale; SF-36(MCS): SF-36 Mental Composite Scale; NRS: Numerical Rating Scale; SCL-90: Symptom Checklist 90; TePs: the number of tender points; PPT: pressure pain threshold; HAM: Hamilton rating scale; PGA: patient's global assessment; MMSE: Mini-Mental State Examination; HF rTMS: high-frequency (repetitive) transcranial magnetic stimulation; LF rTMS: low-frequency repetitive transcranial magnetic stimulation; TDCS: transcranial direct current stimulation; M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex.

primary outcome of pain, moderate heterogeneity was identified ($Q = 19.62$, $df = 15$, $P = 0.187$, $I^2 = 23.56$). Therefore, subgroup analyses, moderator analyses and meta-regression were performed to further explore factors that might have contributed to the heterogeneity.

Sensitivity analysis

No outliers were found, as all effect sizes of each study fell within 2 s.d. of the pooled mean effect size. A sensitivity analysis was performed by removing the study with the largest effect size [28]. The other 15 studies remained statistically significant in reducing pain [effect size 0.557 (95% CI 0.362, 0.751)] without heterogeneity ($Q = 8.995$, $df = 14$, $P = 0.834$, $I^2 = 0$).

Subgroup analysis

The effect size by the modes and sites of stimulation are presented in Table 3. rTMS stimulation over the M1 area was effective at reducing pain and fatigue and improving general health/function, while rTMS stimulation over the DLPFC was effective at reducing pain and depression and improving general health/function. The overall effects of rTMS regardless of stimulation site were significant at reducing pain, depression, fatigue and sleep disturbance and improving general health/function. The overall effect sizes of TDCS were effective at reducing pain, sleep disturbance and tender points and improving general health/function, while TDCS over the M1 area was effective at reducing one symptom domain of pain. The effect sizes on pain, sleep disturbance, fatigue and tender points were large, whereas the effects on depression and general health/function were medium.

Moderator analysis and meta-regression

Moderator analyses were performed according to the categorical moderators of the modes and sites of stimulation for pain reduction in patients with FM. rTMS stimulations yielded a greater effect size compared with TDCS (effect size 0.698 and 0.568, respectively; $P < 0.0001$). To examine the moderator effect between the sites of stimulation, two studies with electrode placement in locations other than M1 and DLPFC were excluded [32, 34]. The M1 locations yielded a greater effect size compared with the DLPFC locations (effect size 0.709 and 0.693, respectively; $P < 0.0001$). However, no significant linear relationships were found between the effect sizes and treatment regimens (i.e. weekly sessions, total sessions and total treatment days) of the included studies (supplementary Fig. S1, available at *Rheumatology* Online).

Publication bias

The fail-safe N was 180, indicating that publication bias was not a problem. According to the Egger test, the intercept of the effect size was 0.860 and $t = 0.937$ (two-tailed $P = 0.364$). According to the Begg test, Kendall's τ with continuity correction was 0.275 and $Z = 1.486$ ($P = 0.137$). The results of both these tests were indicative of publication bias. However, the funnel plot showed a slight selection bias (Fig. 3). Therefore the mean effect size was

TABLE 2 Risk of methodological bias score of the included studies

References	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Avery *et al.* [27]	U	U	L	L	L	L
Yagci et al. [24]	U	U	L	L	L	L
Tekin et al. [28]	L	L	L	L	L	L
Lee *et al.* [33]	U	U	H	H	L	H
Baudic *et al.* [39]	L	L	L	L	H	L
Short et al. [25]	U	U	L	L	H	L
Mhalla *et al.* [26]	L	L	L	H	L	L
Carretero *et al.* [37]	U	U	L	L	L	L
Passard *et al.* [31]	L	U	L	L	L	L
Fagerlund *et al.* [36]	L	L	L	L	L	L
Maestu et al. [32]	U	U	L	H	H	H
Hargrove *et al.* [34]	U	U	L	H	H	L
Riberto *et al.* [30]	U	U	L	L	L	H
Roizenblatt *et al.* [29]	L	L	L	L	H	H
Fregni *et al.* [35]	L	U	H	L	U	L
Boyer *et al.* [38]	L	L	L	L	U	L

L: low risk; H: high risk; U: uncertain risk.

calculated again while imputing missing studies using the trim and fill procedure. The adjusted effect size was 0.677 (95% CI 0.495, 0.858).

