Multiple Sclerosis and Related Disorders 94 (2025) 106276

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Fatigue relief in multiple sclerosis by personalized neuromodulation: A multicenter pilot study [FaremusGE]

Franca Tecchio [a,*], Massimo Bertoli [1,a,b], Elvira Sbragia [1,c,d], Silvia Stara [c], Patrizio Pasqualetti [e], Teresa L'Abbate [a,f], Pierpaolo Croce [b], Arianna Pizzichino [g], Andrea Cancelli [a], Karolina Armonaite [f], Federico Cecconi [a], Luca Paulon [a,h], Matilde Inglese [c,i]

[a] Laboratory of Electrophysiology for Translational neuroScience (LET'S), Istituto di Scienze e Tecnologie della Cognizione (ISTC), Consiglio Nazionale delle Ricerche (CNR), Rome, Italy
[b] Department of Neuroscience, Imaging and Clinical Sciences, University 'G. D'Annunzio' of Chieti-Pescara, Chieti, Italy
[c] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, and Center of Excellence for Biomedical Research, University of Genoa, Genoa, Italy
[d] Department of Neurology, Galliera Hospital, Genoa, Italy
[e] Department of Public Health and Infectious Diseases, Section of Medical Statistics, Sapienza Università di Roma, Rome, Italy
[f] Uninettuno University, Rome, Italy
[g] Ospedale Isola Tiberina - Gemelli Isola, Rome, Italy
[h] Independent Researcher, Rome, Italy
[i] Ospedale Policlinico San Martino – IRCCS, Genoa, Italy

ARTICLE INFO

Keywords:
Non-invasive brain stimulation (NIBS)
Fatigue
Transcranial electric stimulation (tES)
Neuromodulation
Personalization
Depression

ABSTRACT

Background: A recent application of the GRADE guidelines indicated Faremus, a 5-day neuromodulation for 15 min per day via transcranial direct current stimulation (tDCS), as medium to highly recommendable for alleviating fatigue in multiple sclerosis (MS).
Methods: With this pilot study we aimed to evaluate the feasibility, acceptance, safety, and effectiveness of the Faremus treatment carried out in a multicenter context. The Rome unit prepared the intervention, supplied the personalized electrodes to the San Martino Hospital in Genova, where the neurological team enrolled the population of fatigued people with multiple sclerosis (PwMS) and carried out the treatment.
Results: All 17 enrolled patients completed treatment, reporting optimal acceptance and safety when using Faremus in the multicenter setting. The team involved, including neurologists, neurophysiopathology technicians, engineers, physicists, and psychologists expressed high appreciation (average score 8 out of 10). The treatment improved fatigue symptoms by an average of 27%, to levels comparable with previous studies. Similarly, mild depressive symptoms improved by an average of 38%.
Conclusions: The Faremus personalized electroceutical intervention, a 5-day anodal tDCS over bilateral whole-body somatosensory cortex with occipital cathode, is well accepted and can be applied feasibly, safely and effectively in a multicenter setting, offering a reliable tool to relieve fatigue-related symptoms, thus supporting the quality of life of fatigued people with MS. The present study lays a starting point for the involvement of multiple MS units nationwide in offering therapeutic enrichment for their fatigued patients.

1. Introduction

1.1. Fatigue in multiple sclerosis

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease affecting the central nervous system. According to the latest estimates by the Multiple Sclerosis International Federation, the global prevalence of people with MS (pwMS) is around 2.8 million (Walton et al., 2020), with a significant increase compared to 2008 (2.1 million) and 2013 (2.3 million) surveys. MS has an age of onset between

* Corresponding author at: LET'S – ISTC – CNR, via Romagnosi 18A, 00196 Rome, Italy.
E-mail address: franca.tecchio@cnr.it (F. Tecchio).
[1] These Authors contributed equally.

https://doi.org/10.1016/j.msard.2025.106276
Received 27 February 2024; Received in revised form 30 July 2024; Accepted 13 January 2025
Available online 18 January 2025

20 and 40 years, with a prevalence twice as high in females as in males, and represents one of the primary causes of non-traumatic disability in young adults (Compston and Coles, 2008).

Across clinical subtypes, MS most common clinical presentation consists of neurological deficits occurring as a result of lesions in the brain and/or spinal cord due to the autoreactive activity of immune cells affecting the myelin that surrounds the axons. However, almost 80% of individuals affected by MS complain about the symptom of fatigue (Kesselring and Beer, 2005), defined as '*a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities*' (MSCfCP Guidelines, 1998). Independently of their level of disability and disease progression, fatigue represents one of the most disabling symptoms that impacts on daily activities of more than half of the pwMS (Ayache and Chalah, 2017; Bakshi, 2003; Giovannoni, 2006; Kesselring and Beer, 2005; Khan et al., 2014). We commonly mark MS-associated fatigue as primary fatigue, probably raising from a central pathological mechanism. In fact, its nature is deemed multifactorial and depends on the interaction between the nervous, immune and endocrine systems (Braley and Chervin, 2010; Carver et al., 2024; Heesen et al., 2006; Kos et al., 2008; Téllez et al., 2006; Wang and Kasper, 2014).

1.2. Personalized neuromodulation to relieve MS fatigue

A review of studies assessing both structural and functional aspects associated with MS fatigue within the same individuals strongly suggests that MS fatigue follows a functional rather than structural neural alteration (Bertoli and Tecchio, 2020). Crucially, a relevant part of these studies focuses on PwMS exhibiting minimal disability levels and broad fatigue range, pointing at a widespread alteration of neuronal electrical activity within the sensorimotor network as one of the main features of fatigue. Evidence on treatment efficacy in MS fatigue is controversial, concerning non-specific interventions like physical exercise (Latimer-Cheung et al., 2013; Motl and Sandroff, 2015) and pharmacological treatments (Nourbakhsh et al., 2021). Moreover, clinicians often resort to prescribing off-label drugs such as amantadine, modafinil, and amphetamine-like stimulants to mitigate this symptom with the clear limitation that not all PwMS tolerate these drugs equally, suffering from unpleasant side effects. In the absence of an effective treatment for MS fatigue, the emergence of novel strategy interventions capable of directly influencing the neuronal networks' dynamics and their excitability like neuromodulation techniques open to fruitful therapeutic solutions (Akyuz et al., 2023; Ayache et al., 2022a; Ayache and Chalah, 2018; Chalah et al., 2017; Fiene et al., 2018; Hanken et al., 2016; Uygur-Kucukseymen et al., 2023).

Among non-invasive brain stimulation solutions, transcranial Direct Current Stimulation (tDCS) has been promising, showcasing its suitability for its user-friendly characteristics, cost-effectiveness, and minimal side effects and displaying a clear efficacy advantage on repetitive transcranial magnetic interventions (Uygur-Kucukseymen et al., 2023).

Our therapeutic tDCS neuromodulation strategy moves from the observations of a framework of altered brain electrical activity in MS fatigued individuals, where the primary motor cortex (M1) exhibits a hyperexcitable profile (Yusuf and Koski, 2013) opposite to a depletion of the primary somatosensory cortex (S1) activity (Tecchio et al., 2008) coupled with alterations in functional connectivity between temporo-parietal hemispheric homologs (Bertoli and Tecchio, 2020; Buyukturkoglu et al., 2017; Cogliati Dezza et al., 2015), and an overall functional reduction in connectivity between S1 and M1 (Dell'Acqua et al., 2010; Padalino et al., 2021; Tecchio et al., 2008; Tomasevic et al., 2013; Vecchio et al., 2017). Accordingly, the neuromodulation protocol called Fatigue Relief in Multiple Sclerosis (Faremus) aims at supporting the parieto-frontal functional connectivity by targeting S1 while carefully avoiding M1. Faremus consists of a 5-days stimulation, 15 min/day and entails an anode electrode shaped on the individual patient's brain circumvolutions extracted from his/her brain magnetic resonance image (Regional Personalized Electrode, RePE) (Cancelli et al., 2015; Tecchio et al., 2013), paired with a double area cathode centered on the occipital region (Cancelli et al., 2018b; Tecchio et al., 2022, 2014). The clinical efficacy of Faremus in specifically alleviating fatigue has been consistently confirmed over time in several independent randomized controlled trials (RCTs) with an overall effect size (ES) well above the large effect threshold (Cancelli et al., 2018b; Tecchio et al., 2022, 2014). Moreover, a recent quantitative review and meta-analysis (Gianni et al., 2021) applied the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) classification criteria (Schünemann et al., 2013) to review RCTs using tDCS to alleviate symptoms stemming primarily from neuronal electrical activity imbalances. Combining a meta-analysis with substantial evidence of negligible side effects and a user-friendly, cost-effective procedure, this review advanced a recommendation level of Faremus ranging between moderate and high, paving the way for a dialogue with relevant regulatory agencies for the inclusion of tDCS treatments such as Faremus in the management of fatigue symptom. To further extend its promising effectiveness against fatigue, Faremus treatment was also evaluated in a home setting, following international guidelines for the implementation of remotely controlled and supervised neurostimulation protocols (Tecchio et al., 2022). Administered through an ad-hoc adaptable helmet frame for precise repositioning using a standardized procedure (Cancelli et al., 2018b), home-based Faremus was well-received by PwMS. This positive response was attributed not only to its safety and usability features but also to its robust efficacy, evidenced by an effect size comparable to that obtained in clinical settings.

