cerebellum,[7] whereas Cerasa and colleagues found increased activity after attention training in the posterior cerebral lobule and superior parietal lobule.[8] Innovative non-invasive brain stimulation treatments for cognitive neuropsychological deficits are on the horizon, although presently no studies have been reported for MS. Transcranial direct current stimulation (tDCS) is a technique that allows the modulation of cortical excitability. A direct current of low-level intensity is applied for a few minutes via electrodes placed on the patient's scalp. This current reaches the cortex and modulates the membrane polarity of neurons within a region of underlying neural tissue. tDCS-induced changes during stimulation result from changes in the permeability of the neural membrane, which is depolarized by anodal stimulation (a-tDCS).[9] These polarization effects persist beyond the tDCS period,[10] and the after-effects involve the participation of glutamatergic N-methyl-D-aspartic (NMDA) receptors.[11]

The capacity of a system to acquire or improve skills through a learning process has been labeled neural plasticity. This learning process implies changes in cognitive functions that are intimately tied to orderly changes in the central nervous system at various levels of organization. Therefore neuroplasticity defines the brain's ability to modify its function by strengthening or weakening its synaptic connections, and rewiring or even creating new neural pathways as a result of "experience." Substantially neural plasticity is based on changes in cortical excitability that should regulate the connection strength between neurons in the brain, and a-tDCS is thought to favor cortical excitability and therefore plasticity.[9] Based on these observations and on the safety record of tDCS, potential therapeutic applications of a-tDCS have been tested, with the goal of improving motor,[12,13] perceptual[14] and cognitive performance[15,16] in patients who have suffered a stroke. The availability of a neuroplasticity induction technique using neuromodulation allows the opportunity to explore its potential role in conjunction with the execution of specific cognitive training to treat cognitive impairments in relapsing–remitting MS patients.

The aim of this double-blind controlled study is to assess whether a remediation plan that uses a-tDCS applied over the left DLPFC in conjunction with an attention and information processing rehabilitation treatment could maximize benefits to patients. Moreover, in showing the efficiency of this protocol we would underline also the role of the DLPFC in the compromised cognitive function of these patients. It is expected that stimulation over the right DLPFC, combined with rehabilitation, will provide favorable cognitive conditions to support therapy.

Participants and methods

Patients

A total of 45 MS patients, aged 18–65 years, who were referred to the Brescia MS Center and diagnosed with the relapsing–remitting type of MS[17] with mild disability (Expanded Disability Status Scale score <5) were assessed for eligibility. The eligible patients were neither demented nor affected by psychiatric disorders (requiring treatment with neuroleptics) and free from any relapse that required steroid therapy during the month preceding the date of the baseline neuropsychological assessment. Previous brain surgery, the presence of clips in the brain and seizures were additional exclusion criteria. Patients were included if they were impaired in attention/information processing according to their baseline score (more than –2 standard deviations (SD) lower than that of healthy controls) of either the Paced Auditory Serial Addition Test (PASAT) at two- and three-second intervals or the Symbol Digit Modality Test (SDMT) of the Brief Repeatable Battery (BRB)—eventually used also as a baseline evaluation for the included patients.[18] Twenty-five out of 45 patients did not meet these criteria and were not included in the study.

A total of 20 right-handed patients were included and randomized, with a 1:1 ratio of the active (a-tDCS) treatment group (n = 10) to the placebo (sham) treatment group (n = 10), and then submitted to a baseline neuropsychological evaluation that included the complete BRB[18] and the Wisconsin Card Sorting Test (WCST).[19] An evaluation of the brain T2-fluid-attenuated inversion recovery (FLAIR) lesion volume was available for each patient, based on a routine brain MRI exam performed before the study began (median time from MRI and baseline evaluation 30 days; range 16–50). Additionally, all participants submitted to a cognitive reserve index questionnaire.[20]

Overall, three evaluations were planned: T0, baseline before treatment; T1, immediately after treatment; and T2, six months after treatment was completed. A flow diagram is provided in Figure 1. The same psychologist conducted the T0, T1, and T2 follow-up evaluations. Alternative test forms, with the exception of the WCST, were used to minimize learning effects. A different psychologist administered the rehabilitation procedure. Both psychologists were blinded to the group assignment of each patient.

