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Personalized, bilateral whole-body somatosensory cortex stimulation to relieve fatigue in multiple sclerosis

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Abstract

Background: The patients suffering from multiple sclerosis (MS) often consider fatigue the most debilitating symptom they experience, but conventional medicine currently offers poorly efficacious therapies.
Objective: We executed a replication study of an innovative approach for relieving MS fatigue.
Methods: According to the sample size estimate, we recruited 10 fatigued MS patients who received 5-day transcranial direct current stimulation (tDCS) in a randomized, double-blind, Sham-controlled, crossover study, with modified Fatigue Impact Scale (mFIS) score reduction at the end of the treatment as primary outcome. A personalized anodal electrode, shaped on the magnetic resonance imaging (MRI)-derived individual cortical folding, targeted the bilateral whole-body primary somatosensory cortex (S1) with an occipital cathode.
Results: The amelioration of fatigue symptoms after Real stimulation (40% of baseline) was significantly larger than after Sham stimulation (14%, $p = 0.012$). Anodal whole body S1 induced a significant fatigue reduction in mildly disabled MS patients when the fatigue-related symptoms severely hampered their quality of life.
Conclusion: This second result in an independent group of patients supports the idea that neuromodulation interventions that properly select a personalized target might be a suitable non-pharmacological treatment for MS fatigue.

Keywords: Multiple sclerosis, fatigue, quality of life, transcranial direct current stimulation (tDCS), regional personalized electrode (RePE)

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Introduction

A significant percentage of individuals affected by multiple sclerosis (MS) report fatigue as their most disabling symptom.[1] International guidelines indicate physical activity, diet features, and energy effectiveness strategies among the multimodal approaches able to ameliorate fatigue.[2] Nevertheless, none of these approaches applies in a systematic manner.[3–5] In particular, recent reviews[6,7] report studies indicating the variety of exercise and behavior change interventions, the two most common being progressive resistive training and fatigue management programs. They found that exercise studies mostly involve people who are less disabled, while behavior change interventions include a broader population, and the effect size (ES) for exercise and behavior change interventions are similar. Furthermore, drug therapies provide only partial improvements in fatigue treatment and there is none specifically indicated for this symptom.[1,2,8] In fact, currently available medications such as amantadine, acetyl L-carnitine, and amino-pyridines (3-4-diaminopyridine, 4-aminopyridine) showed relatively small efficacy and presented various degrees of non-marginal side-effects.[1,9]

We have previously shown that a personalized anodic transcranial direct current stimulation (tDCS) targeting the whole-body primary somatosensory areas (S1)

bilaterally[10] is effective in reducing fatigue symptoms. The treatment protocol consisted of a 5-day tDCS, delivered for 15 minutes/day, via an anodic electrode derived from individual 3D-rendered brain magnetic resonance images (MRI, regional personalized electrode (RePE)),[11–13] with the cathode on the occipital area. We targeted S1 since the literature on MS fatigue indicates a specific involvement of the sensorimotor networks, with primary motor areas (M1) reported as excessively excitable[14] while S1 and primary[15–17] and post-parietal nodes[18,19] of the somatosensory network are less excitable than normal. In addition, connectivity between S1 and M1 appears to be impaired in fatigued patients when compared to non-fatigued individuals.[20] In particular, S1-M1 communication of fatigued people with MS appears compromised and sensitive to miniscule alterations of neural networking.[20] Specifically, tDCS is able to enhance parietal-frontal functional connectivity.[21]

We adjusted a tDCS intervention that increases endurance to fatigue in healthy subjects[22] in order to counterbalance the alterations of the sensorimotor networks, which, at least in part, produce MS fatigue. Therefore, the "adjustment" we conceived aimed at enhancing S1 excitability, avoiding a direct involvement of M1. To maximize effects on the bilateral whole-body S1 and minimize direct effects on the M1 counterpart, we built personalized electrodes that matched the individual cortical folding along the central sulcus. Our intervention was able to reduce MS fatigue[10] and we called it "Fatigue Relief in Multiple Sclerosis (FaReMuS)."