Discussion

Overall effects

With the meta-analysis of present studies, we found the favourable effects of NBS can be noted in multiple domains, including pain, depression, fatigue, sleep, tender points and general health/function in FM patients. These findings are consistent with previous research done in chronic pain [11, 40] and support that NBS could be a feasible modality to treat FM. In a previous meta-analysis, Perrot *et al.* [40] found that non-pharmacological approaches in FM patients may be associated with wider effects on several non-pain symptoms compared with pharmacological approaches. Consistently, they found rTMS had favourable effects on pain, sleep disturbance, fatigue and functional deficit in FM patients.

Nevertheless, we found most of present studies still suffer from significant bias and small sample size. The small sample size and heterogeneity of design resulted in large CIs of effect size in the present meta-analysis. More well-designed RCTs are still needed.

rTMS *vs* TDCS

There is no direct arm-to-arm study comparing the effects of TDCS with rTMS in FM patients. We found the favourable effects in multiple domains such as pain, fatigue, general health/ function are generally comparable between rTMS and TDCS. Although the underlying mechanisms of rTMS and TDCS are quite different, their gross effects on neuropathic pain surprisingly similar.

Furthermore, previous studies also found that endogenous opioids may play a role in NBS-induced analgesia [26, 41]. These physiological changes are also associated with the after-effects of NBS.

That FM patients are sensitive to placebo effects of interventions has been suggested [37]. Therefore, establishing an adequate sham model is important to justify the real effects of NBS. Although different models of sham stimulations were used in rTMS and TDCS, the efficacy of blinding is still questionable. Sham stimulation may be more difficult to blind in patients treated with rTMS compared with TDCS [42]. It is possible that the difference in effect size in the meta-analysis is biased from the different efficacy of blinding between rTMS and TDCS. rTMS has been approved for treatment-resistant major depression in several countries. Therefore rTMS, as an established treatment modality, can be quickly applied in FM patients as an off-label treatment. However, rTMS has the disadvantages of high cost and relatively bulky instruments. On the other side, TDCS has the disadvantages of poor spatial resolution compared with rTMS [13]. In addition, there is still no approved clinical indication for TDCS. Nevertheless, TDCS has the advantages of relatively low cost and small instruments. Since the favourable effects are generally comparable between rTMS and TDCS, the advantages of TDCS may make it highly suitable and cost effective in the scenario of long-term treatment [43].

Stimulation sites

The effects of TDCS and rTMS are both highly site specific [13, 15, 18]. A complex pain matrix of the brain serves as a fundamental physiological basis of brain stimulation. Several brain areas that are involved in the pain process and the affective and attention network are proposed for

TABLE 3 Effect sizes of non-invasive cortical stimulation on FMS symptom domains

Type	Site	Pain	Depression	Anxiety	Fatigue	Sleep	General health and function	Tender point	Cognition
rTMS	M1	**0.670 (0.124, 1.216)**	0.246 (−0.056, 0.549)	0.162 (−0.243, 0.568)	**0.795 (0.250, 1.340)**	0.800 (−0.284, 1.884)	**0.581 (0.219, 0.943)**	—[a]	—[a]
	DLPFC	**0.708 (0.240, 1.175)**	**0.543 (0.074, 0.993)**	—[b]	0.090 (−0.509, 0.688)	—[a]	**0.631 (0.065, 1.197)**	0.432 (−0.126, 0.991)	—[b]
	Subtotal TMS	**0.698 (0.390, 1.006)**	**0.377 (0.148, 0.607)**	0.263 (−0.061, 0.588)	**0.500 (0.177, 0.824)**	**0.692 (0.173, 1.212)**	**0.536 (0.293, 0.778)**	**0.436 (0.014, 0.858)**	—[a]
TDCS	M1	**0.744 (0.160, 1.328)**	0.159 (−0.268, 0.586)	—[a]	—[b]	—[a]	0.319 (−0.110, 0.748)	—[a]	—[a]
	DLPFC	—[a]	—[a]	—[b]	—[a]	—[a]	—[a]	—[a]	—[a]
	Subtotal TDCS	**0.568 (0.265, 0.871)**	0.229 (−0.069, 0.526)	—[a]	—[a]	**0.706 (0.186, 1.227)**	**0.377 (0.078, 0.677)**	**1.615 (1.021, 2.209)**	0.194 (−0.555, 0.943)
Overall effect		**0.667 (0.446, 0.889)**	**0.322 (0.140, 0.504)**	0.249 (−0.033, 0.530)	**0.511 (0.247, 0.774)**	**0.682 (0.350, 1.014)**	**0.473 (0.285, 0.661)**	**0.867 (0.310, 1.425)**	0.120 (−0.413, 0.653)

All values are stated as mean (95% CI). Bold values indicate effect sizes with $P > 0.5$. [a]The effect size for the domain was not calculated; data available from only one study. [b]The domain was not measured in the study or not enough information was provided to calculate the effect size. FMS: fibromyalgia syndrome; M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex.