1.3. Multicenter Faremus setup

The aim of this pilot study is to provide evidence in support of the feasibility of Faremus treatment within a multicenter collaboration in the national Italian territory. The collaboration involves remote personalization of the RePE electrode based on a 3D-MRI procedure for shaping and positioning, and delivery of the treatment at the MS unit in the hospital where the patients are referred to. As an important part of the protocol, especially for future developments, we will take into account the safety of the procedures, acceptance by all stakeholders (PwMS, neurologists, neurophysiopathology technicians, engineers), and intervention efficacy.

2. Materials and methods

2.1. Participants

We enrolled 17 PwMS according to the diagnostic criteria outlined in (Lublin et al., 2014; McDonald et al., 2001) with relapsing-remitting (RRMS) clinical subtype. All PwMS underwent brain MRI for inclusion/exclusion criteria, also used to tailor the regional personalized electrode RePE. Given the Faremus intervention target on primary somatosensory cortex, the inclusion criterion of experiencing physical fatigue has been applied (modified Fatigue Impact Scale physical items, mFIS_phys 14). Nevertheless, we subsequently updated the inclusion criterion to the total mFIS score, which is a more robust global index able to capture the impact of fatigue. The Multiple Sclerosis Council for Clinical Practice and Guidelines recommends this scale, although there is no consensus on the definition of cut-off scores (Larson, 2013). The mFIS is a shorter version of the Fatigue Impact Scale, with 9 items for the "physical" domain, 10 for the "cognitive" domain, and 2 for the "psychosocial" domain. Each item consists of a statement about how fatigue has impacted the above mentioned domains in the past 4 weeks and the person is asked to rate it on a Likert scale from 1 (never) to 4 (almost always). The total possible score is 84, with higher scores indicating a greater impact on quality of life. The subscale score ranges are 0 −36 for physical, 0 −40 for cognitive, and 0 - 8 for psychosocial domain. Typical cut-off scores on total mFIS range from 30 to 40. exclusion criteria were:

(a) assumption of symptomatic drugs for fatigue (suspended at least 3 months before inclusion in the study) and depression treatment; (b) epilepsy or other central/peripheral nervous system comorbidities; and (c) systemic conditions that may cause fatigue—assessed by clinical examination and history collection: anaemia, pregnancy, infectious diseases, hypo- or hyperthyroidism, cardiovascular disease, pulmonary disease, renal disease, and hepatic disease. Aware of the strong correlation between fatigue and depressive symptoms, we did not exclude PwMS exhibiting depressive symptoms but only those who suffered by severer levels treated by pharmacological treatment for depression. Thus, for completeness of information, we also collected BDI before and after treatment. The inventory consists of 21 items, each rated on a 4-point scale (0–3), which reflect various symptoms of depression. Scores between 10 and 19, 20–30, ≥31 represent the ranges for mild, moderate, and severe depression respectively (Kendall et al., 1987). BDI has been deemed sensitive to changes in depression severity over time in PwMS, making it useful for both diagnostic and monitoring purposes (Minden et al., 2014). For the enrolled PwMS, we assessed disability levels through the Expanded Disability Status Scale (EDSS) and collected a detailed personal and clinical profile (Table 1).

2.2. Study design

The Ethics Committee of Liguria region (CER Liguria) approved the protocol (n. 2919, 20/04/2016). All PwMS signed an informed consent form before their recruitment. The planned study was a randomized double-blind cross-over study with mFIS collection every 4 weeks up to reaching baseline values before directing PwMS to the second block (Cancelli et al., 2018b; Tecchio et al., 2014). According to the main aim of the present pilot study, which is the multicenter Faremus protocol setup and assessment of its feasibility and acceptance, we defined the procedures and implemented all steps proposing it to PwMS enrolled with eligibility criteria consistent with previous studies (Cancelli et al., 2018b; Tecchio et al., 2022, 2014).

Feasibility was assessed by the number of PwMS who dropped out. Safety was considered after adopting the international guidelines with respect to the device, the setup and execution of the tDCS treatment. In agreement with international regulatory indications (Fertonani et al., 2015), we collected from the PwMS possible known side effects, including discomfort during or after the treatment, skin redness or tingling, headache, or nausea. Efficacy was assessed by fatigue levels reduction as scored by mFIS and personal acceptance by a scoring between 0 and 10 the individual feeling of the treatment along the setting up and the 5-days application.

2.3. Experimental procedure

As represented in Fig. 1, after the patient's enrolment, the Rome-CNR Unit received the brain MR images collected at San Martino Hospital in Genoa (1.5T General Electric Signa HDX 15.0 scanner). The Rome-CNR unit shaped the bilateral whole body S1 electrode as a 2-cm-width band fitting the personal cortical folding (RePE), keeping the electrode area to 35 cm2, via the computerized procedure detailed in (Cancelli et al., 2018a) and briefly reported below. The personalized S1 was the anode electrode, while the cathode (7×10 cm^2) was centered on Oz according to the EEG 10–20 system, with the longer side pointing in the left-right direction.

2.4. Shaping of the RePE electrode and information for placing it

We used off-line individual MRI to shape RePE via an ad-hoc computerized procedure, while an ad-hoc developed adjustable helmet frame was used to proper positioning in multisession treatments. As a preliminary step, we manually traced the central sulcus on the standard MNI152_T1_1 mm_brain MR template, selecting 123 points in the middle of the pre- and post-central sulcus walls, one for each of the 123 sagittal slices passing across the template central sulcus. These points span from the Sylvian sulcus of the left hemisphere to the same sulcus of the right hemisphere. The computerized process for shaping the personalized RePE electrode from individual MRI consisted of the following steps. Steps 1–7 were executed in Rome; Steps 8–10 in Genoa. 1. individual scalp and brain tissues segmentation; 2a. normalization to standard MNI152_T1_1 mm_brain template; 2b. storing of individual central sulcus identified points; 3. mapping of the 123 central sulcus points back to the individual space using the inverted spatial normalization matrix; 4. projecting the 123 central sulcus points onto the individual scalp applying the minimal distance brain-scalp tissues for each point; 5. projecting the scalp point to a plane; 6. RePE was designed starting from the plane 123 points by AutoCAD software that gave the 2-cm width and set to 35 cm^2 the area; 7. the shape of RePE was exported to the PDF format, which also included a 10 cm scale. 8. printing the PDF document maintaining the 1:1 dimensions (verifiable via the 10 cm scale) to be cut into conductive silicon electrode. 9 and 10. To easily and quickly position RePE over the scalp of each subject in a way that the electrode would overlap her/his central sulcus (0.5 mm frontally, 1.5 posteriorly), we developed an MRI-based procedure using external landmarks on the subject's scalp. We measured on the scalp surface segmented by the MRI the distances between Nasion and the three points of the electrode: the central point and right and left vertices of the frontal side of the RePE (0.5 frontally to the scalp points obtained at step 4). The three distances were included in the PDF document with the personalized S1 electrode shape.

2.5. RePE electrode positioning and adaptable helmet frame

Upon receiving the PDF document, the technician in Genoa set the circumference of the adaptable helmet frame for the patient and positioned it just above the ears using the nose pads as a reference for the nasion. Thereafter, she/he placed the zero (0) of a flexible meter on the nasion extending the meter along the line connecting nasion and inion. According to the distances indicated in the PDF, once positioned the central point of RePE along this line, she/he adjusted the RePE orientation with respect to the left and right reference points. Holding the electrode in its final position, the operator glued the electrode to two velcro strips and attached them to the helmet. Finally, the operator took out the helmet to put the gel on the electrodes and positioned the adaptable helmet frame as described above. With the PwMS comfortably seated in an armchair, the operator switched on the tDCS stimulator (BrainSTIM, EMS srl, Bologna, Italy) with a constant current of 1.5 mA delivered for 15 min, 5 consecutive days, in the Real condition and 30 s for the Sham condition.

Table 1
MS patient demographic and clinical profile.

