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Review article

Non-invasive brain stimulation for fatigue in multiple sclerosis patients: A systematic review and meta-analysis

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ABSTRACT

Background: To investigate the efficacy and safety of non-invasive brain stimulation for fatigue in multiple sclerosis patients.

Methods: We searched MEDLINE, Embase, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure, and Wanfang databases up to October 25, 2018 (PROSPERO registration number: CRD42018112823). Randomized or pseudo-randomized, sham-controlled clinical trials evaluating the effect of non-invasive brain stimulation (NIBS) such as transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), transcranial random noise stimulation (tRNS), transcranial alternating current stimulation (tACS), cranial electrotherapy stimulation, and reduced impedance non-invasive cortical electrostimulation were included. Two authors independently performed data extraction and risk of bias assessment according to Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1. The primary outcome was fatigue scores before and after stimulation and the secondary outcome was adverse events.

Results: Data from cross-over and parallel group studies were pooled using a generic inverse-variance approach. A total of 14 studies (11 for tDCS, 2 for TMS, and 1 for tRNS) recruiting 207 patients were included in the systematic review and meta-analysis. No eligible tACS, cranial electrotherapy stimulation or reduced impedance non-invasive cortical electrostimulation studies were found. Short-term and long-term treatment effects were significant for tDCS, whereas TMS and tRNS were not superior to sham stimulation. The available evidence supported the effectiveness of the 1.5 mA subgroup and bilateral S1 subgroup of tDCS. Adverse events were minor and transient but comparable between real and sham stimulation.

Conclusions: tDCS is a safe and effective treatment for fatigue in MS patients. However, further studies are required to confirm our results in a large-scale population and to investigate the effectiveness of other NIBS subtypes.

1. Introduction

Multiple sclerosis (MS) is the most common immune-mediated demyelinating disease affecting the central nervous system. A variety of symptoms can emerge as the disease advances, decreasing the quality of life and increasing the disease burden (Kesselring and Beer, 2005). Among these symptoms, fatigue is particularly common and can occur in up to 90% of MS patients (Chalah and Ayache, 2018; Patejdl and Zettl, 2017). Fatigue has been described as a lack of physical or mental energy that hampers daily activity or the abnormally persistent feeling of tiredness/weakness, yet a generally accepted definition has not been provided (Tur, 2016; Flachenecker et al., 2002). Medications that are sometimes prescribed for MS fatigue, such as pemoline, Prokarin and carnitine, lack sufficient evidence (Miller and Soundy, 2017). And clinical data for modafinil are also limited and conflicting (Shangyan et al., 2018; Yang et al., 2017). Although pooled results validate the

Abbreviation: AMT, Active Motor Threshold; BDI, Beck Depression Inventory; CO, Cross-Over; DLPFC, Dorsolateral Prefrontal Cortex; ET, Exercise Therapy; FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; iTBS, Intermittent Theta-Burst Stimulation; M1, Primary Motor Cortex; MFIS, Modified Fatigue Impact Scale; PA, Parallel Group; PFC, Prefrontal Cortex; PPC, Posterior Parietal Cortex; PROMIS, Patient-Reported Outcomes Measurement Information System; RMT, Resting Motor Threshold; rTMS, Repetitive Transcranial Magnetic Stimulation; S1, Primary Sensory Cortex; SM1, Primary Sensorimotor Cortex; tACS, Transcranial Alternating Current Stimulation; tDCS, Transcranial Direct Current Stimulation; TMS, Transcranial Magnetic Stimulation; tRNS, Transcranial Random Noise Stimulation; WEIMuS, Würzburger Fatigue Inventory for MS

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efficacy of amantadine, most of its trials were conducted more than a decade ago (Yang et al., 2017) . However, its effect is moderate and unsatisfactory, with unclear benefits to quality of life (Kesselring and Beer, 2005). Therefore, non-pharmacological intervention and multi-discipline management are currently recommended to treat MS complications (Tur, 2016).

Non-invasive brain stimulation (NIBS) is a novel neuro-modulatory technique that has shown promising treatment effects on several neurological disorders such as sequelae of stroke and chronic pain (Palm et al., 2014). The most common types of NIBS consist of transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), transcranial random noise stimulation (tRNS), transcranial alternating current stimulation (tACS), cranial electrotherapy stimulation, and reduced impedance non-invasive cortical electrostimulation (O'Connell et al., 2018; Tavakoli and Yun, 2017) . TMS uses rapidly changing magnetic fields to induce electric fields in the target brain regions (Chung et al., 2015). In other types of NIBS, the stimulation applied is a weak electrical current as constant (tDCS), randomly varying (tRNS), rhythmically reversed (tACS) or pulsed (cranial electrotherapy stimulation) (O'Connell et al., 2018; Tavakoli and Yun, 2017). Reduced impedance non-invasive cortical electrostimulation decreases electrical impedance of cranial soft tissue via characteristic electrical current frequency (Bronfort et al., 2004). TMS can be further classified into repetitive transcranial magnetic stimulation, intermittent theta-burst stimulation (iTBS), and continuous theta-burst stimulation, based on differences in the stimulating wave pattern (Chung et al., 2015).

Several recent RCTs have addressed the potential therapeutic effect of NIBS on MS fatigue. However, these studies are limited by small sample sizes and the results are inconsistent (Lefaucheur et al., 2017). Therefore, this meta-analysis reviews the current studies of NIBS on MS fatigue, assessing its efficacy and safety.

2. Materials and methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews and meta-analysis (Shamseer et al., 2015). The protocol was registered in PROSPERO (ID: CRD42018112823).

2.1. Search strategies

We systematically searched MEDLINE (accessed through PubMed), Embase, Web of Science, Cochrane Central Register of Controlled Trials, Chinese National Knowledge Infrastructure, and Wanfang databases for all relevant studies in November, 2018. Publication dates ranged from database inception to October 25, 2018. Key words used for the searches included multiple sclerosis, brain or cortical stimulation and clinical trial. Detailed search terms are provided in the Appendix. We limited our results to peer-reviewed studies published in English or Chinese. We did not include records published only as abstracts. Studies were excluded if data were still insufficient after trying to contact the authors.

Literature searches were performed independently by two reviewers (LM and FS). Disagreements were solved by discussion or consultation with a third author (CL).

2.2. Criteria for study selection

2.2.1. Study design

We included randomized and quasi-randomized controlled trials using parallel groups or a cross-over design.