applying NBS in FM treatment. These areas may also play different roles in contributing to the symptom profile in FM. The stimulation area selected may induce different effects in treating FM patients by NBS. The most common sites selected in previous studies are M1 and DLPFC [18]. Early studies showed a direct analgesic effect can be found in neuropathic pain patients treated with invasive M1 stimulation with dural-implanted electrodes [44]. Hirayama et al. [45] showed M1 stimulation may be a more effective target to reduce pain than the premotor cortex, primary sensory cortex or supplementary motor area with navigation-guided rTMS. Motor disinhibition may play a role in chronic neuropathic pain [46]. The analgesic effects of M1 stimulation can change thalamic and subthalamic nuclei and modulate the affective component of pain [31, 47]. O'Reardon et al. [48] found that left DLPFC stimulation had an unexpected effect on pain reduction in the clinical trials for treating refractory depression. DLPFC coupling with the limbic system can modulate pain processing and perception. A top-down mechanism of pain inhibition with descending fibre through the prefrontal cortex has been proposed [49]. Nevertheless, there is some evidence to indicate the analgesic effects of M1 and DLPFC stimulation may be on different mechanisms [26].

We found that M1 and DLPFC stimulation yielded a close effect size in pain reduction of all pooled studies. Previous studies suggest stimulation of these two sites may have different selective effects, as active stimulation of M1 is associated with direct pain reduction and DLPFC is associated with anti-depressant effects [35]. Nevertheless, data regarding the association between the induced effects and stimulation sites of NBS are still inconclusive. Consistently, we found significant favourable effect size in depression can be noted in FM patients with DLPFC stimulation, but not with M1 stimulation with rTMS. However, the data are too limited to verify the effects of TDCS. Fregni et al. [35] conducted a three-arm study comparing the effects of sham and anodal stimulation by TDCS on the M1 and DLPFC. They found significant analgesic effects only with anodal stimulation at the M1 but not DLPFC. Valle et al. [50] conducted a similar study to compare the effects of TDCS on the M1 and DLPFC. They found only M1 stimulation was associated with long-term benefit at 60 days follow-up.

Adverse effects

The adverse effects of NBS, including rTMS and TDCS, are generally minor and well tolerated. The most observed adverse effects were skin discomfort at the stimulation site, headache, neck pain and dizziness. Many studies showed no significant difference in adverse effects between real and sham stimulation of NBS. There were some temporary neurobehavioral adverse events such as insomnia, sleepiness, restless sensation and worsening of depressive symptoms. However, no detrimental effects on cognition were noted in the studies with detailed neuropsychological

FIG. 2 Forest plot of overall mean effect sizes for included studies measuring pain
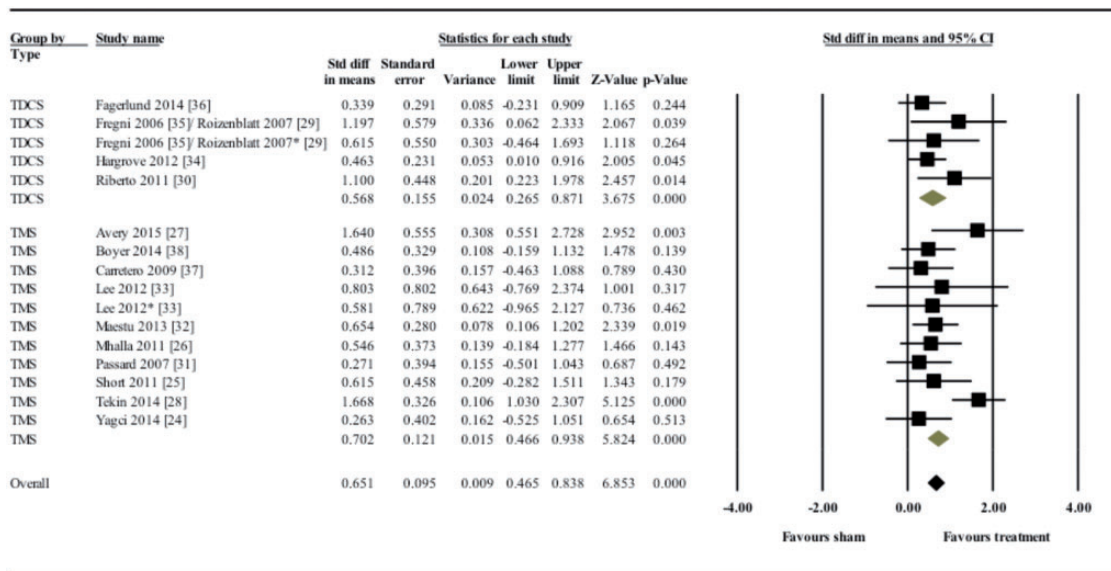
Std diff: standard difference.