	Sex	Age	DisDur	EDSS	mFIS	mFIS_phys	BDI
Mean/*Median*	14F/3M	52.62	16.5	*2*	*37*	21	10.5
SD/[Range]		6.55	10.3	[1–5.5]	[20–80]	6.95	7.40

Clinical profile of the 17 PwMS involved in the study. M=male, F=female; Mean or *Median* in italics and standard deviations (SD) or range in squared parentheses of: DisDur=disease duration (years); Scores of: EDSS=Expanded Disability Status Scale; Fatigue and depression scores at baseline: mFIS = total modified Fatigue Impact scale and physical subscale (mFIS_phys), BDI=Beck Depression Inventory.

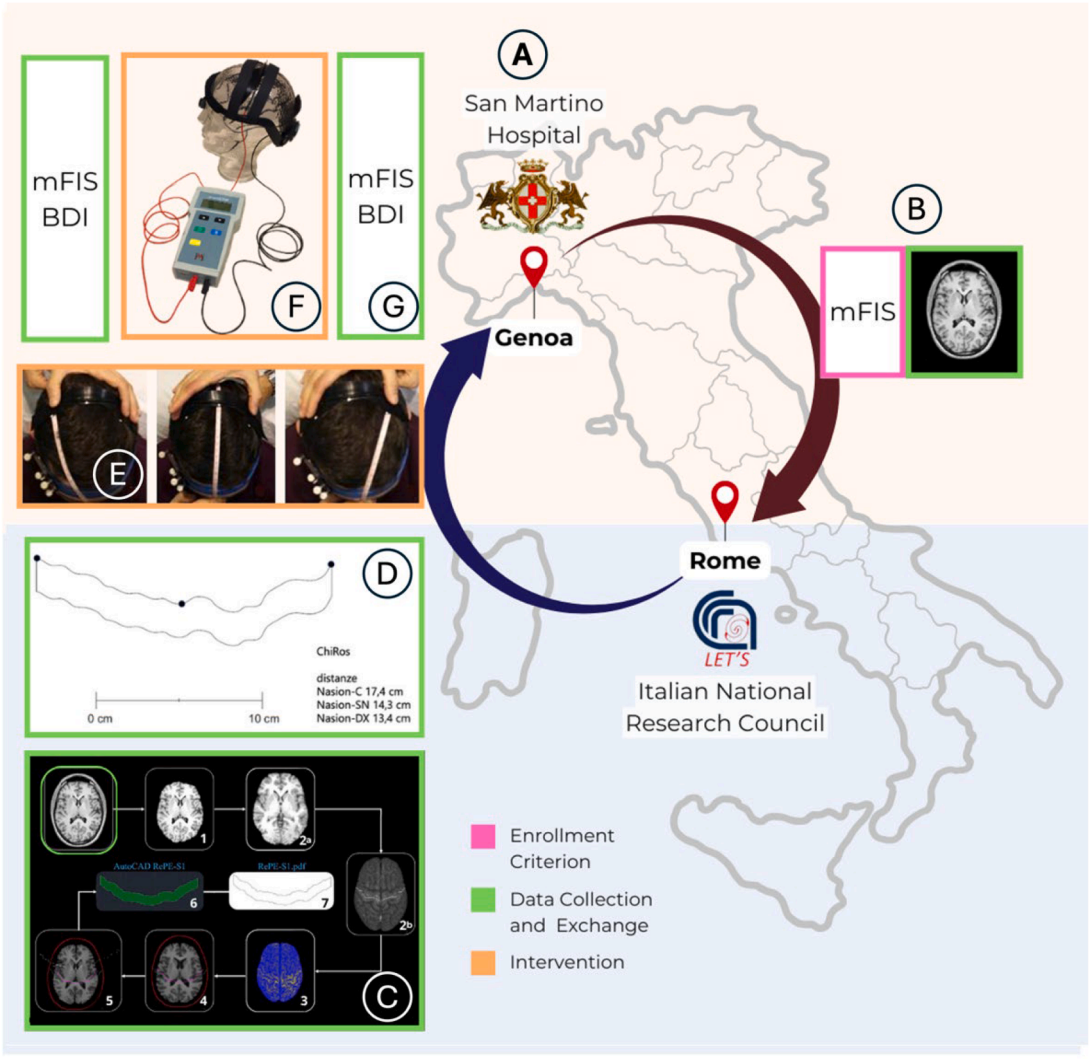

Fig. 1. Visual representation of the multicenter Faremus treatment organization.
Once the team at Genoa IRCCS San Martino Hospital enrolled the fatigued PwMS (A), they sent individual brain magnetic resonance imaging (MRI) scans and the modified Fatigue Impact Scale (mFIS) to the Rome CNR partner (B). The CNR team processed the MRI data by extracting the cortical surface (C.1) and transforming it to the standard Montreal Neurological Institute brain model, where the central sulcus was identified and stored (C.2). They then applied the inverse transformation (C.3) to retrieve the individual central sulcus (C.4), projected it onto the scalp surface (C.5), and mapped it onto a plane to obtain a 35 cm^2 area surface (C.6), with the borders printed in real dimensions (C.7).
The CNR team sent the Genoa IRCCS team an A4 paper containing the RePE electrode shape, a scale for checking dimensions, and three reference points with distances from the Nasion to facilitate accurate positioning of the RePE on the PwMS head (D). The Genoa team called the PwMS, positioned the RePE precisely (E), and secured it using Velcro strips on an adaptable helmet frame for home use over the next 5 days (F). Before and after the 5-day Faremus treatment, mFIS and Beck Depression Inventory (BDI) data were collected and sent back to the Rome team (G).

2.6. Statistical analysis

Assumption of normality of mFIS and BDI scores was assessed by visual inspection of Q-Q plots and Shapiro-Wilk tests. Statistical analyses were conducted with R Statistical language (version 4.3.2; R Core Team, 2023) using parametric tests unless stated otherwise. We evaluated the effects of the treatment on fatigue levels changes between post- and pre-Faremus by using paired-samples *t*-test (or Wilcoxon two-sample paired signed-rank test), and mFIS percentage change, i.e. pre- vs. post-treatment difference normalized to the baseline level, in agreement with the relevance of the identification of responders to tDCS treatments as those changing more than 20% of the pre-treatment value (Ferrucci et al., 2014; López-Alonso et al., 2015; Saiote et al., 2014). A p-value of 0.05 was considered significant for all statistical analyses. We tested the dimension of the efficacy as the effect size (ES) estimated by Cohen's d coefficient (Cohen, 2013) or a variant of the Cohen's *d* for non-parametric tests, i.e. rank-biserial r coefficient (Rosenthal, 1992). For reference, a Cohen's $d = 0.2$ indicates a small ES, 0.5 a medium ES and 0.8 large ES (Sawilowsky, 2009). Rank biserial *r* coefficient can range from −1 to 1 with the sign indicating the direction of the effect. $|r| = 0.1$ indicates a small ES, $|r| = 0.3$ a medium ES and $|r| = 0.5$ a large ES.

3. Results

All recruited PwMS completed the conducted study. None reported the occurrence of side effects. PwMS, neurologist, and technicians graded at 8 ± 2 their satisfaction with Faremus treatment (Fig. 2).

3.1. Faremus effects on fatigue

We noted that among the 12 PwMS who underwent the Real stimulation 5 were responders with a change in fatigue levels greater than or