2.2.2. Participants

This study focused on participants diagnosed with MS. We did not limit the gender, age, MS type, the Expanded Disability Status Scale (EDSS) range or severity of fatigue. Because fatigue level may be influenced by MS relapse, we only included studies where participants were clinically stable for at least 1 month.

2.2.3. Interventions

We included trials exploring the therapeutic effect of tDCS, TMS, tRNS, tACS, cranial electrotherapy stimulation, or reduced impedance non-invasive cortical electrostimulation. The effect of active stimulation should be compared to that of sham stimulation with or without concomitant physical therapy. Both real and sham stimulations should be restricted to the brain.

2.2.4. Outcomes

The primary outcome was fatigue level measured before and after stimulation. Modified Fatigue Impact Scale (MFIS), Fatigue Severity Scale, Visual Analogue Scale, or other validated quantitative scales were acceptable. The secondary outcome was adverse events during or after interventions.

2.2.5. Data extraction

Data extraction was first performed by LM and then checked by FS. We extracted the following data from included studies: baseline demographic characteristics of participants (e.g., gender distribution, age range and EDSS score), types and parameters of active stimulation (e.g., intensity, duration, site of stimulation), fatigue scores at baseline and different follow-up time points, adverse events and information used for risk of bias assessment.

2.2.6. Quality assessment

Risk of bias was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1. (Higgins JPT and Green S, n.d.) We also evaluated the carry-over effect for cross-over studies and the reliability of sham stimulations. Reporting bias was investigated using the funnel plot, whose asymmetry was further identified and corrected using the trim and fill method. Two reviewers (LM and FS) independently assessed the risk of bias. Disagreements were solved by discussion or consultation with a third author (CL).

2.2.7. Data synthesis and analysis

We used standardized mean differences (SMD) and confidence intervals (CI) to show the treatment effect of the intervention. Heterogeneity was investigated using the I^2. We reported short-term ($\leq$1 w after stimulation finished) and long-term (>1 w post-intervention) outcomes separately. If data were available for more than one time point for each period, we extracted the earliest post-stimulation data for short-term measurement and the data closest to 4 weeks post-stimulation for long-term follow-up. As suggested by the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1, (Higgins JPT and Green S, n.d.) we combined the results of parallel group and cross-over studies by imputing the between-condition correlation coefficient (0.55) from an included cross-over study (Cancelli et al., 2018). Subsequent sensitivity analyses were conducted by decreasing the correlation coefficient to 0.35 and increasing it to 0.75 to examine whether the conclusion remained consistent. Subgroup analyses based on stimulation types and parameters were performed if no less than three studies were available for a particular subgroup.

The trim and fill analysis was performed using Stata 15.1 (a). Other statistical process was conducted using RevMan 5.3 (b).

3. Results

3.1. Study selection

A total of 1899 records were retrieved from databases, from which 459 items were removed because of duplication and another 1394 items were excluded after reviewing the title/abstract. Of the 46 potential

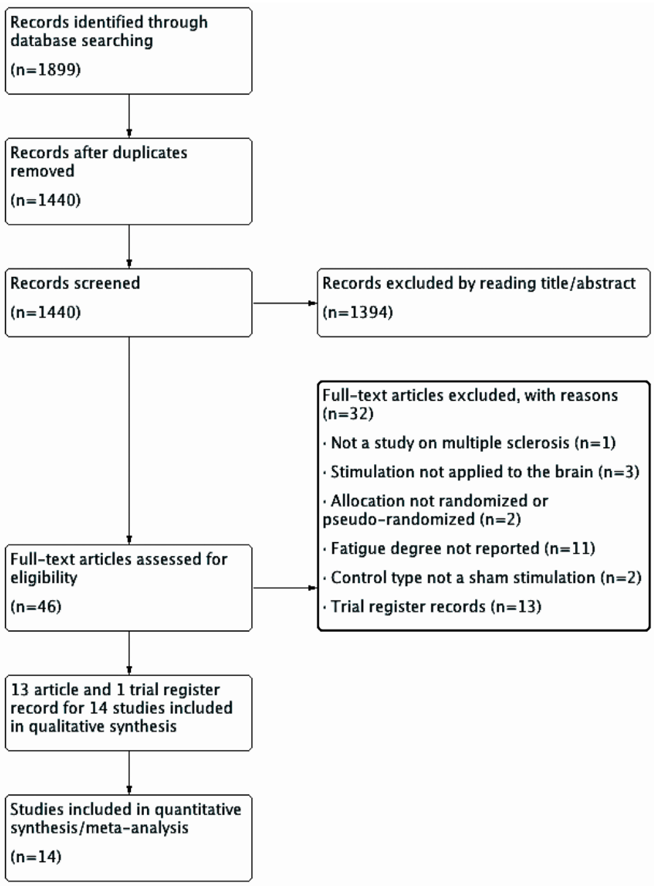

Fig. 1. Flowchart of study selection.

articles remaining, 32 were removed for the following reasons: not a study on MS (1); stimulation not applied to the brain (3); subject allocation was not randomized or pseudo-randomized (2); fatigue degree not reported (11); control type not a sham stimulation (2); and trial register records lacked results (13) (Fig. 1). Finally, 13 articles and one trial register record for 14 independent studies were included in this systematic review and meta-analysis.

3.2. Study characteristics

Table 1 lists the characteristics of the included studies and their baseline demographic information. The 14 included studies were published from 2011 to 2018. All but one of these trials (Charvet et al., 2017) were performed in Europe. A total of 207 MS patients were recruited. The majority of the studies adopted a cross-over design (10 studies), while four trials were a parallel group design. In one study (Catarina et al., 2014), the order of real and sham stimulation sessions was pseudo-randomly determined. The other 13 trials were randomized controlled trials. Inclusion criteria for MS patient recruitment differed across studies. A total of 10 studies recruited MS patients with fatigue. Other requirements for MS patient enrollment included accompanying neurological pain (Ayache et al., 2016; Palm et al., 2016) and spasticity (Mori et al., 2010). All trials required the participants to be relapse-free for at least 1 month to minimize the potential bias induced by MS fluctuation.