Here, we aim at strengthening the reliability of the FaReMuS treatment efficacy, replicating our previous study. We carried out the same intervention in a new sample of patients: despite a reduced sample size, it is consistent with the estimate (detailed below and based on the preceding study).

Materials and methods

Participants

We enrolled MS patients according to the diagnostic criteria outlined in the study of Lublin and Reingold[23] and McDonald et al.[24] The inclusion criteria were as follows: a minimal clinical state (Expanded Disability Status Scale (EDSS) ≤ 2) and experiencing fatigue (modified Fatigue Impact Scale (mFIS) > 35). The exclusion criteria were as follows: depression (Beck Depression Inventory (BDI) > 19) or in treatment for depression, clinical relapse or radiological evidence of disease activity for the past 3 months, and other central/peripheral nervous system comorbidities.[17]

Study design

The design of the clinical trial is a randomized, double-blind, Sham-controlled, crossover study testing whether our FaReMuS treatment produces a reduction in MS fatigue, as assessed by the mFIS (primary outcome) after Real application higher than after Sham.[10]

We applied a restricted randomization procedure, so that the two arms were balanced (five patients Sham $\rightarrow$ Real and five Real $\rightarrow$ Sham). Once a patient was recruited, the neurophysiologist or the technician responsible for the tDCS delivery called the Statistical Unit and received the indication of the assigned treatment—on the basis of the randomization list prepared in advance and kept concealed. The patient was kept blind to the delivered treatment. Being the patients themselves the outcome evaluator, the study design is double-blind. The patient was kept blind to the delivered treatment.

The fatigue scale scores were collected before (T0) treatment and at the end of treatment (at least 4 hours after the 5th day tDCS, T1). Primary outcome was mFIS reduction at T1 with respect to T0. mFIS scores and the tDCS treatments were performed in the early afternoon. In addition, we collected mFIS every 4 weeks (T4, T8, … weeks later) to wait a value similar to the baseline before directing patients to the second treatment block.[10] In addition to EDSS and BDI, a detailed clinical history was collected at baseline (Table 1). All patients underwent brain MRI screen for inclusion/exclusion criteria and to tailor the S1 personalized electrode.[13]

The Ethics Committee of the 'S. Giovanni Calibita' Fatebenefratelli Hospital in Rome approved the protocol. All patients signed an informed consent form before their recruitment.

Sample size

We estimated the sample size according to the study design and the data gathered from the study of Tecchio et al.,[10] which had the same goal as this study. We took the variability of test–retest mFIS differences into account, with the scale collected 1-week apart and in baseline conditions (standard deviation $= 4.4\%$), together with the relatively large variability of changes found in Tecchio et al.,[10] where we observed 16.9%

Table 1. MS patient demographic and clinical profile.

Group	Sex		Age	DD	ARR	EDSS	BDI	mFIS
Present study	8F/2M	Mean/median	43.2	6.6	**0**	**0.9**	8.1	46.6
		SD/range	13.1	3.7	[0–2]	[0–3.5]	2.9	15.9
Published group	7F/3M	Mean/median	45.8	7.1	**0**	**1.5**	12.7	41.6
		SD/range	7.6	8.2	[0–2]	[0–3.5]	3.5	6.4

M: male; F: female; mean or **median** in bold and SD: standard deviations or ranges [min–max] across the group of DD: disease duration; ARR: annual relapse rate; scores of EDSS: Expanded Disability Status Scale; BDI: Beck Depression Inventory; mFIS: modified Fatigue Impact Scale.

after Sham and 21.1% after Real. Thus, we assumed a variability in pre–post stimulation changes of 19%. In addition, we observed that the correlation between changes after Sham and after Real was $r = 0.55$, resulting in difference in the variability of changes of 0.18. To recognize a difference of 20% between Real and Sham treatments as significant (at two-tailed alpha level of 0.05), a sample size of 10 cases provides a power of 88%. Thus, we recruited 10 patents.