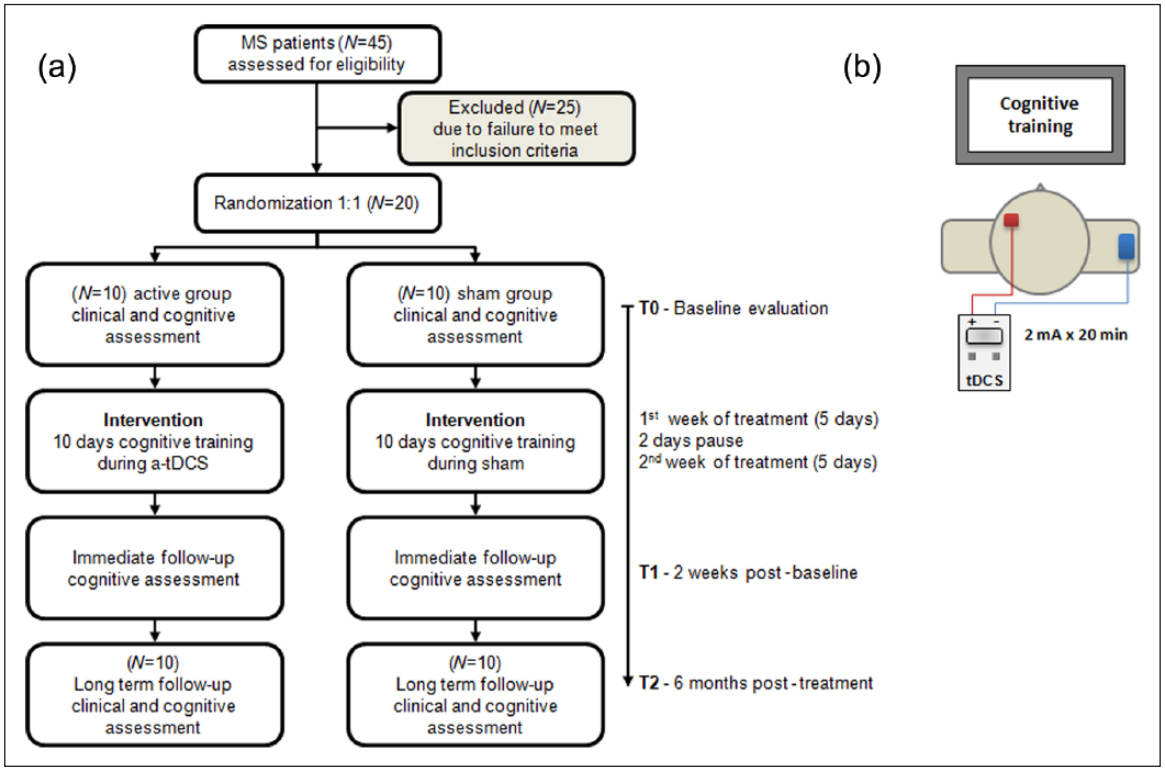

Figure 1. (a) Flow diagram of the progression of participants through the study. (b) Experimental protocol of anodal transcranial direct current stimulation (a-tDCS) combined with intensive attention and information processing cognitive training

After the treatment (T1), all patients completed a questionnaire on the tDCS-induced sensations[21] to determine whether the stimulation protocol (active vs. sham) affected the sensations experienced.

Cognitive treatment

All of the patients submitted to an intensive cognitive training program with the goal of improving attention and information processing speed, consisting of 10 daily sessions (five days per week for two weeks) that lasted approximately 30 minutes each. The training program consisted of modified PASAT tasks: months and words task,[22] which have been proven to be effective in both post-traumatic brain injury and MS patients.[6,23] In the months tasks, 60 randomly presented nouns consisting of the names of months were verbally presented to the patient, who was then asked to state which of the last two presented months occurred first on the calendar. In the words task, a list of 60 words was verbally presented to the patient, and after each word, the patient was asked to generate a new word beginning with the third letter of the previously presented word. Each type of exercise included four levels of increasing difficulty based on the speed of presentation (with inter-stimulus intervals that ranged from 3000 to 1800 msec). During the first session (first day), each patient was challenged with the easiest version of the exercise for both the months and words tasks; the patient then passed to the more difficult task (i.e. faster) whenever he or she showed the minimum number of errors according to the published age/education normative values reported by Serino et al. (2006).[22] In the following session (following day), the patient began at the last exercise of the previous day.