Types of NIBS investigated were tDCS (11 studies), TMS (1 repetitive transcranial magnetic stimulation study and 1 iTBS study), and tRNS (1 study). No eligible tACS, cranial electrotherapy stimulation or reduced impedance non-invasive cortical electrostimulation studies were found. The iTBS study (Mori et al., 2010) assessed the effect of real versus sham iTBS with concomitant exercise therapy, whereas other trials focused on the effect of NIBS alone. Parameters of the intervention varied across studies. Included studies applied anodal stimulation to the left dorsolateral prefrontal cortex (DLPFC) or prefrontal cortex (6 studies), right posterior parietal cortex (1 study), left DLPFC or right posterior parietal cortex (1 study), bilateral S1 (3 studies), bilateral hand primary sensorimotor cortex (1 study), bilateral M1 (1 study), and M1 contralateral to the affected limb (1 study). Electric current intensity was 1 mA, 1.5 mA, or 2 mA for tDCS studies and ranged from 0–2 mA in the tRNS study. For the two TMS trials, stimulation strength was 120% resting motor threshold and 80% active motor threshold, respectively. The stimulation was applied for 15 or 20 min per session in most tDCS and tRNS trials, excluding one study whose stimulation time differed across participants (Fiene et al., 2018). In terms of the two TMS studies, treatment continued for 18 min and 200 s, respectively. The total numbers of sessions in the 14 studies ranged from a single session to 18 sessions.

3.3. Risk of bias of included studies

Supplemental Fig. 1 presents the risk of bias in the included studies. Potential bias mainly originated from the randomization method, blinding process, and carry-over effect. One study was pseudo-randomized and seven other trials were considered to have an unclear risk of bias due to insufficient information provided about the randomization procedure. One tDCS study was single-blinded (Fiene et al., 2018) with the examiners aware of the type of the stimulation. Other trials were blinded to both patients and examiners. Bias due to blinding of Catarina 2014 (Catarina et al., 2014) was judged as high risk because 4 among 13 patients reported stronger skin sensations during real than sham stimulation whereas other adverse events were balanced between the two sessions. Given that arranging the coils at different positions during sham and real stimulations may allow patients to distinguish between the two interventions, another TMS study (Mori et al., 2010) was considered to have an unclear risk of bias in terms of blinding. Only two cross-over trials (Cancelli et al., 2018; Tecchio et al., 2014) monitored the residual effect during the washout period and did not begin the second stimulation block until this effect fell below a reliable threshold. Therefore, we considered the other eight cross-over studies to have an unclear risk of bias due to carry-over effect. A total of 23 patients dropped out in all included studies.

3.4. Short-term effect

All included studies reported fatigue severity outcomes immediately after the last stimulation session, which were pooled to the meta-analysis of short-term effects. When the correlation coefficient was imputed as 0.55 according to Cancelli et al. (2018), tDCS showed a positive effect on MS fatigue (SMD: −0.64 [95% CI: −1.18, −0.11]) (Fig. 2). Although there was a trend in favor of TMS treatment, the difference between real and sham stimulation was not significant (SMD: −0.41 [95% CI: −1.05, 0.23]). The only tRNS study included also did not provide a conclusive result (SMD: −0.03 [95% CI: −0.47, 0.52]). There was considerable heterogeneity among tDCS studies (I^2 = 85%), validating the use of a random-effect model. The heterogeneity mainly originated from three studies, which were outside of the 95% CI scope in the funnel plot (Fig. 3). After removing the three outliers, I^2 decreased to 39% and the pooled effect of tDCS on fatigue remained significant (SMD: −0.54 [95%CI: −0.80, −0.27]). The funnel plot was basically symmetric and no trimming was performed during trim and fill analysis.

Reducing and increasing the imputed correlation coefficient by a value of 0.2 did not change the significance of the treatment effect, indicating that the pooled effects were fairly robust.

Subgroup analyses evaluating the short-term effects of tDCS were performed based on current strength (1.5 mA and 2 mA) and stimulation site (left DLPFC and bilateral S1). Comparisons for which fewer

Table 1
Characteristics of included studies

Study	Design	Country of study	Participants Condition	Number	Age (year)	EDSS	Sex
Ayache et al. (2016)	RCT, CO	France	MS patients with neuropathic pain	16 (11RR + 4SP + 1PP)	48.9 ± 10.0	4.3 ± 1.4	13 F/3 M
Cancelli et al. (2018)	RCT, CO	Italy	MS patients with MFIS > 35 and BDI ≤ 19	10RR	43.2 ± 13.4	0.9 [0–3.5]	8 F/2 M
Catarina et al. (2014)	Pseudorandomized controlled trial, CO	Germany	MS patients with FSS ≥ 4 and BDI < 19	13RR	46.9 ± 6.8	3.5 ± 6	10 F/3 M
Chalah et al. (2017)	RCT, CO	France	MS patients with FSS > 5 and BDI ≤ 19	10 (9RR + 1SP)	40.5 ± 11.2	2.3 ± 2.5	4 F/6 M
Charvet et al. (2017)	RCT, PA	USA	MS patients	27	44.2 ± 15.9	4.9 [0–8.5]	16 F/11 M
Fiene et al. (2018)	RCT, CO	Germany	MS patients with WEIMuS ≥ 9 and BDI ≤ 19	15 (14RR + 1SP)	43.2 ± 15.0	3.5 ± 1.9	8 F/7 M
Hanken et al. (2016)	RCT, PA	Germany	MS patients experiencing cognitive fatigue	40 (15RR + 25SP)	49.1 ± 9.5	4.2 ± 1.5	25 F/15 M
Roberta et al. (2014)	RCT, CO	Italy	MS patients with MFIS > 45	23 (19RR + 4SP)	44.5 ± 6.6	3.3 ± 0.6	16 F/7 M
Tecchio et al. (2014)	RCT, CO	Italy	MS patients with MFIS > 38 and BDI < 19	10 (7RR + 1SP + 2PP)	45.8 ± 7.6	1.5 [0–3.5]	7 F/3 M
Tecchio et al. (2015)	RCT, CO	Italy	MS patients with MFIS > 15 without depression (no medication)	13RR	45.8 ± 7.6	1.5 [0–3.5]	9 F/4 M
Tecchio et al. (2015)	RCT, CO	Italy	MS patients with MFIS >15 without depression (no medication)	8RR	38.1 ± 9.8	2 [1–2.5]	6 F/2 M
Gaede et al. (2018)	RCT, PA	Germany	MS patients with FSS ≥ 4 or BDI-IA ≥ 12	19 (17RR + 2SP)	43.8	2.8	14 F/5 M
Mori et al. (2010)	RCT, PA	Italy	MS patients with spasticity	20RR	38.4 ± 11.2	3.7 ± 1.4	7 F/13 M
Palm et al. (2016)	RCT, CO	France	MS patients with neurological pain	16 (11RR + 4SP + 1PP)	47.4 ± 8.9	4.2 ± 1.3	13 F/3 M