FIG. 3 Funnel plot of the 16 included studies
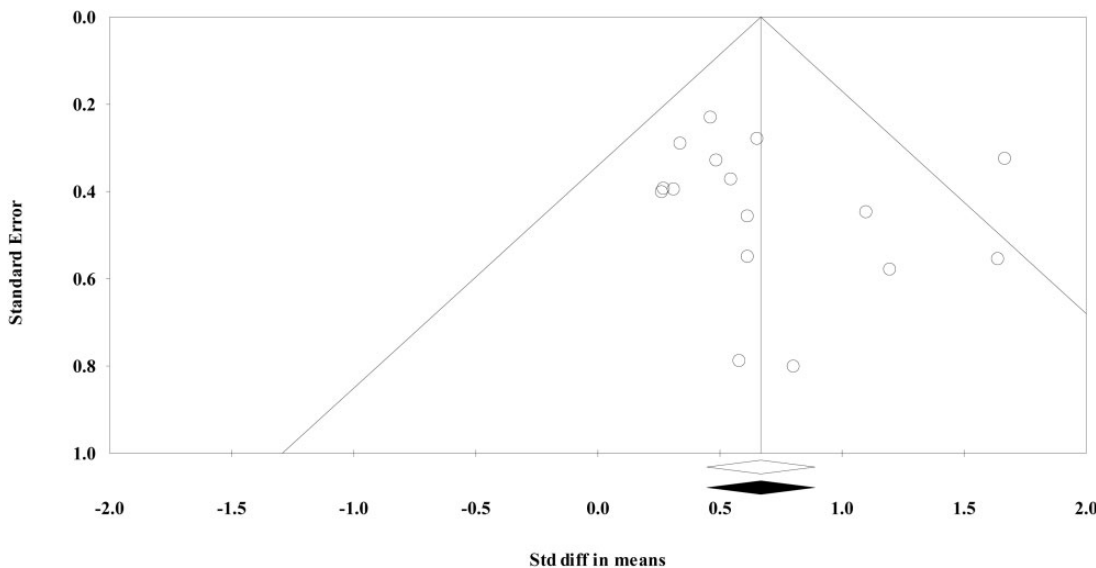
The circles represent included studies. The triangular region represents a 95% confidence region based on a fixed effects meta-analysis can be included in the plot. Std diff: standard difference.

tests [39]. Although seizure following NBS has been reported previously, no seizure event was observed among the included studies.

Dose–effect response

The minimal effective dose and the ceiling effect of NBS are poorly investigated. We found no clear dose–response effect of rTMS and TDC in reducing pain in FM patients in the present analysis. This finding may be due to small sample sizes and the heterogeneity of treatment protocol design among the studies. Applying rTMS in treating resistant major depression typically requires 4–6 weeks on a daily basis in a clinical setting. It may be reasonable to assume the longer duration of inducing significant effects from the experience of the studies with major depression patients.

Limitations

We found most included studies lacked of comprehensive outcome assessment of FM patients. In addition, the potential overlapping of psychometric properties of the measurements across the different domains should be addressed. For example, an FM impact questionnaire is used to evaluate patients' global functioning, which also includes the subjective rating of fatigue and sleep in its subscales. The properties of different measurement tools can introduce measurement bias during comparisons among the studies. Consensus regarding standardized outcome measures in FM patients may be needed to evaluate patients and improve outcome reporting. We found that men with FM may be underrepresented in the included studies. In addition, although the ethnicity of study the population is not specified in many studies, Asian and African populations may be underrepresented in the included studies. Furthermore, the inclusion criteria of FM patients are mainly based on two versions of diagnostic criteria: ACR 1990 and 2010. Differences in diagnostic criteria may cause a change in the features of included patients. For ethical reasons, most of studies allowed patients to continue use of their medications during the study period. Therefore, NBS was treated as an add-on treatment with medication. It is possible that NBS can interact with pharmacological effects in FM patients. Lastly, although all currently included studies used two-sample independent t-test or one-way analysis of variance to test the differences in mean changed scores, primarily because these studies showed no significant differences in baseline covariates between the comparison groups, further individual participant data meta-analyses or analysis of covariance estimates should be a crucial concern for studies with imbalanced baseline values.

Conclusions

NBS, including rTMS and TDCS, may be a feasible and safe add-on treatment in FM. NBS is associated with favourable effects in multiple domains of FM patients. The favourable effects between TDCS and rTMS are generally compatible. The current evidence is still too limited to verify the optimal stimulation parameters and models of NBS.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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