During the cognitive training, patients submitted to either an active treatment of a-tDCS or to sham tDCS over the left DLPFC for 20 minutes (Figure 1(b)).

Each patient was given information about the results of the neuropsychological evaluation at T1; nevertheless, in order to avoid interference with the patients' behavior on the experimental outcomes, no exercise was assigned to the patients between T1 and T2.

a-tDCS treatment

A pre-programmed battery-driven DC stimulator (BrainStim EMS, Bologna) delivered a constant

current flow of 2 mA via two conducting electrodes covered with a saline-soaked sponge. The anodal electrode (25 cm², current density: 0.08 mA/cm²) was placed on the left DLPFC, 8 cm frontally and 6 cm laterally (Fp1/F3 in 10–20 nomenclature for electroencephalogram (EEG) electrode positioning) with respect to the scalp vertex (Cz). This position was chosen in accordance with previous fMRI results.[7] The reference electrode (60 cm², current density: 0.03 mA/cm²) was fixed extracephalically to the right shoulder. We used an extracephalic reference to avoid interference effects from brain areas beneath the reference electrode. The current was ramped up and down over the first and last 10 seconds of stimulation and applied for 20 minutes in the a-tDCS condition, but during only the first and last 30 seconds (10 up, 10 at level, and 10 down) in the sham tDCS condition.

Randomization to the active and sham conditions was performed by an independent researcher based on a computerized list of random numbers. Those numbers were delivered to the pre-programmed stimulator that delivered the appropriate stimulation (active vs. sham) based on the number. The relationship between the code and type of stimulation was deciphered only at the end of the study.

The protocol was performed in accordance with safety procedures for non-invasive brain stimulation[24,25] and was approved by the Spedali Civili Ethical Committee. Written informed consent was obtained from all participants before treatment began.

Statistical analyses

The performance improvements in the neuropsychological tests, measurements of attention and information processing, and the time (number of sessions) to reach the most difficult level during cognitive rehabilitation were the outcome measures. Descriptive statistics were performed using the means and SD to make between-group comparisons of single test scores or score changes at T1 or T2.

Statistical analysis was performed using the Mann-Whitney test for unpaired samples to assess differences at baseline, between-group changes between the two follow-up examinations or differences in the time to reach the highest performance level, Wilcoxon test to assess within group differences. Data from the sensations induced by tDCS were also analyzed using the Mann-Whitney test for unpaired samples. A p value of 0.05 was considered significant for all statistical analyses. The effect size (Cohen's d)[26] was calculated and reported using G*Power.[27]

Results

At baseline, the two groups were similar in terms of demographic and disease characteristics, disease-modifying therapy, neuropsychological tests scores, and brain T2 lesion volume (Table 1). The cognitive reserve index, a comprehensive measure that includes education, cultural enrichment, leisure, employment, and factors known to be determinant for cognitive status,[20,28,29] did not show any significant difference between groups. We did not observe any relapses during the study.

After treatment (T1), both groups showed significant improvement in their overall performance on several neuropsychological tests compared to baseline performance ([b] in Table 2), although the active treatment group showed a significant improvement on more tests relative to that of the sham group ([a] in Table 2). This improvement in the active group was still present at T2. Although both groups improved in the specific rehabilitated function (attention/speed in information processing), only the a-tDCS group showed a generalization of the effect to other domains.

The changes in test scores after treatment (delta T1–T0) were significantly higher in the a-tDCS group on the SDMT (U = 19.0; p = 0.019, d = 1.15); WCST total errors (U = 12.5; p = 0.003, d = 1.31); WCST perseverative responses (U = 22.5; p = 0.035; d = 0.98); WCST perseverative errors (U = 23.5; p = 0.043; d = 1.11); and WCST non-perseverative errors (U = 16.0; p = 0.009; d = 1.29) compared to the sham group, revealing greater improvements in the attention/information processing speed and executive function in the active group compared to the sham group.