Study	Participants Type	Intervention Site	Intensity	Duration	Control type	Outcomes Measure	Retention period post-stimulation
Ayache et al. (2016)	tDCS	Left DLPFC	2 mA	20 min qd × 3 days	Sham stimulation	MFIS	0 day
Cancelli et al. (2018)	tDCS	Bilateral S1	1.5 mA	15 min qd × 5 days	Sham stimulation	MFIS	0 day
Catarina et al. (2014)	tDCS	Left DLPFC	1 mA	20 min qd × 5 days	Sham stimulation	MFIS	0, 3, 5, 10, 15 days
Chalah et al. (2017)	tDCS	Left DLPFC or right PPC	2 mA	20 min qd × 5 days	Sham stimulation	MFIS	0 day
Charvet et al. (2017)	tDCS	Left DLPFC	2 mA	20 min × 20 sessions	Sham stimulation	PROMIS Fatigue scores	0 day

(*continued on next page*)

Table 1 (*continued*)

Study	Participants Type	Intervention Site	Intensity	Duration	Control type	Outcomes Measure	Retention period post-stimulation
Fiene et al. (2018)	tDCS	Left DLPFC	1.5 mA	27.29 ± 1.15 min, single session	Sham stimulation	Subjective fatigue (10-point rating scale)	0 day
Hanken et al. (2016)	tDCS	Right PPC	1.5 mA	20 min, single session	Sham stimulation	VAS	0 day
Roberta et al. (2014)	tDCS	Bilateral M1	1.5 mA	15 min qd × 5 days	Sham stimulation	FIS	0, 1, 3 weeks
Tecchio et al. (2014)	tDCS	Bilateral S1	1.5 mA	15 min qd × 5 days	Sham stimulation	MFIS	0, 4, 8 weeks
Tecchio et al. (2015)	tDCS	Bilateral S1	1.5 mA	15 min qd × 5 days	Sham stimulation	MFIS	0 day
Tecchio et al. (2015)	tDCS	Bilateral hand SM1	1.5 mA	15 min qd × 5 days	Sham stimulation	MFIS	0 day
Gaede et al. (2018)	rTMS	Left PFC	120% RMT, 36 stimuli at 18 Hz × 50 trains, ITI 20 s	18 min × 18 sessions in 6 weeks	Sham stimulation	FSS	0, 2, 4, 6 weeks
Mori et al. (2010)	iTBS + ET	M1 contralateral to the spastic limb	80% AMT, 3 stimuli at 50 Hz × 10 bursts at 5 Hz × 20 blocks	200 s × 5 days for 2 weeks	Sham stimulation + ET	FSS	0 day
Palm et al. (2016)	tRNS	Left DLPFC	1 ± 0.325 mA, oscillation 0–500 Hz	20 min qd × 3 days	Sham stimulation	MFIS	0 day

AMT, Active Motor Threshold; BDI, Beck Depression Inventory; CO, Cross-Over; DLPFC, Dorsolateral Prefrontal Cortex; EDSS, the Expanded Disability Status Scale; ET, Exercise Therapy; F, Female; FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; iTBS, Intermittent Theta-Burst Stimulation; M1, Primary Motor Cortex; M, Male; MFIS, Modified Fatigue Impact Scale; MS, Multiple Sclerosis (RR, Relapsing–Remitting; PP, Primary Progressive; SP, Secondary Progressive); PA, Parallel Group; PFC, Prefrontal Cortex; PPC, Posterior Parietal Cortex; PROMIS, Patient-Reported Outcomes Measurement Information System; RCT, Randomized Controlled Trial; RMT, Resting Motor Threshold; rTMS, Repetitive Transcranial Magnetic Stimulation; S1, Primary Sensory Cortex; SM1, Primary Sensorimotor Cortex; tDCS, Transcranial Direct Current Stimulation; TMS, Transcranial Magnetic Stimulation; tRNS, Transcranial Random Noise Stimulation; VAS, Visual Analog Scale; WEIMuS, Würzburger Fatigue Inventory for MS.
Data were presented as mean ± SD or mean [range].

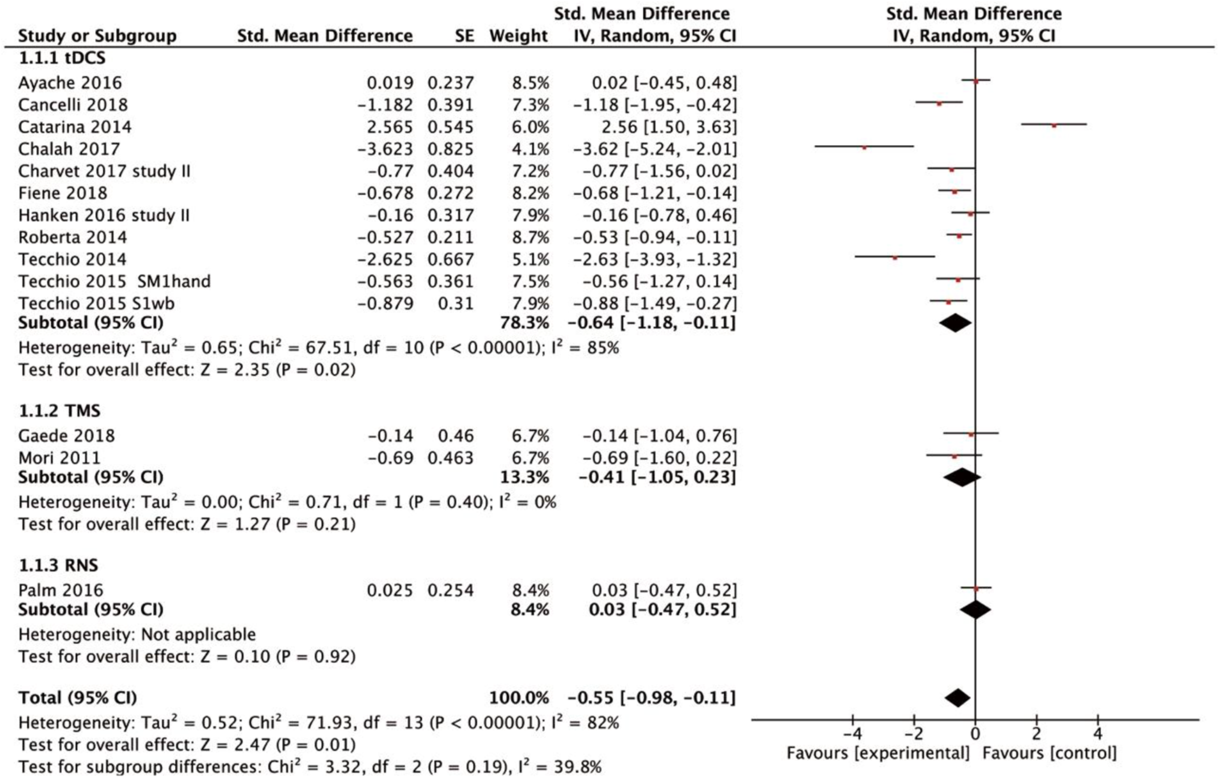

Fig. 2. Forest plot of the short-term effects of non-invasive brain stimulation on multiple sclerosis fatigue. Data derived from a random effects model.