Experimental procedure

Brain MRIs were collected from a standard scanner operating at 1.5 Tesla (Philips Medical Systems, Best, The Netherlands). SofTaxic Neuronavigation System ver.2.0 (http://www.softaxic.com, E.M.S., Bologna, Italy) was used to elaborate individual brain MRI data to guide the stereotaxic procedure for electrode personalization. We shaped the bilateral whole-body S1 electrode as a 2-cm-width band along the central sulcus trace (setting the electrode area to 35 cm^2).[13] SofTaxic navigation was also used to place the S1 electrode 5 mm anteriorly in line with the central sulcus. The reference electrode (7 × 10 cm^2) was centered on Oz position of the electroencephalographic (EEG) 10-20 system, with the longer side pointing in the left–right direction (Figure 1).

tDCS was delivered through the electrodes wired to an electrical stimulator (BrainSTIM, EMS srl, Bologna, Italy). The customized S1 was the anode. A constant current of 1.5 mA intensity was applied for 15 minutes a day for five consecutive days. Sham condition consisted of 4 s of active stimulation at the beginning and the end of each daily 15-minute stimulation. Every day, at the end of the 15-minute tDCS stimulation, we asked the patient to quantify how much she or he felt the stimulation, in terms of weariness and tingling under the electrode (from 1 to 10). For a 5-day treatment, in a crossover design, we considered the tingling sensation as the most suitable way to assess whether the subject distinguished the Real from the Sham stimulation.

Statistical analysis

To test that we properly executed the crossover design, we calculated the two-tailed paired *t*-test between the baseline mFIS scores of the two blocks (Real and Sham, executed in random order across subjects).

We evaluated the effects of the treatment on fatigue in terms of mFIS percentage change, that is, pre- versus post-treatment difference normalized to the baseline level, in agreement with the relevance of the identification of responders to tDCS treatments.[25,26] After fitting a Gaussian of scores distribution (checked by the Shapiro–Wilk test), we executed an analysis of variance (ANOVA) model on the mFIS percentage change with *Stimulation* (Real, Sham) as a within-subject factor.

To quantify the personal feelings during the stimulations, since the 1–10 score distributions differed from a Gaussian, we examined the difference among the Real and Sham stimulations of weariness and tingling levels by two-group non-parametric Wilcoxon's test of the median across the 5 days for each subject.

To test that the conditions of this replication study did not differ from those of the published investigation,[10] we checked the homogeneity of the two groups at baseline. We executed an ANOVA of the mFIS score before Real and Sham in the two groups, with *Stimulation* (Real, Sham) as a within-subject factor and *FaReMuS group* (published and present group) as a between-subject factor. Furthermore, we checked the overall homogeneity of the two groups in their responses to the treatment with a similar ANOVA design, including also the *FaReMuS* (pre-, post-) within-subject factor, verifying the absence of the