Between-groups changes from post treatment to the six-month follow-up evaluation (T2–T1) were not significantly different in any test, confirming that the improvements obtained after treatment was maintained six months later. Additional analysis to determine differences at six months in comparison to baseline performance (T2–T0) revealed that the a-tDCS group still performed significantly better than the sham group on the PASAT 2" (U = 18.0; p = 0.015; d = 1.23) and WCST total errors (U = 22.5; p = 0.035; d = 1.05). The increases in the PASAT 3" and SDMT were higher in the a-tDCS group compared to the sham-tDCS group, although this difference was not significant (Figure 2 and Table 2). An outlier analysis was performed on T1–T0 and T2–T1 delta scores, no outliers were identified in the a-tDCS or in the sham group.

Table 1. Baseline clinical and neuropsychological characteristics and scores of the active group (a-tDCS) and the sham group (sham).

	a-tDCS (n = 10)	Sham (n = 10)	p value
Male (%)	30	10	ns[b]
Age, years (mean ±SD)	38.2 ± 10.0	47.4 ± 10.4	ns[a]
Brain lesion volume (T2-FLAIR mm$^{3)}$ (mean ±SD)	4716 ± 1751	4572 ± 2147	ns[a]
Cognitive Reserve Index, raw score (mean ±SD)	97.7 ± 8.4	91.8 ± 8.7	ns[a]
Duration of illness, years (mean ±SD)	6.6 ± 6.1	11.0 ± 6.5	ns[a]
EDSS (mean ±SD)	2.1 ± 1.2	2.9 ± 1.1	ns[a]
Therapy	(%)	(%)	ns[b]
No therapy	10	40	
β-Interferons	60	30	
Glatiramer acetate	20	10	
Natalizumab	10	10	
Fingolimod	0	10	
Neuropsychological test raw scores	(mean ±SD)	(mean ±SD)	
SRT – LTS	35.1 ± 8.5	36.3 ± 8.1	ns[a]
SRT – CLTR	26.0 ± 13.5	22.8 ± 7.7	ns[a]
SRT-D	7.1 ± 2.2	7.2 ± 1.9	ns[a]
SPART	17.3 ± 3.4	16.5 ± 4.5	ns[a]
SPART-D	6.3 ± 1.8	5.5 ± 2.0	ns[a]
SDMT	43.8 ± 9.3	36.4 ± 8.2	ns[a]
PASAT 3”	22.9 ± 13.1	15.2 ± 10.5	ns[a]
PASAT 2”	6.1 ± 6.5	4.1 ± 6.7	ns[a]
WLG	20.5 ± 5.4	18.6 ± 3.8	ns[a]
WCST (total error)	31.1 ± 22.3	28 ± 17.0	ns[a]

[a]Mann-Whitney test. [b]χ^2 test.
a-tDCS: anodal transcranial direct current stimulation; FLAIR: fluid-attenuated inversion recovery; EDSS: Expanded Disability Status Scale; SRT-LTS: Select Reminding Test-Long-Term Storage; SRT-CLTR: Select Reminding Test-Consistent Long-Term Retrieval; SRT-D: Select Reminding Test-Delayed Recall; SPART: Spatial Recall Test; SPART-D: Spatial Recall Test-Delayed Recall; SDMT: Symbol Digit Modalities Test; PASAT: Paced Auditory Serial Addition Task 3” and 2” intervals; WLG: Word List Generation Task (Amato et al., 2006); WCST: Wisconsin Card Sorting Test (Heaton et al., 2000).

Importantly, the time (the number of training sessions) to reach the most difficult training level was significantly shorter for the a-tDCS group compared to the sham group (mean: 6.3 sessions for the a-tDCS group, mean: 7.4 sessions for the sham group; U = 20.5; p = 0.02, d = 0.51).

The analysis did not reveal any significant differences between the groups (stimulation conditions) in the perceived sensations. Each participant reported tolerating the stimulation without discomfort. The results of the questionnaire are reported in Table 3.