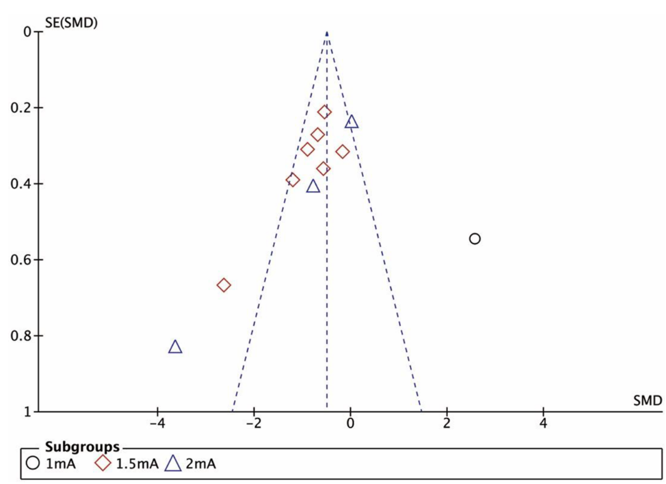

Fig. 3. Funnel plot of the short-term effects of transcranial direct current stimulation on multiple sclerosis fatigue.

than three studies were available (e.g., 1 mA tDCS and bilateral M1 tDCS) were excluded due to uncertainty of their results. When the imputed correlation coefficient was 0.55, seven 1.5 mA tDCS studies showed an SMD = −0.77 (95% CI −1.14, −0.40), while three 2 mA tDCS studies showed an effect crossing zero (SMD: −1.24 [95% CI: −2.75, 0.27]). The pooled effect of four left DLPFC tDCS trials did not reach significance (SMD: 0.20 [95% CI: −0.86, 1.27]), whereas three bilateral S1 tDCS studies showed a significant treatment effect (SMD: −1.38 [95% CI: −2.20, −0.56]). Removing the outliers (Catarina et al., 2014 and Tecchio et al., 2014) or changing the correlation coefficient did not meaningfully affect the result.

3.5. Long-term effect

Final follow-up took place 0 to 8 weeks after the last session. Long-term treatment effect was measured in four trials (Catarina et al., 2014; Gaede et al., 2018; Roberta et al., 2014; Tecchio et al., 2014). Fatigue scores improved in tDCS studies (SMD: −0.65 [95% CI: −0.97, −0.34]), but not in the TMS study (Fig. 4). I^2 showed mild heterogeneity. Changing the imputed correlation coefficient did not significantly affect the results. Data extracted for analyzing the long-term effect were collected 21 to 28 days after stimulation finish for three tDCS studies and 6 weeks after stimulation for the TMS trial.

3.6. Adverse events

Definition and reporting format of adverse events varied markedly across studies. Six studies systematically reported the incidence of adverse events while information about safety and tolerability was not mentioned at all in six studies. Adverse events were generally moderate and self-limited, the most common being headache, insomnia, pain, and tingling sensation (Table 2). No study showed a significant difference in terms of adverse events between real and sham stimulations.

4. Discussion

4.1. Summary of evidence

To the best of our knowledge, this study is the first systematic review and meta-analysis investigating the efficacy and safety of NIBS on MS fatigue. The pooled data revealed statistically significant improvement in MS fatigue over both the short and long period after tDCS treatment compared with sham stimulation. In terms of different stimulating intensity and location, significance was also demonstrated in 1.5 mA and bilateral S1 subgroups. The overall effect of TMS crossed but was close to the null line. The only tRNS trial included suggested no benefit. Overall, NIBS was an effective and safe procedure for MS.

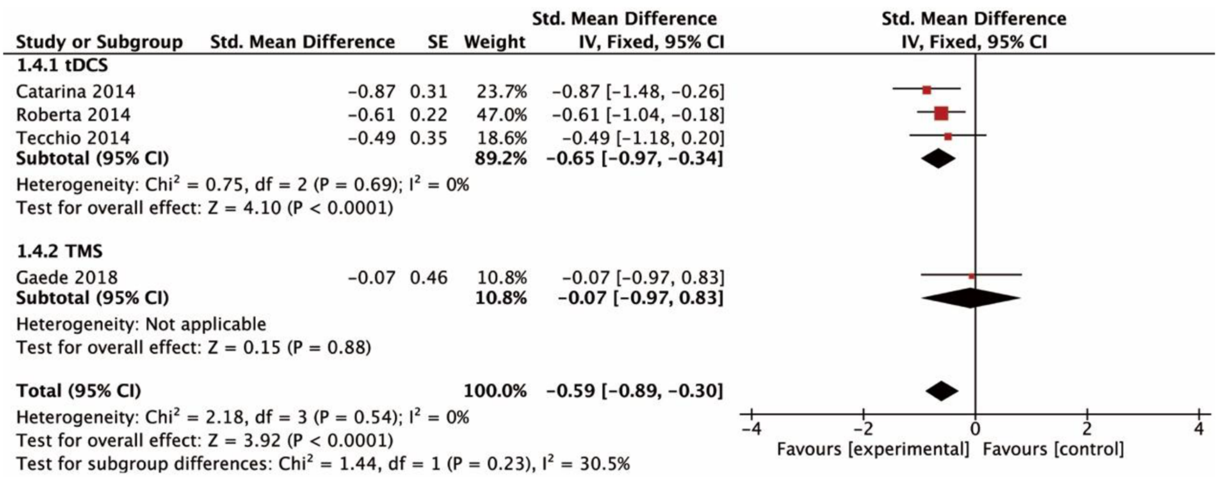

Fig. 4. Forest plot of the long-term effects of non-invasive brain stimulation on multiple sclerosis fatigue. Data derived from a fixed effects model.