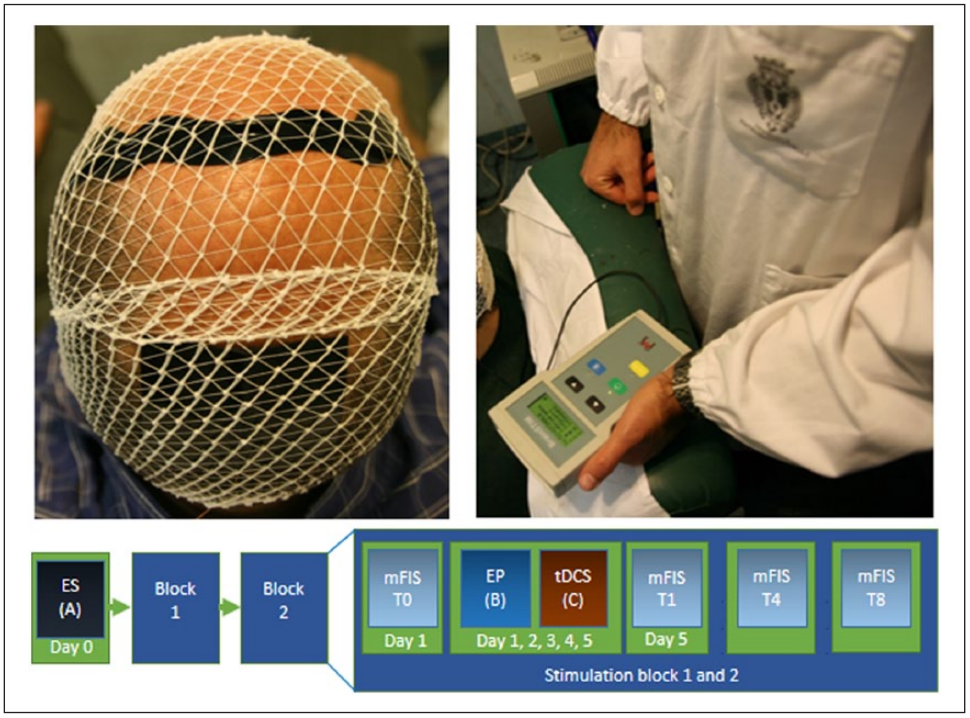

Figure 1. Experimental procedure and study design.
Main steps of the experimental procedure: personalized electrode shaped (ES) and positioned (EP) for each patient. The tDCS stimulation (C) repeated for the 5 days of treatment. The sequence of these operations is sketched in the bottom part of the figure (the two consecutive blocks are equal, but each stimulation is either Real or Sham).

triple interaction factor *FaReMuS*Stimulation* FaReMuS group*.

Finally, we tested the dimension of the Real treatment effects by Cohen's[27] *d* coefficient calculated as the difference between the two pairwise means of mFIS before and after treatment divided by the pooled standard deviations

$$\text{Cohen's } d = \frac{M_1 - M_2}{\sigma_{\text{pooled}}}$$

where

$$\sigma_{\text{pooled}} = \frac{\sqrt{\sigma_1^2 + \sigma_2^2}}{2}$$

A Cohen's $d = 0.2$ indicates a small ES, 0.5 a medium ES and higher than 0.8 large ESs. Sawilowsky[28] further classified as very large effects with corresponding Cohen's *d* above 1.2 and huge above 2.

We note that, in agreement with the 0.2 group ES, we define as Responder a person who changes her or his level more than 20% of the baseline level.

The sample size has not enough power to test the main *Duration* effect and the *Duration*tDCS Treatment* interaction. Nevertheless, since to realize the crossover design, we collected the mFIS every 4 weeks after T0, we presented descriptively the observed values.

Results

The MS patients had relapsing-remitting MS form and presented with mild clinical symptoms and no sign of depression (Table 1). The mFIS did not relate to any clinical measure (mFIS with EDSS, BDI, disease duration, annual relapse rate $p > 0.200$ consistently).

The Shapiro–Wilk test indicated that the mFIS score distributions did not differ from a Gaussian ($p > 0.500$). The second block started 4.4 ± 2.0 months from the first. The two-tailed paired sample *t*-test comparing the mFIS scores at baseline in the two Real and Sham blocks showed $t(9) = -0.819$, $p = 0.435$. The fatigue symptom reductions were 42% after Real (range between 8% and 100%) and 20% after Sham (range between −3% and 77%, ($F(1, 9) = 9.923$, $p = 0.012$)). Considering changes in fatigue level that were greater than or equal to 20% of baseline, we found them in