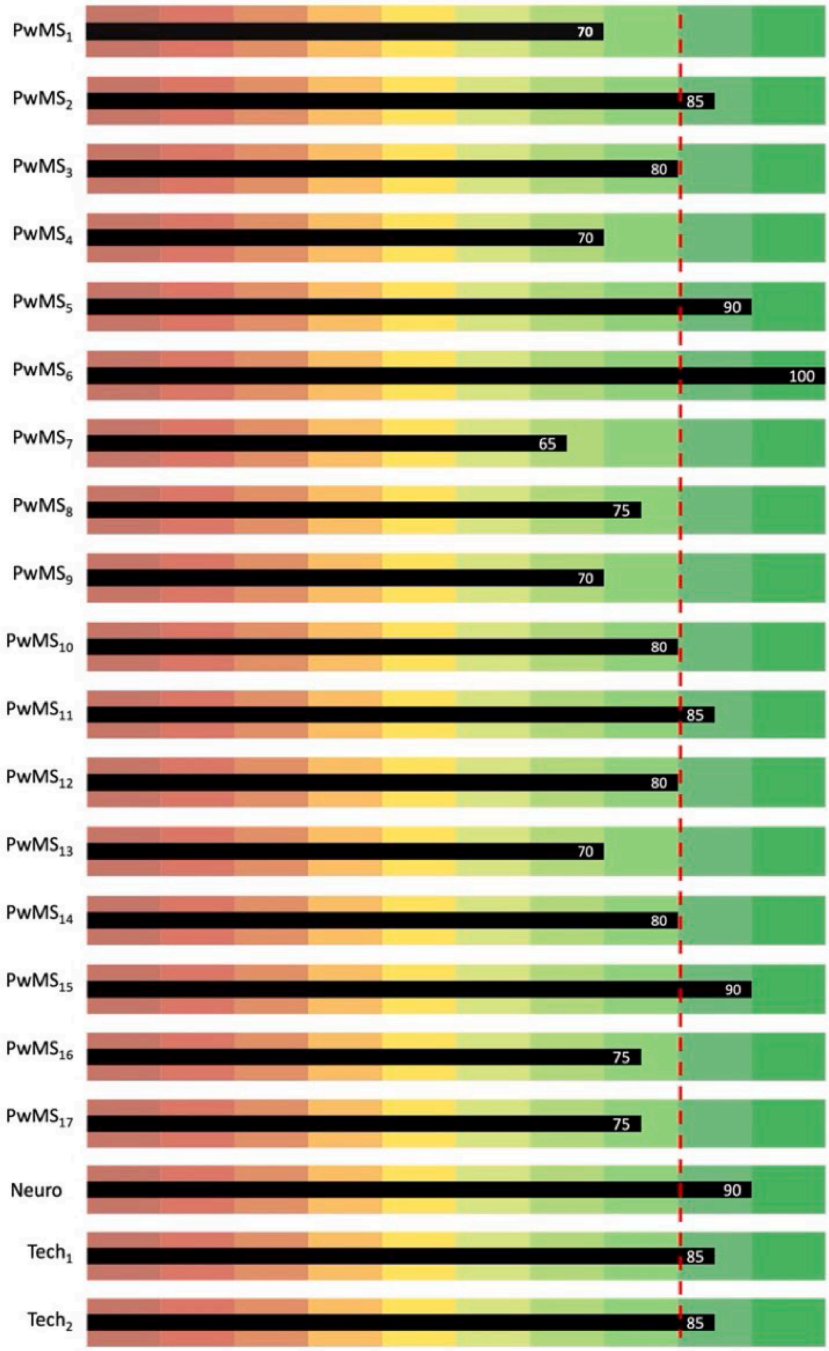

Fig. 2. All stakeholders satisfaction with Faremus treatment.
Level of satisfaction with Faremus treatment from all stakeholders expressed as a percentual rate on a scale from 1 to 10. The dashed red vertical line represents the average satisfaction, around 80%. (PwMS= person with MS; Neuro= Neurologist; Tech=Technician).

equal to 20% of baseline and 3 after Sham (Fig. 3A, top). Given the presence of an outlier who skewed the distribution of mFIS scores, we opted for a Wilcoxon signed rank test with continuity correction to assess the mFIS scores before (μ_{median}=32) and after (μ_{median} =26) Faremus yielded a statistic of V (11) = 59.5, p= .02 for Real stimulation. The same test was conducted for the Sham stimulation group before (μ_{median}=43) and after (μ_{median} =33) Faremus, resulting in V (10) = 48.00, p= .042 (Fig. 3A, bottom). The fatigue symptom reduction after Real stimulation was on average 27% of the pre-treatment level, with a huge range between 3% and 86% for the 11 pwMS who ameliorated. One pwMS worsened fatigue symptoms, with mFIS that scored 30 at T0 and 41 at T1 (Fig. 3A, top). The rank biserial r coefficient used to estimate the ES of Real Faremus treatment was 0.80 and 0.75 for Sham (both large ESs).

3.2. Faremus effects on depressive symptoms

Among the 12 PwMS who underwent the Real stimulation, 9 were responders (3 after Sham) (Fig. 3B, top). Paired-samples t-test comparing the BDI scores at baseline (μ_{mean}=13.08 and after Faremus (μ_{mean}=8.92) yielded a significant t(11) = 3.94, p= .002 for Real stimulation and t(10) = −0.60, p= .56 for Sham (μ_{mean} before =7.73, after=8.82) (Fig. 3B, bottom). The depressive symptoms reduction after Real stimulation was on average 44% of the pre-treatment level, with a

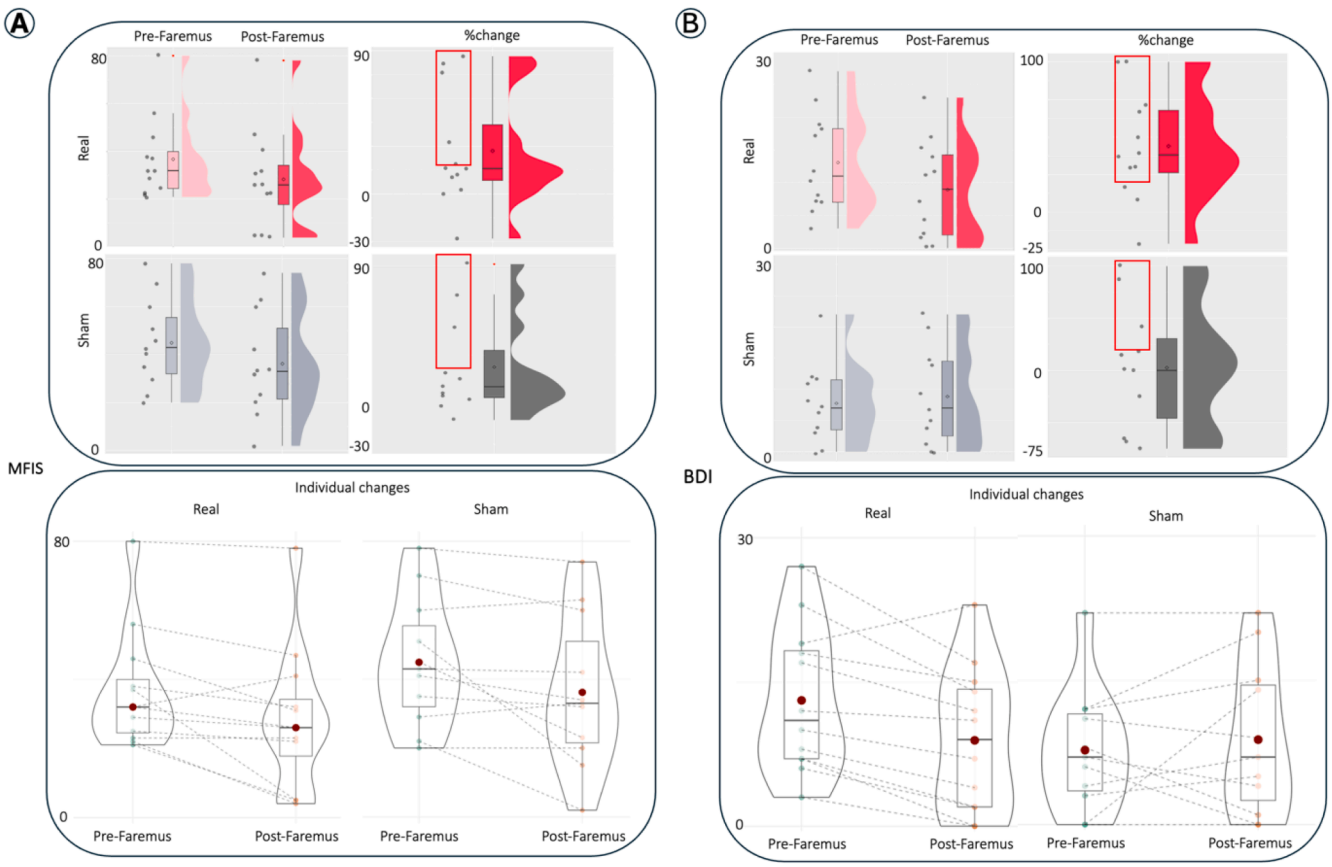

Fig. 3. Faremus-induced changes in fatigue and depressive symptoms.
A Top: individual change in fatigue levels before and after Real (respectively pink and red) and Sham Faremus (light and dark grey); fatigue levels percentage change after Real (dark red) and Sham (dark grey) calculated as the difference between pre- vs. post-treatment normalized to the baseline level. Bottom: Boxplots for individual changes in fatigue levels before and after Real (left) and Sham (right) treatment indicating a significant effect. Fatigue was measured using the modified Fatigue Impact Scale (mFIS).
B Top: individual change in depressive symptoms before and after Real and Sham Faremus; depressive symptoms percentage change after Real and Sham. Bottom: Boxplots for individual changes in depressive symptoms before and after Faremus treatment indicating a significant effect for Real but not Sham. Depressive symptoms were measured using the Beck Depression Inventory (BDI). Color coding as in Fig. 2A.

huge range between 8% and 100% for the 10 PwMS who ameliorated. One PwMS worsened depressive symptoms, with BDI that scored 19 at T0 to 23 at T1 (Fig. 3B, top). The Cohen's *d* coefficient was 1.14 for Real and −0.18 for Sham.