Table 2
Adverse events.

	tDCS, *n*/*N* (%)	TMS, *n*/*N* (%)	tRNS, *n*/*N* (%)	Sham-stimulation, *n*/*N* (%)
Headache	3/20 (15)	12/16 (75)	0/10 (0)	9/45 (20)
Phosphene	nr	nr	0/10 (0)	1/10 (10)
Insomnia	3/10 (30)	nr	5/10 (0)	6/19 (31.6)
Nausea	nr	nr	2/10 (0)	4/10 (40)
Discomfort/pain/ paresthesia	1/10 (10)	6/16 (37.5)	nr	12/26 (46.2)
Spasticity of bladder or limb	nr	3/16 (18.8)	nr	0/16 (0)
Gait disturbance	nr	nr	nr	nr
Dizziness	nr	nr	nr	nr
Skin sensation (tingling)	4/10 (40)	nr	nr	0/10 (0)

4.2. Possible mechanisms

The pathophysiology of MS fatigue is not fully understood. Previous studies have shown that fatigue severity of MS patients correlates with the functional connectivity between different brain regions (e.g., caudate nucleus and motor cortex) (Finke et al., 2015). Abnormal excitability in M1 and somatosensory network may also contribute to fatigue in MS patients (Yusuf and Koski, 2013; Cancelli et al., 2018). The clinical picture is further complicated by the interaction between fatigue and other symptoms such as depression (Flachenecker et al., 2002) and spasticity (Milinis et al., 2016). In multiple sclerosis patients, depression severity has been shown to correlate significantly with fatigue score (Bakshi et al., 2000), which may be partially explained by their shared pathways in frontal and fronto-temporal white matter tracts demonstrated in neuro-imaging studies (Gobbi et al., 2014).

A possible mechanism of NIBS is neuroplasticity through long term potentiation (LTP) or long term depression (LTD), which are enduring enhancement or attenuation of synaptic signal transmission induced by patterned stimuli (Iodice et al., 2017). It has been proved in mouse model that impaired LTP/LTD in the corticostriatal pathway could be the cellular mechanism of exercise-induced fatigue (Ma et al., 2018) . The inflammatory process of MS can interfere with LTP/LTD, whereas NIBS functions by inducing LTP-like plasticity and produce cortical excitability change, therefore promoting recovery (Stampanoni Bassi et al., 2017). Therapists can increase or decrease the cortical excitability of MS patients by switching the current direction in tDCS, or changing the frequency and stimulation pattern in TMS (Salazar et al., 2018). In this way, NIBS can modulate the network topology pattern related to MS fatigue. Other studies have shown promising effects of NIBS on other MS comorbidities (e.g., depression (Chalah et al., 2017) and spasticity (Centonze et al., 2007)), which are positively associated with fatigue symptoms, thus facilitating fatigue improvement.

4.3. Limitations

Our study has several limitations. First of all, meta-analyses of NIBS on MS fatigue demonstrated certain heterogeneity, which may be attributed to several differences among studies. The included studies employed diverse study designs (e.g., cross-over versus parallel group, double-blind versus single-blind (Fiene et al., 2018)), and one of the outliers (Catarina et al., 2014) was the only pseudo-randomized trial. Additionally, participant baseline characteristics differed across studies. For example, the mean EDSS score ranged from 1.5–4.9. Given that fatigue alleviation after tDCS treatment has been shown to correlate with MRI lesion load (Catarina et al., 2014; Roberta et al., 2014), it seems reasonable that differences in MS severity may contribute to the heterogeneity. Meanwhile, a variety of rating scales were used in the 14 studies, the two most common being MFIS and the Fatigue Severity Scale. These assessment tools reflect different aspects of fatigue level. For example, the Fatigue Severity Scale believed to correlate with MFISphy and MFISpsych but not the MFIScog subscale (Flachenecker et al., 2002).

Secondly, eligible studies were limited and small-scale. In the 2 mA subgroup and the left DLPFC subgroup, real tDCS demonstrated no superiority over sham stimulation. Nevertheless, these results should be considered with caution because both subgroups contained a limited number of studies and the pooled effects were influenced by the outliers.

Thirdly, although the appreciable placebo effect of NIBS on MS fatigue validates the use of a cross-over design (Cancelli et al., 2018) that composes the majority of clinical trials in this field (10 of the 14 studies included), certain problems should be addressed before incorporating cross-over studies into the meta-analysis. Data required for the participant-specific paired analysis, such as standard deviation of the individual differences between interventions, were not provided in the included studies. Thus, we decided to approximate a paired analysis by imputing the correlation coefficient between real and sham stimulation, which was reported by only one included study (Cancelli et al., 2018). Subsequent sensitivity analyses were performed by adjusting its value within a rather large range (0.35–0.75), which did not significantly affect the results of overall and subgroup analyses. Secondly, as for the carry-over effect, only two studies monitored the outcome after the first block and started the second block after the value decreased below a pre-determined threshold. In other cross-over studies, the washout period ranged from 1 week to at least 1 month; thus, potential bias from the carry-over effect should certainly be acknowledged. The observed difference between the two periods tends to be less significant if the effect of the first period persists into the second. This might to some extent explain the non-significant results found in the 2 mA and the left DLPFC subgroups. Nevertheless, we assume that our method was acceptable and offered an estimate at best because no study has reported outcomes after the first period, and excluding studies with unclear risk of bias due to carry-over effect does not change the significance of overall treatment effect. Moreover, carry-over effect typically results in underestimation of the pooled treatment effect, making the conclusion more conservative (Higgins and Green, 2011). Thus, the significant results revealed by this article are unlikely to be an exaggeration of the true treatment effect.

Other limitations of this systematic review include: (1) excluding Charvet et al., 2017, all included studies were conducted in Europe; (2) fatigue levels were assessed at different times during follow-up; and (3) few studies investigated the effect of TMS or tRNS.

4.4. Implications for future research

To increase our understanding of NIBS's therapeutic efficacy on MS fatigue, a large-scale RCT recruiting multiple ethnic groups is required. Since the carry-over effect is problematic and reduces the statistical power to detect the difference between treatments, a parallel group design could be more appropriate than cross-over study. A reliable blinding protocol is warranted, especially for heavier-current tDCS. Otherwise, blinding integrity should be demonstrated through approaches such as asking the patients to guess their intervention allocation.

5. Conclusions

In MS patients, tDCS decreases fatigue level immediately after cessation of treatment, and this positive effect outlasts the stimulation for at least three weeks. However, the quality of evidence is limited by considerable heterogeneity and small sample sizes. Our results are insufficient to support the use of TMS or tRNS for MS fatigue, but NIBS was generally a safe and easy-to-use option for fatigue management in MS patients. Well-designed studies with a larger sample size are required in the future.