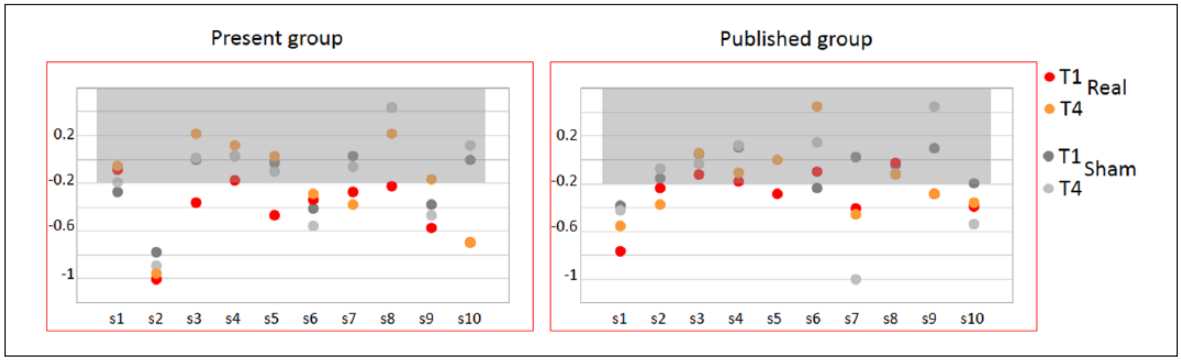

Figure 2. FaReMuS effects on MS fatigue.
In the two independent groups, mFIS percentage changes (post–pre/pre) in single subjects at T1 (main outcome) and at T4. Dark area indicates the changes below "Responders" threshold. In the published group, the mean fatigue reduction at T1 was 28% of the baseline after Real stimulation (range between 2% and 76%) and 8% after Sham (range between −11% and 38%, ($F(1, 8)=9.357$, $p=0.016$)); responders were seven after Real and three after Sham.

nine patients after Real stimulation and in four after Sham (Figure 2).

Wilcoxon's test of the median across the 5 days of the individual perception of daily stimulation indicated that people perceived no differences during the Real and Sham stimulations. In fact, they perceived a median tingling of "1" during both Real and Sham stimulations ($p=0.999$, Table 2). They also did not feel different weariness during Real and Sham stimulations ($p=0.414$, Table 2).

The mFIS baseline values did not differ in the present and the published groups ($F(1, 17)=0.153$, $p=0.701$). Furthermore, the two groups did not differ in response to the treatment as indicated by the lack of a triple interaction *FaReMuS*Stimulation* FaReMuS group* ($F(1, 17)=0.410$, $p=0.531$; Table 3), together with the *FaReMuS*Stimulation* effect ($F(1, 17)=8.202$, $p=0.011$).

We note that the response to the FaReMuS treatment was greater in persons with more severe fatigue at baseline for the Real treatment (Pearson's correlation between mFIS percentage change and mFIS at T0: $r=0.590$, $p=0.017$), while this relationship did not appear in the case of Sham treatment ($r=-0.101$, $p=0.780$).

Cohen's *d* coefficient of the Real treatment resulted 1.1, indicating an ES classified near a very large one (1.2). We note that in the previous published group, Cohen's *d* coefficient – which we did not estimate in the publication – was 1.6 indicating an ES between very large (1.2) and huge (2). Altogether, the 20 people treated by FaReMuS showed a 1.3 Cohen's *d*

Table 2. Personal perception during daily tDCS stimulations.

	Real		Sham	
	Weariness	Tingling	Weariness	Tingling
S1	7	1	7	1
S2	1	1	1	1
S3	1	1	1	1
S4	1	1	2	1
S5	1	1	2	2
S6	3	1	5	1
S7	1	1	1	1
S8	2	2	2	2
S9	1	1	1	1
S10	2	2	5	5
Median	1	1	2	1

In each fatigued people with MS, median weariness and tingling across the 5-day stimulation blocks of Real and Sham FaReMuS treatments.