Discussion

The present study suggests that a-tDCS over the left DLPFC might be useful to increase the efficacy of cognitive training used to improve attention and information processing deficits in MS patients, although further testing with an increased sample size is needed. Although preliminary and on a limited sample of patients, the present results show greater improvements in attention/information processing and executive function both immediately and six months after treatment, when patients are treated with a-tDCS in comparison to sham. Moreover patients in the active stimulation group reached the most difficult training level faster than those in the sham group, suggesting that a-tDCS enhances the effects of the cognitive training by reducing the treatment duration needed to induce a significant improvement. Such augmentation may be, in our opinion, specifically related to the type of treatment and not to differences in other factors, such as disease duration, baseline brain lesion volume, general cultural enrichment (i.e. education), occupation type or social activities –which were similar among groups-. Additionally we can exclude that the effects were related to differences in

Table 2. Neuropsychological Δ (T1–T0) and Δ (T2–T0) scores at various times following neuropsychological testing in the active group (a-tDCS) and the sham group (sham).

Neuropsychological test	Δ (T1–T0)			Δ (T2–T0)		
	a-tDCS (n = 10)	Sham (n = 10)	p value	a-tDCS (n = 10)	Sham (n = 10)	p value
	(mean ± SD)	(mean ± SD)		(mean ± SD)	(mean ± SD)	
SRT – LTS	**1.8** ± 8.9	–5.6 ± 10.9	ns[l]	**8.1** ± 8.6[b]	**2.8** ± 10.5	ns[a]
SRT – CLTR	**1.5** ± 10.0	–2.2 ± 7.9	ns[l]	**4.7** ± 6.9[b]	**6.4** ± 8.4[b]	ns[a]
SRT-D	–0.7 ± 1.2	–0.5 ± 1.3	ns[l]	**0.8** ± 1.6	**0.9** ± 1.2	ns[a]
SPART	**2.9** ± 5.0	**1.2** ± 4.9	ns[a]	**3.2** ± 4.3	**1.2** ± 5.6	ns[a]
SPART-D	**0.9** ± 1.6	**1.9** ± 2.2[b]	ns[a]	**0.7**± 2.1	**0.4** ± 2.4	ns[a]
SDMT	**8.8*** ± 8.6[c,b]	–0.1 ± 6.7	0.019[a]	**7.2** ± 10.4[b]	**1.6** ± 6.0	ns[a]
PASAT 3”	**14.6** ± 8.3[b]	**11.7** ± 10.1[b]	ns[a]	**14.5** ± 5.0[b]	**11.3** ± 10.4[b]	ns[a]
PASAT 2”	**14.3** ± 9.7[b]	**8.2** ± 10.7	ns[a]	**18.4** ± 7.8[c,b]	**8.8** ± 7.7[b]	0.015[a]
WLG	**0.6** ± 4.4	**3.0** ± 10.1	ns[a]	**1.2** ± 4.9	**1.8** ± 8.9	ns[a]
WCST (total error)	**–11.8** ± 17.9[c]	9.7 ± 14.7	0.00a	**–6.9** ± 14.0[c]	8.6 ± 15.4	0.035[a]
WCST (perseverative responses)	**–8.7** ± 10.6[c,b]	3.7± 14.2	0.035[a]	**–6.7**± 11.4	4.2 ± 14.1	ns[a]
WCST (perseverative errors)	**–8.0** ± 10.4[c,b]	3.2 ± 9.7	0.043[a]	**–5.8**± 8.7[b]	3.6 ± 9.8	ns[a]
WCST (non-perseverative errors)	**–4.1** ± 8.6[c]	6.8 ± 8.2	0.009[a]	**–1.5** ± 5.6	5.5 ± 8.5	ns[a]

[a]Mann-Whitney test. [b]Wilcoxon test.
[c]Significant a-tDCS improvement compared to sham. [b]Within-group significant improvement compared to baseline. Data reported in bold highlight a general score improvement from baseline, present in both conditions after intervention. a-tDCS: anodal transcranial direct current stimulation; SRT-LTS: Select Reminding Test-Long-Term Storage; SRT-CLTR: Select Reminding Test-Consistent Long-Term Retrieval; SRT-D: Select Reminding Test-Delayed Recall; SPART: Spatial Recall Test; SPART-D: Spatial Recall Test-Delayed Recall; SDMT: Symbol Digit Modalities Test; PASAT: Paced Auditory Serial Addition Task 3” and 2” intervals; WLG: Word List Generation Task (Amato et al., 2006); WCST: Wisconsin Card Sorting Test (Heaton et al., 2000).

the subjective sensations induced by the a-tDCS vs. sham treatments, which resulted to be similar between groups, or to other pharmacological treatments. Though in our sample the type and the percentage of patients receiving therapies were different between groups, the EDSS and the brain lesion volume were not and we did not observe relapses during the study.