Declaration of Competing Interest

The authors declare no competing interests.

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Supplementary materials

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References

Ayache, S.S., Palm, U., Chalah, M.A., Al-Ani, T., Brignol, A., Abdellaoui, M., Dimitri, D., Sorel, M., Créange, A., Lefaucheur, J.-P., 2016. Prefrontal tDCS decreases pain in patients with multiple sclerosis. Front. Neurosci. 10, 147. https://doi.org/10.3389/fnins.2016.00147.

Bakshi, R., Shaikh, Z., Miletich, R., Czarnecki, D., Dmochowski, J., Henschel, K., Janardhan, V., Dubey, N., Kinkel, P., 2000. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. Mult. Scler. 5.

Bronfort, G., Nilsson, N., Haas, M., Evans, R., Goldsmith, C.H., Assendelft, W.J.J., Bouter, L.M., 2004. Non-invasive physical treatments for chronic/recurrent headache. Cochr. Database Syst. Rev. 3, CD001878. https://doi.org/10.1002/14651858.CD001878.pub2.

Cancelli, A., Cottone, C., Giordani, A., Migliore, S., Lupoi, D., Porcaro, C., Mirabella, M., Rossini, P.M., Filippi, M.M., Tecchio, F., 2018. Personalized, bilateral whole-body somatosensory cortex stimulation to relieve fatigue in multiple sclerosis. Mult. Scler. 24, 1366–1374. https://doi.org/10.1177/1352458517720528.

Catarina, S., Thomas, G., Charles, T., Steenwijk, M.D., Alexander, O., Andrea, A., Walter, P., Nitsche, M.A., 2014. Impact of transcranial direct current stimulation on fatigue in multiple sclerosis. Restor. Neurol. Neurosci. 3, 423–436. https://doi.org/10.3233/RNN-130372.

Centonze, D., Koch, G., Versace, V., Mori, F., Rossi, S., Brusa, L., Grossi, K., Torelli, F., Prosperetti, C., Cervellino, A., Marfia, G.A., Stanzione, P., Marciani, M.G., Boffa, L., Bernardi, G., 2007. Repetitive transcranial magnetic stimulation of the motor cortex ameliorates spasticity in multiple sclerosis. Neurology 68, 1045–1050. https://doi.org/10.1212/01.wnl.0000257818.16952.62.

Chalah, M.A., Ayache, S.S., 2018. Is there a link between inflammation and fatigue in multiple sclerosis? J. Inflamm. Res. 11, 253–264. https://doi.org/10.2147/JIR.S167199.

Chalah, M.A., Riachi, N., Ahdab, R., Mhalla, A., Abdellaoui, M., Créange, A., Lefaucheur, J.-P., Ayache, S.S., 2017. Effects of left DLPFC versus right PPC tDCS on multiple sclerosis fatigue. J. Neurol. Sci. 372, 131–137. https://doi.org/10.1016/j.jns.2016.11.015.

Charvet, L.E., Dobbs, B., Shaw, M.T., Bikson, M., Datta, A., Krupp, L.B., 2017. Remotely supervised transcranial direct current stimulation for the treatment of fatigue in multiple sclerosis: Results from a randomized, sham-controlled trial. Mult. Scler. 24, 1760–1769. https://doi.org/10.1177/1352458517732842.

Chung, S.W., Hoy, K.E., Fitzgerald, P.B., 2015. Theta-burst stimulation: a new form of tms treatment for depression?: Theoretical review: theta-burst stimulation. Depress. Anxiety. 32, 182–192. https://doi.org/10.1002/da.22335.

Fiene, M., Rufener, K.S., Kuehne, M., Matzke, M., Heinze, H.-J., Zaehle, T., 2018. Electrophysiological and behavioral effects of frontal transcranial direct current stimulation on cognitive fatigue in multiple sclerosis. J. Neurol. 265, 607–617. https://doi.org/10.1007/s00415-018-8754-6.

Finke, C., Schlichting, J., Papazoglou, S., Scheel, M., Freing, A., Soemmer, C., Pech, L., Pajkert, A., Pfüller, C., Wuerfel, J., Ploner, C., Paul, F., Brandt, A., 2015. Altered basal ganglia functional connectivity in multiple sclerosis patients with fatigue. Mult. Scler. 21, 925–934. https://doi.org/10.1177/1352458514555784.

Flachenecker, P., Kümpfel, T., Kallmann, B., Gottschalk, M., Grauer, O., Rieckmann, P., Trenkwalder, C., Toyka, K.V., 2002. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. Mult. Scler. 8, 523–526. https://doi.org/10.1191/1352458502ms839oa.

Gaede, G., Tiede, M., Lorenz, I., Brandt, A.U., Pfueller, C., Dörr, J., Bellmann-Strobl, J., Piper, S.K., Roth, Y., Zangen, A., Schippling, S., Paul, F., 2018. Safety and preliminary efficacy of deep transcranial magnetic stimulation in MS-related fatigue. Neurol. Neuroimmunol. Neuroinflamm. 5, e423. https://doi.org/10.1212/NXI.0000000000000423.

Gobbi, C., Rocca, M.A., Pagani, E., Riccitelli, G.C., Pravatà, E., Radaelli, M., Martinelli-Boneschi, F., Falini, A., Copetti, M., Comi, G., Filippi, M., 2014. Forceps minor damage and co-occurrence of depression and fatigue in multiple sclerosis. Mult. Scler. 20, 1633–1640. https://doi.org/10.1177/1352458514530022.

Hanken, K., Bosse, M., Möhrke, K., Eling, P., Kastrup, A., Antal, A., Hildebrandt, H., 2016. Counteracting fatigue in multiple sclerosis with right parietal anodal transcranial direct current stimulation. Front. Neurol. 7, 154. https://doi.org/10.3389/fneur.2016.00154.

Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. In: Higgins, JPT, Green, S (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration 2011. Available from. www.handbook.cochrane.org.

Iodice, R., Manganelli, F., Dubbioso, R., 2017. The therapeutic use of non-invasive brain stimulation in multiple sclerosis – a review. Restor. Neurol. Neurosci. 35, 497–509. https://doi.org/10.3233/RNN-170735.

Kesselring, J., Beer, S., 2005. Symptomatic therapy and neurorehabilitation in multiple sclerosis. Lancet Neurol. 4, 643–652. https://doi.org/10.1016/S1474-4422(05)70193-9.