Table 3. Fatigue levels.

Stimulation	Real		Sham	
Time	Pre	Post	Pre	Post
Mean	52.5	27.6	51.3	46.0
SD	9.8	19.4	12.2	18.6
ES*	1.1		0.6	

mFIS mean and standard deviation of the present group.
ES is the effect size estimated by Cohen's *d* coefficient (see methods). In the other group published in Tecchio et al.,[10] the Real ES was 1.6 and the Sham was 0.4, with the mean across the 20 people of 1.3 for Real and 0.5 for Sham.

coefficient. Considering the mFIS collected at later times with respect to T1 (outcome measure) to ensure that the second block baseline was similar to the first block baseline, we can say that we did not observe residual effect at 4 weeks.

Discussion

The main achievement of this replication study is the demonstration that an innovative, personalized, bilateral, whole-body somatosensory cortex tDCS confirmed in a second and independent group a significant reduction in MS fatigue symptoms as previously reported.

Clinical relevance of personalized neuromodulation

Remarkably, two studies treating MS fatigue by standard-electrode tDCS with the same parameters as this study and the previous one[10] (current intensity, 35 cm^2 electrodes' area, 5-day duration), but selecting different cortical areas, did not find a higher Real than Sham effect.[25,26] In particular, the Italian group led by Ferrucci et al.[25] posed the pad anode on the left and right primary sensorimotor areas devoted to hand control (C3 and C4 scalp positions of the international EEG 10/20 system—$SM1_{hand}$) with the cathode on the shoulder. The German group led by Saiote et al.[26] targeted the left dorsolateral prefrontal cortex (DLPFC) with the cathode placed on the contralateral forehead. The success of FaReMuS treatment against fatigue suggests that its efficacy is due to the selection of the whole-body primary somatosensory area, realized by a RePE.

We have concurrently proven that the personalization of the electrode shape is a specific requirement for modifying the neuronal excitability of this 'crown-shaped' cortical region. In fact, a non-personalized electrode allows for the changing of the excitability of a section of the area, but not the entire whole-body representation.[11] In absence of a medically indicated, efficacious drugs for this debilitating symptom, the proposed personalized neuromodulation intervention, now confirmed to be efficacious in a second independent group of patients, represents a simple, low-cost, and risk-free procedure.[29] We are working to make easy the procedure for shaping and positioning the personalized electrode.

tDCS target selection to relieve MS fatigue

As detailed in the "Introduction" section, we decided to develop the personalized tDCS targeting bilateral whole-body S1 based on indications in the literature of frontal motor regions being too excitable and S1 being poorly excitable in fatigued people with MS. Moreover, tDCS can support parietal-frontal projection[21] altered in this condition.[20] The present further evidence of FaReMuS efficacy in this independent group of patients, together with the lack of overall effect in the other two studies,[25,26] supports the selection of parietal somatosensory area in the treatment. We targeted the whole bilateral[13,30,31] S1 covering the individual cortical folding from left to right mediolateral areas, where face, upper, and lower limbs of both body sides are represented. As the Ferrucci et al.'s[25] group study targeted bilateral hand representation in somatosensory and motor counterparts, we can conceive that selecting only somatosensory, the whole body with respect to the hand section, or both of these elements, grounds the enhanced efficacy of FaReMuS treatment.

An fMRI study on MS indicated that the activation of the left posterior parietal cortex correlated to experienced fatigue[18] and a wider involvement of parietal networking appeared in an EEG-derived functional connectivity study.[17] In the FaReMuS treatment, we used an occipital cathode, which enhances a parietal prevalence of the induced intracerebral currents. We can also hypothesize that FaReMuS might cause the neuromodulation of the posterior parietal cortex. In fact, finite element computational modeling shows that, depending on the real brain anatomy, current densities induced in perielectrode regions—and in-between anode and cathode—can be even stronger than in the region under the electrodes.[32–34] We will further evaluate how to optimize the tDCS montage in relationship to the MS fatigue brain alterations.