Given the observed Faremus effect on depressive symptoms, Spearman's rank correlation was computed to assess whether a correlation existed between mFIS and BDI scores. We found that the two variables strongly correlated before and after the treatment both for real (at T0: $\rho(9)=0.71$, $p= <0.01$; at T1: $\rho(9)=0.82$, $p\leq.001$) and Sham group (at T0: $\rho(9)=0.77$, $p\leq.01$; at T1: $\rho(9)=0.81$, $p\leq.01$).

4. Discussion

In this study, we tested the feasibility of Faremus applied in a multicenter setting. We found that a 5-days bilateral S1 anodal tDCS through a personalized electrode, shaped on the MRI-derived bilateral S1 cortical strip, is feasible within the cooperation of two centers in the Italian territory (Italian National Research Council – CNR in Rome, and San Martino Hospital in Genoa).

4.1. Feasibility

Considering the feasibility purpose of the present study, all the participants were able to complete the treatment with the assistance of the technician who repositioned every day the adaptable helmet frame embedding the personalized and occipital electrodes that delivered the Faremus treatment at the MS unit of San Martino hospital in Genoa. On the Rome-CNR unit side, no difficulties whatsoever were encountered in receiving the MRI images from the MS unit in Genoa and delivering the personalized anode together with the instructions required for precise repositioning.

4.2. Safety

As regards safety, one of the major strengths of this treatment, all the necessary precautions were adopted both with respect to the device and the setup and execution of the treatment. The technician became familiar with the use of the PDF-transmitted information for the shaping of RePE and its positioning on the patient's head. Concerning the stimulation protocol, the stimulator was designed to monitor the impedance of the electrode (>5 kΩ) before delivering electricity and to detect the disconnection of the electrode or the reaching of output voltage saturation. Overall, none of the participants from this study reported any adverse effects secondary to the safety aspects of tDCS stimulation, in line with the data reported by numerous clinical trials (Buchanan et al., 2021; Kessler et al., 2012; Nikolin et al., 2018; Poreisz et al., 2007) where the adverse events reported were in any case mild and transient. This characteristic aspect of tDCS holds even when employed in home settings (Charvet et al., 2020), whether remotely-supervised (Charvet et al., 2018; Pilloni et al., 2022) or in

asynchronous mode (Tecchio et al., 2022)

4.3. Acceptance

In the context of chronic conditions such as MS, disease management challenges patients to adhere to long-term treatments (Costello et al., 2008), confronting them with a balance of risks and benefits that ultimately threatens treatment adherence. The efficacy of pharmacological therapy is negatively impacted by patients' perceived limitations in terms of efficacy and adverse events (Burkhard et al., 2021), and in the case of MS fatigue especially by the indiscriminate use of drugs not justified by greater efficacy than placebo (Nourbakhsh et al., 2021). Therefore, in offering a targeted treatment of fatigue, it is essential to assess its acceptance by all stakeholders. In the present investigation, we have adopted a broad definition of acceptance, i.e. an a posteriori assessment following the execution of the Faremus treatment. Such a retrospective assessment integrates the concept of acceptability, i.e. an a priori assessment, which in this case positively connotes all neuromodulation techniques like Faremus characterized by ease of use and minimal discomfort (Tecchio et al., 2022). Although it is not possible to isolate specific criteria to define acceptance, we can take into account several meta-criteria emerging from the literature such as usefulness, ease of use, and aesthetics (Bobillier-Chaumon and Dubois, 2009) in the context of individual variability stemming from subjective experience. Our assessment based on direct interaction with PwMS who attended the clinic for five consecutive days made it possible to form a qualitative evaluation of the PwMS acceptance. Considering that fatigue is a major obstacle to patients' daily lives, regardless of the degree of clinical disability, and also considering the absence of a specific treatment for this symptom, motivation to undergo Faremus treatment was high. Moreover, elicited emotions were positive, even in the presence of depressive symptoms. The personalization of the anode electrode and its placement process, distributed between the two units, did not compromise the ease of use of the technology, as demonstrated by the fact that all recruited subjects completed the treatment as expected within 5 consecutive days.

In conclusion, although not yet systematic, the acceptance assessment represents a fruitful valuable insight into PwMS needs and how meeting them is an essential part of the treatment (Lambert et al., 2018).

4.4. Faremus efficacy in multicenter setup

Compared to other studies that similarly aim at fighting the symptom of fatigue with non-invasive electroceutical interventions like tDCS (for a review see Ayache et al., 2022b), Faremus still showed consistent results also in the present multicenter setting. To our knowledge, this is the first study to propose a tDCS intervention specifically for MS fatigue by developing an electrode personalization procedure based only on the individual MRI (which is already available to patients as it is necessary for diagnosis) and can be displaced for the actual location where the treatment is ultimately delivered. Further potential for enhancing treatment efficacy comes from some evidence in favor of increasing responsiveness to the effects of tDCS through the induction of a more receptive state (Li et al., 2019) using mindfulness meditation protocols (Divarco et al., 2023), music sensory stimulation(Husain et al., 2002; Thompson et al., 2001) or combined somatosensory stimulation (Sun et al., 2021).

4.5. Faremus efficacy on fatigue and depressive symptoms

Fatigued PwMS often suffer from the co-occurrence of depression (Tarasiuk et al., 2022a), combining cognitive fatigue, difficulties in concentration, memory deficits, and emotional dysregulation. The incidence of depression in PwMS is estimated to be as high as 50% (Feinstein et al., 2014), primarily manifesting through anhedonia—a common component observed in various psychopathologies, characterized by diminished motivation and an inability to find pleasure. Given this context, we interpreted the results of a preliminary analysis carried out on a subgroup of the present population who underwent Faremus treatment characterized by mild clinical severity and mild depressive symptoms (Tecchio et al., 2020). We observed that after Real stimulation, BDI scores were significantly reduced while Sham had no effect. Standing as a genuine case of serendipity, our observation fitted the results of Jaeger and colleagues (Jaeger et al., 2019) who performed an investigation on functional brain alterations in PwMS with the same characteristics as us and reported that an increase in depressive symptoms was associated with greater alteration of the functional connectivity between the upper ventral striatum and post-central gyrus in the left hemisphere. Coherently, we expected that Faremus intervention and its bilateral symmetric neuromodulation of the entire post-central gyrus, with a midline-centered occipital cathode, would exert its effects by targeting both the intra-hemispheric and inter-hemispheric functional connectivity. Given that symptoms of depression frequently occur alongside MS-related fatigue, even in cases of minimal clinical disability, the recent results suggest that a decline in parietal brain function could significantly influence the intensity of both depression and fatigue symptoms. This impact might be crucial not only in how these symptoms develop but also in how they are treated (Feinstein et al., 2014; Mohr et al., 2003; Stein et al., 2023).

4.6. Considerations for multicenter Faremus execution

PwMS scored the mFIS in the clinic filling out the questionnaire in electronic form and all the data were collected in a dedicated semi-anonymized database. This feature is especially useful for offering the treatment on multiple sites. However, it might be useful to develop an interface shared between clinicians and patients to prompt the completion of the mFIS also remotely (e.g. from mobile) so that fatigue levels can be monitored longitudinally beyond the follow-ups planned in the study and patients who wish to undergo treatment for fatigue symptom management can be easily identified. Similarly, it would be worth implementing acceptance assessment in real life through dedicated digital tools, which have already proven useful for identifying patients' unmet needs in several chronic diseases including MS (Lambert et al., 2018).

Given the strong co-occurrence of fatigue and depression (Tarasiuk et al., 2022b), the majority of systematic studies only consider the presence of minimal depressive symptoms as an inclusion criterion at the beginning of the study. However, this feasibility study suggests that the presence of mild depressive symptoms not treated pharmacologically is an important aspect of the experience of fatigue and should be taken into account among other indices for a dynamic monitoring along all stages of symptom management.

This indication moves in the same direction as we advocate the need to develop easy-to-implement quantitative measures that take into account the main domains of the patient's life and user experience. This is why we also consider enriching the assessment by measuring the quality of life and the overall impact of fatigue on the physical, cognitive, and social dimensions as expressed by the mFIS total score. For this reason, although the inclusion criterion was based on the mFIS_phys subscale exclusively, the efficacy was assessed considering the total mFIS scores.