Lefaucheur, J.-P., Antal, A., Ayache, S.S., Benninger, D.H., Brunelin, J., Cogiamanian, F., Cotelli, M., De Ridder, D., Ferrucci, R., Langguth, B., Marangolo, P., Mylius, V., Nitsche, M.A., Padberg, F., Palm, U., Poulet, E., Priori, A., Rossi, S., Schecklmann, M., Vanneste, S., Ziemann, U., Garcia-Larrea, L., Paulus, W., 2017. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin. Neurophysiol. 128, 56–92. https://doi.org/10.1016/j.clinph.2016.10.087.

Ma, J., Chen, H., Liu, X., Zhang, L., Qiao, D., 2018. Exercise-induced fatigue impairs bidirectional corticostriatal synaptic plasticity. Front. Cell. Neurosci. 12. https://doi.org/10.3389/fncel.2018.00014.

Milinis, K., Tennant, A., Young, C.A., TONiC study group, 2016. Spasticity in multiple sclerosis: Associations with impairments and overall quality of life. Mult. Scler. Relat. Disord. 5, 34–39. https://doi.org/10.1016/j.msard.2015.10.007.

Miller, P., Soundy, A., 2017. The pharmacological and non-pharmacological interventions for the management of fatigue related multiple sclerosis. J. Neurol. Sci. 381, 41–54. https://doi.org/10.1016/j.jns.2017.08.012.

Mori, F., Codecà, C., Kusayanagi, H., Monteleone, F., Boffa, L., Rimano, A., Bernardi, G.,

Koch, G., Centonze, D., 2010. Effects of intermittent theta burst stimulation on spasticity in patients with multiple sclerosis: iTBS for spasticity in MS. Eur. J. Neurol. 17, 295–300. https://doi.org/10.1111/j.1468-1331.2009.02806.x.
O'Connell, N.E., Marston, L., Spencer, S., DeSouza, L.H., Wand, B.M., 2018. Non-invasive brain stimulation techniques for chronic pain. Cochrane Database Syst. Rev. https://doi.org/10.1002/14651858.CD008208.pub5.
Palm, U., Ayache, S.S., Padberg, F., Lefaucheur, J.-P., 2014. Non-invasive brain stimulation therapy in multiple sclerosis: a review of tDCS, rTMS and ECT results. Brain Stimul. 7, 849–854. https://doi.org/10.1016/j.brs.2014.09.014.
Palm, U., Chalah, M.A., Padberg, F., Al-Ani, T., Abdellaoui, M., Sorel, M., Dimitri, D., Créange, A., Lefaucheur, J.-P., Ayache, S.S., 2016. Effects of transcranial random noise stimulation (tRNS) on affect, pain and attention in multiple sclerosis. Restor. Neurol. Neurosci. 34, 189–199. https://doi.org/10.3233/RNN-150557.
Patejdl, R., Zettl, U.K., 2017. Spasticity in multiple sclerosis: contribution of inflammation, autoimmune mediated neuronal damage and therapeutic interventions. Autoimmun. Rev. 16, 925–936. https://doi.org/10.1016/j.autrev.2017.07.004.
Roberta, F., Maurizio, V., Filippo, C., Tommaso, B., Matteo, C., Emanuele, T., Milena, D.R., Elio, S., Alberto, P., 2014. Transcranial direct current stimulation (tDCS) for fatigue in multiple sclerosis. Neuro. Rehabil. 34, 121–127. https://doi.org/10.3233/NRE-131019.
Salazar, A.P.S., Vaz, P.G., Marchese, R.R., Stein, C., Pinto, C., Pagnussat, A.S., 2018. Noninvasive brain stimulation improves hemispatial neglect after stroke: a systematic review and meta-analysis. Arch. Phys. Med. Rehabil. 99, 355–366.e1. https://doi.org/10.1016/j.apmr.2017.07.009.
Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., PRISMA-P Group, 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 350, g7647. https://doi.org/10.1136/bmj.g7647.
Shangyan, H., Kuiqing, L., Yumin, X., Jie, C., Weixiong, L., 2018. Meta-analysis of the efficacy of modafinil versus placebo in the treatment of multiple sclerosis fatigue. Mult. Scler. Relat. Dis. 19, 85–89. https://doi.org/10.1016/j.msard.2017.10.011.
Stampanoni Bassi, M., Gilio, L., Buttari, F., Maffei, P., Marfia, G.A., Restivo, D.A., Centonze, D., Iezzi, E., 2017. Remodeling functional connectivity in multiple sclerosis: a challenging therapeutic approach. Front. Neurosci. 11, 710. https://doi.org/10.3389/fnins.2017.00710.
Tavakoli, A.V., Yun, K., 2017. Transcranial alternating current stimulation (tACS) mechanisms and protocols. Front. Cell. Neurosci. 11, 214. https://doi.org/10.3389/fncel.2017.00214.
Tecchio, F., Cancelli, A., Cottone, C., Ferrucci, R., Vergari, M., Zito, G., Pasqualetti, P., Filippi, M.M., Ghazaryan, A., Lupoi, D., Smits, F.M., Giordani, A., Migliore, S., Porcaro, C., Salustri, C., Rossini, P.M., Priori, A., 2015. Brain plasticity effects of neuromodulation against multiple sclerosis fatigue. Front. Neurol. 6, 141. https://doi.org/10.3389/fneur.2015.00141.
Tecchio, F., Cancelli, A., Cottone, C., Zito, G., Pasqualetti, P., Ghazaryan, A., Rossini, P.M., Filippi, M.M., 2014. Multiple sclerosis fatigue relief by bilateral somatosensory cortex neuromodulation. J. Neurol. 261, 1552–1558. https://doi.org/10.1007/s00415-014-7377-9.
Tur, C., 2016. Fatigue management in multiple sclerosis. Curr. Treat. Options Neurol. 18. https://doi.org/10.1007/s11940-016-0411-8.
Yang, T.-T., Wang, L., Deng, X.-Y., Yu, G., 2017. Pharmacological treatments for fatigue in patients with multiple sclerosis: a systematic review and meta-analysis. J. Neurol. Sci. 380, 256–261. https://doi.org/10.1016/j.jns.2017.07.042.
Yusuf, A., Koski, L., 2013. A qualitative review of the neurophysiological underpinnings of fatigue in multiple sclerosis. J. Neurol. Sci. 330, 4–9. https://doi.org/10.1016/j.jns.2013.04.012.