Patients who received active stimulation improved more than did the control group also in executive functions. This greater improvement was still present six months after treatment, indicating that the cognitive training associated with a-tDCS over the left DLPFC could be particularly longstanding and effective both on attention/information processing and on executive abilities. This is likely to be ascribed to the enhanced excitability in DLPFC, which is known to be part of cortical networks involved in all these different cognitive functions. This result could be due both to the type of cognitive training applied and to the specific area that was stimulated. Specifically, the cognitive treatment which was adopted was based not only on attention resources but also on the inhibition of impulsive reactions and on executive control. Moreover, the site of stimulation, the DLPFC, is known to be directly involved in executive abilities and is more active in MS patients who have been submitted to cognitive rehabilitation of attention compared to patients who have not been submitted to this type of rehabilitation.[7]

Previously the efficacy of a-tDCS in the cognitive domain has been demonstrated in patients with different cognitive impairments, such as aphasia,[30,31] neglect,[32] memory impairment,[33] and apraxia.[34] This is the first exploratory study investigating the usefulness of tDCS in the rehabilitation of cognitive deficits in MS patients.

The effect of a-tDCS can be attributed to a gating mechanism at a neural level, i.e. the induction of additive neuroplastic changes by modulating the excitability of the targeted neurons.[35] The effect of increased cortical excitability induced by anodal stimulation converges with the activity induced by cognitive training. This effect has been suggested to depend on an increased calcium influx into the targeted cortical neurons during a-tDCS, which facilitates neuronal excitability and eventually leads to long-term changes in synaptic strength.[35] The low strength of the current

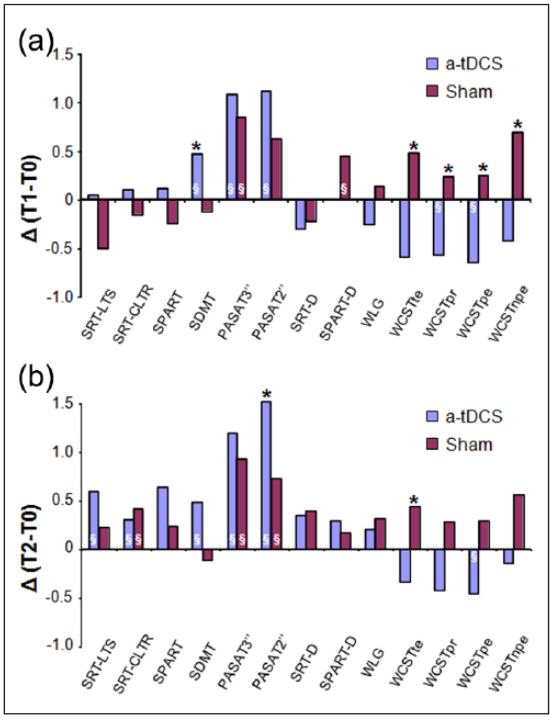

Figure 2. Changes in *z* scores (Δ) of neuropsychological tests for a-tDCS (light blue) and sham (purple) groups at T1 (a) and T2 (b). Significant differences are marked with an *, Mann Whitney test; $p \leqslant 0.05$; § = within group significant improvement compared to baseline, Wilcoxon test.
a-tDCS: anodal transcranial direct current stimulation; SRT-LTS: Select Reminding Test-Long-Term Storage; SLT-CLTR: Select Reminding Test-Consistent Long-Term Retrieval; SPART: Spatial Recall Test; SDMT: Symbol Digit Modalities Test; PASAT 3" or 2": Paced Auditory Serial Addition Task 3 or 2 second; SRT-D: Select Reminding Test-Delayed Recall; SPART-D: Spatial Recall Test-Delayed Recall; WLG: Word List Generation Task; WCST: Wisconsin Card Sorting Test; WCSTte: total errors; WCSTpr: perseverative responses; WCSTpe: perseverative errors; WCSTnpe: non-perseverative errors.
For the WCST scores, a negative difference corresponds to a performance improvement, whereas for the other tests, a positive difference corresponds to a performance improvement.