Bilateral stimulation

We observed that MS fatigue symptoms increase together with the functional inter-hemispheric imbalance of sensorimotor homologous areas.[35] Furthermore, the alterations of the parietal networking increase with the fatigue level in the dominant hemisphere, but not in the other hemisphere.[17] We will devote research to assessing whether the bilateral application of the same stimulation as in FaReMuS is the proper way to reduce such imbalances.

Huge inter-subject variability of the response to FaReMuS

Despite electrode personalization, we observed an enormous variability of the individual response to the

treatment (between 2% and 100%). Overall, 16 people out of the 20 were responders, with an amelioration of fatigue that was greater than 20% of their baseline level. We are testing the effects that FaReMuS induces in the brain organization, believing that, if the response to the treatment is explained partly by the brain organization changes, we can personalize the treatment better in the future. In fact, we can investigate the individual brain organization before directing the person to FaReMuS and verify whether the main alteration, which we compensate for using FaReMuS, occurs in that specific person.

Furthermore, we recently observed signs suggesting that each brain region has an "its" own electrical activity. In fact, we have shown that a cortical area generates neuronal activity, which remains specific to that area in different functional states. That is, diverse structures, differing in local neuronal cells and their connectivity within the cortex and with the whole brain, express neuro-electric activities with diverse dynamics.[36] Furthermore, we found that a fluctuating transcranial electric stimulation (tES) using a current time course that replays the endogenous target activity (called neuro-dynamics) effectively changes the target excitability in humans (paper submitted). Based on these findings, we believe that we can further personalize the intervention using properly modulated currents instead of tDCS.

High response to Sham

Despite none person perceived when the stimulation was Real and when it was Sham, we observed a significant effect of Sham in some patients. This finding indicates the need to use crossover designs when investigating the effects of interventions on such subjective symptoms, as done properly by many authors.[10,25,26] Nevertheless, the Real FaReMuS treatment induced much stronger effects, with more than double the reduction in symptoms for both independent patient groups.

ES with respect to other non-pharmacological treatments

We observed that the proposed FaReMuS treatment induced a mean 1.3 ES across two independent groups. A large body of studies implementing physical and behavioral therapies[6,7] found that ES for the main exercise interventions ranged from 0.2 to 1.7, where the huge variability is consistent with our experience. Since in the two small samples we found ES 1.1 and 1.6, we definitely believe that the results of the FaReMuS neuromodulation treatment are very promising, at least in the case of low-disabled people with MS.

Future perspectives

We believe that we can offer the FaReMuS treatment to patients, since the data are convincing and the side-effects are negligible. In this line, we settled new-tech procedures (submitted) to make it user-friendly, easily exportable, and home-applicable (FaReMuS treatment). Nevertheless, we are planning a larger scale randomized controlled trial (RCT), involving different clinical centers and home treatments. Finally, the overall efficacy of the personalized intervention is yet accompanied by a large inter-subject variability of the response. For this reason, we are moving forward on two parallel lines. Better understanding of the origin of MS fatigue, especially in terms of brain organization alterations – to enhance the personalization of the neuromodulation target selection. Monitoring the other factors known to ameliorate fatigue (physical exercise, diet features, energy effectiveness strategies, behavior therapies) is to direct the individual attention on these crucial elements.

Conclusion

We have confirmed the beneficial effect against MS fatigue of a personalized tDCS treatment targeting the bilateral whole-body primary somatosensory cortex in a second independent group. We worked with MS patients suffering from mild disability, who reported fatigue-related symptoms as the main cause of their reduced quality of life. These results support the need for further development and personalization of non-invasive neuromodulations as simple, low-cost, and risk-free procedures against MS fatigue, a debilitating symptom for which there is no current pharmacological treatment.

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Declaration of Conflicting Interests

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