4.7. Limitations of the current study

4.7.1. Positive effects of Sham stimulation

In line with previous applications of Faremus, we observed a significant improvement in fatigue levels and depression levels in several PwMS. Although participants were unaware of the type of stimulation, per the original experimental design, it is possible that repeated exposure to Sham stimulation for 5 consecutive days induced neuromodulatory effects (Fonteneau et al., 2019). Previously, antidepressant effects not differing between real and Sham stimulation were observed

(Loo et al., 2018). However, in that study the montage targeted different areas (left prefrontal cortex), throughout 20 sessions of 30 min over 4 weeks. However, despite the high interindividual variability, independent RCTs adequately powered show that Faremus real stimulation has consistently induced stronger effects than sham (Cancelli et al., 2018b; Tecchio et al., 2022, 2014). We, therefore, believe that the reduction in both fatigue and mild depression levels also observed following Sham stimulation may be attributable to the holistic nature of Faremus treatment rather than to the stimulation parameters alone.

4.7.2. Prototypical device

One limitation of our study is the reliance on prototype technology, which led to technical difficulties. These issues were primarily due to the developmental stage of the prototype device employed, such as improperly connected wires in the personalized electrode and challenges with applying gel to the electrode once in place.

4.7.3. Unexpected end of study implementation

Despite the lack of allocated funding, the collaboration between the two centers, namely the coordinator Rome-CNR unit and Genoa-MS unit, succeeded in administering treatment to a considerable number of people with MS. This success highlights how the enthusiasm and commitment of PwMS, coupled with a dedicated multidisciplinary team, support the delivery of Faremus intervention. However, due to unforeseen changes in the organizational structure of the Rome-CNR unit, we had to halt the present Faremus project before the intended crossover study could be completed. While the primary aim of this study is not to support the efficacy of Faremus but to provide indications of feasibility and acceptance of a multicenter treatment, the small number of subjects who took part in this study can be considered a limitation. Nevertheless, a cross-disease meta-analysis dedicated to the Sham effect for prospective power analysis of tDCS-based RCTs in several clinical conditions (Gianni et al., 2021), including MS fatigue, suggests that the size of a one-sample study with an expected effect size like the observed ones is 23, not so different from the present one.

4.8. RePE shaping

Our experience in comparing the obtained electrode shapes from the computerized procedure for shaping the personalized S1 electrode with those obtained by the previous neuro-navigated procedure (Cancelli et al., 2018b; Tecchio et al., 2022, 2014) revealed a limitation of the results of the current computerized process. While taking into account the shape of the individual brain using the spatial normalization matrix (step 3 of the computerized procedure), some of the individual variability of the shape of the central sulcus was lost using the standard MNI atlas. The second limitation arose from the AutoCAD modeling of the electrode which introduced sharp edges and tips into the final shape. For this reason, we are searching a new computerized procedure by developing an algorithm that allows the automatic recognition of the shape of the central sulcus from individual brain MRI.

5. Conclusions

The present pilot study paves the way in employing Faremus to relieve MS fatigue even in a multicenter setting.

Role of funding source

No funding was received for this work.

CRediT authorship contribution statement

Franca Tecchio: Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization. **Massimo Bertoli:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **Elvira Sbragia:** Writing – review & editing, Investigation, Data curation. **Silvia Stara:** Writing – review & editing, Investigation, Data curation. **Patrizio Pasqualetti:** Writing – review & editing, Formal analysis. **Teresa L'Abbate:** Writing – review & editing, Writing – original draft. **Pierpaolo Croce:** Writing – review & editing, Software. **Arianna Pizzichino:** Writing – review & editing, Investigation. **Andrea Cancelli:** Writing – review & editing, Software, Data curation. **Karolina Armonaite:** Writing – review & editing, Formal analysis. **Federico Cecconi:** Writing – review & editing, Software, Resources. **Luca Paulon:** Writing – review & editing, Software. **Matilde Inglese:** Writing – review & editing, Validation, Supervision, Resources, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We sincerely thank all MS participants taking part in this study.

References

Akyuz, E., Celik, B.R., Aslan, F.S., Sahin, H., Angelopoulou, E., 2023. Exploring the role of neurotransmitters in Multiple Sclerosis: an expanded review. ACS Chem. Neurosci. 14, 527–553. https://doi.org/10.1021/ACSCHEMNEURO.2C00589.

Ayache, S.S., Chalah, M.A., 2018. The place of transcranial direct current stimulation in the management of multiple sclerosis-related symptoms. Neurodegener. Dis. Manage 8, 411–422. https://doi.org/10.2217/nmt-2018-0028.

Ayache, S.S., Chalah, M.A., 2017. Fatigue in multiple sclerosis - insights into evaluation and management. Neurophysiol. Clin. 47, 139–171. https://doi.org/10.1016/J.NEUCLI.2017.02.004.

Ayache, S.S., Serratrice, N., Abi Lahoud, G.N., Chalah, M.A., 2022a. Fatigue in Multiple Sclerosis: a review of the exploratory and therapeutic potential of non-invasive brain stimulation. Front. Neurol. 13, 754. https://doi.org/10.3389/FNEUR.2022.813965/BIBTEX.

Ayache, S.S., Serratrice, N., Abi Lahoud, G.N., Chalah, M.A., 2022b. Fatigue in Multiple Sclerosis: a review of the exploratory and therapeutic potential of non-invasive brain stimulation. Front. Neurol. 13. https://doi.org/10.3389/FNEUR.2022.813965.

Bakshi, R., 2003. Fatigue associated with multiple sclerosis: diagnosis, impact and management. Mult. Scler. 9, 219–227. https://doi.org/10.1191/1352458503MS904OA.

Bertoli, M., Tecchio, F., 2020. Fatigue in multiple sclerosis: does the functional or structural damage prevail? Multiple Sclerosis Journal. SAGE Publications Ltd. https://doi.org/10.1177/1352458520912175.

Bobillier-Chaumon, M.É., Dubois, M., 2009. Technology acceptance and acceptability in organizations. Trav. Hum. 72, 355–382. https://doi.org/10.3917/TH.724.0355.

Braley, T.J., Chervin, R.D., 2010. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. Sleep 33, 1061–1067. https://doi.org/10.1093/SLEEP/33.8.1061.

Buchanan, D.M., Bogdanowicz, T., Khanna, N., Lockman-Dufour, G., Robaey, P., D'Angiulli, A., 2021. Systematic review on the safety and tolerability of transcranial direct current stimulation in children and adolescents. Brain Sci. 11, 1–21. https://doi.org/10.3390/BRAINSCI11020212.

Burkhard, A., Toliver, J., Rascati, K., 2021. Association between multiple sclerosis disease severity and adherence to disease-modifying therapies. J. Manage Care Spec. Pharm. 27, 915–923. https://doi.org/10.18553/JMCP.2021.27.7.915.

Buyukturkoglu, K., Porcaro, C., Cottone, C., Cancelli, A., Inglese, M., Tecchio, F., 2017. Simple index of functional connectivity at rest in Multiple Sclerosis fatigue. Clin. Neurophysiol. 128, 807–813. https://doi.org/10.1016/j.clinph.2017.02.010.

Cancelli, A., Cottone, C., Di Giorgio, M., Carducci, F., Tecchio, F., 2015. Personalizing the electrode to neuromodulate an extended cortical region. Brain Stimul. 8, 555–560. https://doi.org/10.1016/j.brs.2015.01.398.

Cancelli, A., Cottone, C., Giordani, A., Asta, G., Lupoi, D., Pizzella, V., Tecchio, F., 2018a. MRI-guided regional personalized electrical stimulation in multisession and home treatments. Front. Neurosci. 12. https://doi.org/10.3389/fnins.2018.00284.

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

Carver, J.J., Lau, K.M., Puckett, A.E., Didonna, A., 2024. Autoimmune demyelination alters hypothalamic transcriptome and endocrine function. J. Neuroinflammation 21. https://doi.org/10.1186/s12974-023-03006-2.

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., 2018. Remotely supervised transcranial direct current stimulation for the treatment of fatigue in multiple sclerosis: results from a randomized, sham-controlled trial. Mult. Scler. J. 24, 1760–1769. https://doi.org/10.1177/1352458517732842.

Charvet, L.E., Shaw, M.T., Bikson, M., Woods, A.J., Knotkova, H., 2020. Supervised transcranial direct current stimulation (tDCS) at home: a guide for clinical research and practice. Brain Stimul. 13, 686–693. https://doi.org/10.1016/j.brs.2020.02.011.

Cogliati Dezza, I., Zito, G., Tomasevic, L., Filippi, M.M., Ghazaryan, A., Porcaro, C., Squitti, R., Ventriglia, M., Lupoi, D., Tecchio, F., 2015. Functional and structural balances of homologous sensorimotor regions in multiple sclerosis fatigue. J. Neurol. 262, 614–622. https://doi.org/10.1007/s00415-014-7590-6.

Cohen, J., 2013. Statistical power analysis for the behavioral sciences. Stat. Power Anal. Behav. Sci. https://doi.org/10.4324/9780203771587.