used during tDCS is unable to induce depolarization to the threshold level of "inactive" neurons (i.e. induce an action potential). However, in the presence of ongoing activity (e.g. task-induced activity), the change in membrane potential induced by a-tDCS can promote more effective activation. Using this method, a-tDCS has been proposed to prime the specific stimulated behavioral system by increasing cortical excitability and producing corresponding effects in the targeted cognitive network. Therefore, tDCS-induced effects are more likely to be sensitive to the state of the active network at the moment. Therefore, the polarization of neurons in combination with ongoing synaptic input can be contextualized in a framework of synaptic co-activation. In addition, the findings converge in indicating that the neural network modulated by tDCS could be, at least in part, spared. Whether this functional sparing reflects extra lesional changes involving neural plasticity in structurally spared neural networks taking over the damaged function, enhanced residual function of hypo-functioning regions or both mechanisms remains to be clarified.[12,15,36] It has been shown that a-tDCS-induced effects are related to membrane depolarization because they are affected by ion-channel blocking substances, as well as synaptic changes.[9–11] Therefore, changes in duration of the induced effect should depend on change on one of these mechanisms. Moreover it should be noted that although tDCS technique is in widespread use and has great potential to improve deficits, the precise neural mechanisms responsible for its effects at network level sustaining cognition remain essentially unknown.

The present study has the main limitation of a small sample size. This could account for the lack of significance between the two groups in age, disease duration, which were both higher in the sham group, compared to a-tDCS. This could have had a partial impact on cognitive improvement of older patients, whose neuroplasticity may be reduced by age; however this is unlikely, given the large effect size and the specificity of the cognitive domains improved by neuromodulation. Future experiments with larger population are needed to confirm these results and to address the effects in everyday life of this rehabilitative approach, by using more ecological measures of improvement in executive function, as well as in information processing speed, which were not used in our study. Although larger confirmative studies are needed, the results support the use of this approach to improve attention, information processing and executive deficits in patients with MS. Moreover, considering our previous results[2] reporting the efficacy of a three-month cognitive training program for attention and executive function deficits in MS, the present study supports the usefulness of a shorter duration intensive training program combined with a-tDCS in MS patients. Executive function has been reported to correlate with social functioning in MS;[4] therefore, ameliorating these abilities appears to be relevant in the clinical perspective. Importantly, this procedure could be readily applied to MS patients with minimum discomfort and cost, both for the patient and the health system.

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Table 3. Anodal transcranial direct current stimulation (a-tDCS)-induced sensations according to the mean intensity of the sensations reported by patients after a-tDCS or sham and the percentage of patients who reported each sensation.

Stimulation condition		Itchiness	Pain	Burning	Warmth/ Heat	Pinching	Fatigue	Iron taste	Other[a]
a-tDCS group	Mean intensity ±SD	0.5 ±0.8	0.1 ±0.4	0.5 ±0.8	0.1 ±0.4	1.0 ±0.8	0.4 ±0.7	0.5 ±0.9	0.1 ±0.4
	Participants (%)	30	10	30	10	80	20	20	10
Sham group	Mean intensity ±SD	0.3 ±0.5	0.2 ±0.7	0.7 ±0.9	0.0 ±0.0	0.8 ±0.8	0.3 ±0.7	0.0 ±0.0	0.6 ±1.0
	Participants (%)	30	10	40	0	50	20	0	50
***p* value**		ns[a]	ns[a]	ns[a]	ns[a]	ns[a]	ns[a]	ns[a]	ns[a]

[a]Mann-Whitney test.
Sensation intensity was evaluated on a five-point scale: 0 none, 1 mild, 2 moderate, 3 considerable, and 4 strong; [a]Other included cephalalgia.

Conflict of interest

None declared.

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