Compston, A., Coles, A., 2008. Multiple sclerosis. Lancet 372, 1502–1517. https://doi.org/10.1016/S0140-6736(08)61620-7.

Costello, K., Kennedy, P., Scanzillo, J., 2008. Recognizing nonadherence in patients with multiple sclerosis and maintaining treatment adherence in the long term. Medscape J. Med. 10, 225.

Dell'Acqua, M.L., Landi, D., Zito, G., Zappasodi, F., Lupoi, D., Rossini, P.M., Filippi, M. M., Tecchio, F., 2010. Thalamocortical sensorimotor circuit in multiple sclerosis: an integrated structural and electrophysiological assessment. Hum. Brain Mapp. 31, 1588–1600. https://doi.org/10.1002/hbm.20961.

Divarco, R., Ramasawmy, P., Petzke, F., Antal, A., 2023. Stimulated brains and meditative minds: a systematic review on combining low intensity transcranial electrical stimulation and meditation in humans. Int. J. Clin. Health Psychol. 23. https://doi.org/10.1016/J.IJCHP.2023.100369.

Feinstein, A., Magalhaes, S., Richard, J.-F., Audet, B., Moore, C., 2014. The link between multiple sclerosis and depression. Nat. Rev. Neurol. 10, 507–517. https://doi.org/10.1038/nrneurol.2014.139.

Ferrucci, R., Vergari, M., Cogiamanian, F., Bocci, T., Ciocca, M., Tomasini, E., De Riz, M., Scarpini, E., Priori, A., 2014. Transcranial direct current stimulation (tDCS) for fatigue in multiple sclerosis. NeuroRehabilitation 34, 121–127. https://doi.org/10.3233/NRE-131019.

Fertonani, A., Ferrari, C., Miniussi, C., 2015. What do you feel if I apply transcranial electric stimulation? Safety, sensations and secondary induced effects. Clin. Neurophysiol. 126, 2181–2188. https://doi.org/10.1016/J.CLINPH.2015.03.015.

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.

Fonteneau, C., Mondino, M., Arns, M., Baeken, C., Bikson, M., Brunoni, A.R., Burke, M.J., Neuvonen, T., Padberg, F., Pascual-Leone, A., Poulet, E., Ruffini, G., Santarnecchi, E., Sauvaget, A., Schellhorn, K., Suaud-Chagny, M.F., Palm, U., Brunelin, J., 2019. Sham tDCS: a hidden source of variability? Reflections for further blinded, controlled trials. Brain Stimul. 12, 668–673. https://doi.org/10.1016/J.BRS.2018.12.977.

Gianni, E., Bertoli, M., Simonelli, I., Paulon, L., Tecchio, F., Pasqualetti, P., 2021. tDCS randomized controlled trials in no-structural diseases: a quantitative review. Sci. Rep. 11, 16311. https://doi.org/10.1038/s41598-021-95084-6.

Giovannoni, G., 2006. Multiple sclerosis related fatigue. J. Neurol. Neurosurg. Psychiatry 77, 2–3. https://doi.org/10.1136/jnnp.2005.074948.

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.

Heesen, C., Nawrath, L., Reich, C., Bauer, N., Schulz, K.H., Gold, S.M., 2006. Fatigue in multiple sclerosis: an example of cytokine mediated sickness behaviour? J. Neurol. Neurosurg. Psychiatry 77, 34–39. https://doi.org/10.1136/JNNP.2005.065805.

Husain, G., Thompson, W.F., Schellenberg, E.G., 2002. Effects of musical tempo and mode on arousal, mood, and spatial abilities. Music. Percept. 20, 151–171. https://doi.org/10.1525/MP.2002.20.2.151.

Jaeger, S., Paul, F., Scheel, M., Brandt, A., Heine, J., Pach, D., Witt, C.M., Bellmann-Strobl, J., Finke, C., 2019. Multiple sclerosis-related fatigue: altered resting-state functional connectivity of the ventral striatum and dorsolateral prefrontal cortex. Mult. Scler. 25, 554–564. https://doi.org/10.1177/1352458518758911.

Kendall, P.C., Hollon, S.D., Beck, A.T., Hammen, C.L., Ingram, R.E., 1987. Issues and recommendations regarding use of the Beck Depression Inventory. Cognit. Ther. Res. 11, 289–299. https://doi.org/10.1007/BF01186280.

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

Kessler, S.K., Turkeltaub, P.E., Benson, J.G., Hamilton, R.H., 2012. Differences in the experience of active and sham transcranial direct current stimulation. Brain Stimul. 5, 155–162. https://doi.org/10.1016/j.brs.2011.02.007.

Khan, F., Amatya, B., Galea, M., 2014. Management of fatigue in persons with multiple sclerosis. Front. Neurol. 5, 110403. https://doi.org/10.3389/FNEUR.2014.00177/BIBTEX.

Kos, D., Kerckhofs, E., Nagels, G., D'hooghe, M.B., Ilsbroukx, S., 2008. Origin of fatigue in multiple sclerosis: review of the literature. Neurorehabil. Neural Repair. 22, 91–100. https://doi.org/10.1177/1545968306298934.

Lambert, J., Chekroun, M., Gilet, H., Acquadro, C., Arnould, B., 2018. Assessing patients' acceptance of their medication to reveal unmet needs: results from a large multi-diseases study using a patient online community. Health Qual. Life Outcomes 16, 1–9. https://doi.org/10.1186/S12955-018-0962-3/TABLES/3.

Larson, R.D., 2013. Psychometric properties of the modified fatigue impact scale. Int. J. MS. Care 15, 15. https://doi.org/10.7224/1537-2073.2012-019.

Latimer-Cheung, A.E., Pilutti, L.A., Hicks, A.L., Martin Ginis, K.A., Fenuta, A.M., MacKibbon, K.A., Motl, R.W., 2013. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. Arch. Phys. Med. Rehabil. 94, 1800–1828. https://doi.org/10.1016/j.apmr.2013.04.020 e3.

Li, L.M., Violante, I.R., Leech, R., Ross, E., Hampshire, A., Opitz, A., Rothwell, J.C., Carmichael, D.W., Sharp, D.J., 2019. Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. Hum. Brain Mapp. 40, 904–915. https://doi.org/10.1002/HBM.24420.

Loo, C.K., Husain, M.M., McDonald, W.M., Aaronson, S., O'Reardon, J.P., Alonzo, A., Weickert, C.S., Martin, D.M., McClintock, S.M., Mohan, A., Lisanby, S.H., Krystal, A. D., Peterchev, A.V., Davis, W., Sklar, J., Colagiuri, B., Galvez, V., 2018. International randomized-controlled trial of transcranial Direct Current Stimulation in depression. Brain Stimul. 11, 125–133. https://doi.org/10.1016/j.brs.2017.10.011.

López-Alonso, V., Fernández-del-Olmo, M., Costantini, A., Gonzalez-Henriquez, J.J., Cheeran, B., 2015. Intra-individual variability in the response to anodal transcranial direct current stimulation. Clin. Neurophysiol. 126, 2342–2347. https://doi.org/10.1016/j.clinph.2015.03.022.

Lublin, F.D., Reingold, S.C., Cohen, J.A., Cutter, G.R., Sørensen, P.S., Thompson, A.J., Wolinsky, J.S., Balcer, L.J., Banwell, B., Barkhof, F., Bebo, B., Calabresi, P.A., Clanet, M., Comi, G., Fox, R.J., Freedman, M.S., Goodman, A.D., Inglese, M., Kappos, L., Kieseier, B.C., Lincoln, J.A., Lubetzki, C., Miller, A.E., Montalban, X., O'Connor, P.W., Petkau, J., Pozzilli, C., Rudick, R.A., Sormani, M.P., Stüve, O., Waubant, E., Polman, C.H., 2014. Defining the Clinical Course of Multiple sclerosis: The 2013 revisions, Neurology. Lippincott Williams and Wilkins. https://doi.org/10.1212/WNL.0000000000000560.

McDonald, W.I., Compston, A., Edan, G., Goodkin, D., Hartung, H.P., Lublin, F.D., McFarland, H.F., Paty, D.W., Polman, C.H., Reingold, S.C., Sandberg-Wollheim, M., Sibley, W., Thompson, A., van den Noort, S., Weinshenker, B.Y., Wolinsky, J.S., 2001. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann. Neurol. 50, 121–127.

Minden, S.L., Feinstein, A., Kalb, R.C., Miller, D., Mohr, D.C., Patten, S.B., Bever, C., Schiffer, R.B., Gronseth, G.S., Narayanaswami, P., 2014. Evidence-based guideline: assessment and management of psychiatric disorders in individuals with MS: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 82, 174–181. https://doi.org/10.1212/WNL.0000000000000013.

Mohr, D.C., Hart, S.L., Goldberg, A., 2003. Effects of treatment for depression on fatigue in multiple sclerosis. Psychosom. Med. 65, 542–547. https://doi.org/10.1097/01.PSY.0000074757.11682.96.

Motl, R.W., Sandroff, B.M., 2015. Benefits of exercise training in multiple sclerosis. Curr. Neurol. Neurosci. Rep. https://doi.org/10.1007/s11910-015-0585-6.

Guidelines, MSCfCP, 1998. Fatigue and Multiple sclerosis: Evidence-Based Management Strategies for Fatigue in Multiple Sclerosis. Paralyzed Veterans of America, Whashigton, DC.

Nikolin, S., Huggins, C., Martin, D., Alonzo, A., Loo, C.K., 2018. Safety of repeated sessions of transcranial direct current stimulation: a systematic review. Brain Stimul. 11, 278–288. https://doi.org/10.1016/j.brs.2017.10.020.

Nourbakhsh, B., Revirajan, N., Morris, B., Cordano, C., Creasman, J., Manguinao, M., Krysko, K., Rutatangwa, A., Auvray, C., Aljarallah, S., Jin, C., Mowry, E., McCulloch, C., Waubant, E., 2021. Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis: a randomised, placebo-controlled, crossover, double-blind trial. Lancet Neurol. 20, 38–48. https://doi.org/10.1016/S1474-4422(20)30354-9.

Padalino, M., Scardino, C., Zito, G., Cancelli, A., Cottone, C., Bertoli, M., Gianni, E., L'Abbate, T., Trombetta, E., Porcaro, C., Bini, F., Marinozzi, F., Filippi, M.M., Tecchio, F., 2021. Effects on motor control of personalized neuromodulation against multiple sclerosis fatigue. Brain Topogr. https://doi.org/10.1007/s10548-021-00820-w.

Pilloni, G., Vogel-Eyny, A., Lustberg, M., Best, P., Malik, M., Walton-Masters, L., George, A., Mirza, I., Zhovtis, L., Datta, A., Bikson, M., Krupp, L., Charvet, L., 2022. Tolerability and feasibility of at-home remotely supervised transcranial direct current stimulation (RS-tDCS): single-center evidence from 6,779 sessions. Brain Stimul. 15, 707–716. https://doi.org/10.1016/J.BRS.2022.04.014.

Poreisz, C., Boros, K., Antal, A., Paulus, W., 2007. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res. Bull. 72, 208–214. https://doi.org/10.1016/J.BRAINRESBULL.2007.01.004.

Rosenthal, R., 1992. Parametric measures of effect size. In: Cooper, H., Hedges, L.V. (Eds.), The Handbook of Research Synthesis. Russell Sage Foundation, New York, pp. 231–244.

Saiote, C., Goldschmidt, T., Timaus, C., Steenwijk, M.D., Opitz, A., Antal, A., Paulus, W., Nitsche, M.A., 2014. Impact of transcranial direct current stimulation on fatigue in multiple sclerosis. Restor. Neurol. Neurosci. 32, 423–436. https://doi.org/10.3233/RNN-130372.

Sawilowsky, S.S., 2009. Very large and huge effect sizes. J. Mod. Appl. Stat. Methods 8, 597–599. https://doi.org/10.22237/jmasm/1257035100.

Schünemann, H., Brożek, J., Guyatt, G., Oxman, A., 2013. GRADE handbook for grading quality of evidence and strength of recommendations.

Stein, C., O'Keeffe, F., Strahan, O., McGuigan, C., Bramham, J., 2023. Systematic review of cognitive reserve in multiple sclerosis: accounting for physical disability, fatigue, depression, and anxiety. Mult. Scler. Relat. Disord. 79. https://doi.org/10.1016/j.msard.2023.105017.

Sun, J.B., Tian, Q.Q., Yang, X.J., Deng, H., Li, N., Meng, L.X., Zhao, Z.X., Zhu, Y.Q., Xi, Y. Bin, Yang, Q., Qin, W., 2021. Synergistic effects of simultaneous transcranial direct current stimulation (tDCS) and transcutaneous auricular vagus nerve stimulation

(taVNS) on the brain responses. Brain Stimul. 14, 417–419. https://doi.org/10.1016/J.BRS.2021.02.010.

Tarasiuk, J., Kapica-Topczewska, K., Czarnowska, A., Chorąży, M., Kochanowicz, J., Kułakowska, A., 2022a. Co-occurrence of Fatigue and Depression in People With Multiple Sclerosis: a Mini-Review. Front. Neurol. 12, 2546. https://doi.org/10.3389/FNEUR.2021.817256/BIBTEX.

Tarasiuk, J., Kapica-Topczewska, K., Czarnowska, A., Chorąży, M., Kochanowicz, J., Kułakowska, A., 2022b. Co-occurrence of Fatigue and Depression in People With Multiple Sclerosis: a Mini-Review. Front. Neurol. 12, 817256. https://doi.org/10.3389/FNEUR.2021.817256/BIBTEX.

Tecchio, F., Bertoli, M., Gianni, E., L'Abbate, T., Sbragia, E., Stara, S., Inglese, M., 2020. Parietal dysfunctional connectivity in depression in multiple sclerosis. Mult. Scler. J. https://doi.org/10.1177/1352458520964412.

Tecchio, F., Cancelli, A., Cottone, C., Tomasevic, L., Devigus, B., Zito, G., Ercolani, M., Carducci, F., 2013. Regional personalized electrodes to select transcranial current stimulation target. Front. Hum. Neurosci. https://doi.org/10.3389/fnhum.2013.00131.

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.

Tecchio, F., Cancelli, A., Pizzichino, A., L'Abbate, T., Gianni, E., Bertoli, M., Paulon, L., Zannino, S., Giordani, A., Lupoi, D., Pasqualetti, P., Mirabella, M., Filippi, M.M., 2022. Home treatment against fatigue in multiple sclerosis by a personalized, bilateral whole-body somatosensory cortex stimulation. Mult. Scler. Relat. Disord. 63. https://doi.org/10.1016/J.MSARD.2022.103813.

Tecchio, F., Zito, G., Zappasodi, F., Dell'Acqua, M.L., Landi, D., Nardo, D., Lupoi, D., Rossini, P.M., Filippi, M.M., 2008. Intra-cortical connectivity in multiple sclerosis: a neurophysiological approach. Brain 131, 1783–1792. https://doi.org/10.1093/brain/awn087.

Téllez, N.L., Comabella, M., Julià, E., Río, J., Tintoré, M., Brieva, L., Nos, C., Montalban, X., 2006. Fatigue in progressive multiple sclerosis is associated with low levels of dehydroepiandrosterone. Mult. Scler. 12, 487–494. https://doi.org/10.1191/135248505MS1322OA.

Thompson, W.F., Schellenberg, E.G., Husain, G., 2001. Arousal, mood, and the Mozart effect. Psychol. Sci. 12, 248–251. https://doi.org/10.1111/1467-9280.00345.

Tomasevic, L., Zito, G., Pasqualetti, P., Filippi, M.M., Landi, D., Ghazaryan, A., Lupoi, D., Porcaro, C., Bagnato, F., Rossini, P.M., Tecchio, F., 2013. Cortico-muscular coherence as an index of fatigue in multiple sclerosis. Mult. Scler. J. 19, 334–343. https://doi.org/10.1177/1352458512452921.

Uygur-Kucukseymen, E., Pacheco-Barrios, K., Yuksel, B., Gonzalez-Mego, P., Soysal, A., Fregni, F., 2023. Non-invasive brain stimulation on clinical symptoms in multiple sclerosis patients: a systematic review and meta-analysis. Mult. Scler. Relat. Disord. 78. https://doi.org/10.1016/J.MSARD.2023.104927.

Vecchio, F., Miraglia, F., Porcaro, C., Cottone, C., Cancelli, A., Rossini, P.M., Tecchio, F., 2017. Electroencephalography-derived sensory and motor network topology in multiple sclerosis fatigue. Neurorehabil. Neural Repair. 31, 56–64. https://doi.org/10.1177/1545968316656055.

Walton, C., King, R., Rechtman, L., Kaye, W., Leray, E., Marrie, R.A., Robertson, N., La Rocca, N., Uitdehaag, B., van der Mei, I., Wallin, M., Helme, A., Angood Napier, C., Rijke, N., Baneke, P., 2020. Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS, third edition 26, 1816–1821. https://doi.org/10.1177/1352458520970841.

Wang, Y., Kasper, L.H., 2014. The role of microbiome in central nervous system disorders. Brain Behav. Immun. 38, 1–12. https://doi.org/10.1016/j.bbi.2013.12.015.

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.