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RESEARCH ARTICLE

Walking in multiple sclerosis improves with tDCS: a randomized, double-blind, sham-controlled study

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Abstract

Objective: To evaluate whether multiple sessions of transcranial direct current stimulation (tDCS) applied to the primary motor (M1) cortex paired with aerobic exercise can improve walking functions in multiple sclerosis (MS). **Methods**: MS participants were recruited for a double-blind, parallel-arm, randomized, sham-controlled trial and assigned to 10 sessions (5 d/wk for 2 weeks) of either active or sham tDCS paired with unloaded cycling for 20 minutes. Stimulation was administered over the left M1 cortex (2.5 mA; anode over C3/cathode over FP2). Gait spatiotemporal parameters were assessed using a wearable inertial sensor (10-meter and 2-minute walking tests). Measurements were collected at baseline, end of tDCS intervention, and 4-week postintervention to test for duration of any benefits. **Results**: A total of 15 participants completed the study, nine in the active and six in the sham condition. The active and sham groups were matched according to gender (50% vs. 40% female), neurologic disability (median EDSS 5.5 vs. 5), and age (mean 52.1 $\pm$ 12.9 vs. 53.7 $\pm$ 9.8 years). The active group had a significantly greater increase in gait speed (0.87 vs. 1.20 m/s, $p < 0.001$) and distance covered during the 2-minute walking test (118.53 vs. 133.06 m, $p < 0.001$) at intervention end compared to baseline. At 4-week follow-up, these improvements were maintained (baseline vs. follow-up: gait speed 0.87 vs. 1.18 m/s, $p < 0.001$; distance traveled 118.53 vs. 143.82 m, $p < 0.001$). **Interpretation**: Multiple sessions of tDCS paired with aerobic exercise lead to cumulative and persisting improvements in walking and endurance in patients with MS.

Introduction

Multiple sclerosis (MS) is the leading cause of progressive functional impairments, such as motor, sensory, and cognitive dysfunctions, in adults of working age.[1,2] Among the spectrum of potential symptoms, up to 70% of patients with MS rank gait dysfunction to be one of the most troublesome and life-altering consequences of the disease.[3] The most effective nonpharmacological approach to manage walking impairment and improve ambulation is the practice of physical exercise.[4–6] Given MS is a chronic, long-lasting, and disabling disease, ideally rehabilitative interventions should minimize motor impairments and maximize walking function, while simultaneously facilitating activation of neural pathways that execute walking in order to achieve long-term restoration of the function.[7,8] Transcranial direct current stimulation (tDCS) is an emerging technique for adjunctive use in motor rehabilitation.[9–12] Beyond symptom management, tDCS has been theorized to be a neuromodulation tool that can induce long-term potentiation (LTP) phenomena causing specific changes in synaptic efficacy of the targeted brain region,[10,13,14] and promote synergistic effects when paired with a training activity.[15,16] Thus

far, studies using tDCS over M1 have shown mixed results in the treatment of gait functions in patients with MS.[17–22] However, these studies have used tDCS in only one or a few sessions, where multiple repeated treatments are necessary for behavioral effects.

This randomized, double-blind, sham-controlled study measured the immediate, cumulative, and persisting effects of multiple tDCS sessions over M1 paired with aerobic exercise training on walking and endurance in patients with MS.

Material and Methods

Study design

The study was a two-arm, parallel-group, double-blind, randomized, sham-controlled design to assess the effects of anodal tDCS paired with aerobic exercise on gait performance.

All study procedures were approved by the Institutional Review Board Committee of the New York University School of Medicine and followed the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki and prospectively registered at clinicaltrials.gov (NCT03658668).

All participants were fully informed about all concerning experimental procedures and signed a written informed consent form prior to participation.

Participants

Individuals with MS aged 18–70 years were recruited through the MS Comprehensive Care Center, NYU Langone Health in New York City, from September 2018 to March 2019. Eligible participants met MS diagnostic criteria,[23] with either relapsing remitting (RR) or secondary progressive (SP) subtype, and had an Expanded Disability Status Scale (EDSS) score ranging from 1.0 to 6.5. Participants to be included in the study had to be physically able to independently walk with or without an assistive device (i.e., cane, crutches, or walking frames) for at least 100 meters. Participants were excluded if they presented primary neurologic (other than MS), psychiatric, or other medical disorders, had a WRAT-4 Word Reading Test level below average (<85) (estimated general intellectual functioning), were currently enrolled in a physical activity or physical rehabilitation program, had any skin disorder or skin-sensitive area near the stimulation locations, or experienced a clinical relapse or use of high dose of steroids in the past month. All participants were evaluated by a study clinician to ensure the exclusion of any major health concerns, as required by the exclusion criteria (i.e., cardiorespiratory or severe osteoarticular disorders). Participants were specifically asked to maintain the same level of physical activity and not to engage in any supplemental physical routine program throughout the entire study period. Once consent was obtained, participants were randomized into one of two study arms (active vs. sham) in a 1:1 allocation using random block sizes of 4 and 6 to control for age and level of neurologic disability (stratified factors: EDSS score 0-3.5 and 4.0-6.5; age 18-45 and 46-70). Randomization was completed by an independent technician who took no part in the study visits or daily sessions, to maintain the double-blind nature of the study. Both the study technician involved in the outcome assessment and patients were blinded to treatment allocation.

Interventional protocol

The interventional protocol was structured in five daily physical training sessions over 2 weeks (10 sessions in total) of 20 min duration. The aerobic exercise-conditioning program was performed simultaneously with either active or sham tDCS.

Study schedule

Eligible participants attended a baseline visit scheduled the week before the first treatment session. Individuals completed motor assessments consisting of the 10-meter walk test (10-mwt), 2-minute walk test (2-mwt), and questionnaires (see *Clinical Assessment Section*).

Baseline procedures included familiarization with the equipment used for the physical training, as well as 90 sec tDCS tolerability test performed at 2.5 mA and decreasing in steps of 0.5 mA on participant's request. The same motor assessments and questionnaires were administered during the 10th session and the 4-week follow-up visit. In order to assess the potential acute and cumulative effects of the intervention, the 10-mwt was performed after each tDCS session. The assessment was performed only after that participant's heart rate returned to its resting value.

Transcranial direct current stimulation

The equipment employed to deliver the constant direct electrical current was the 1x1 tDCS mini-clinical trial device (mini-CT; Soterix Medical Inc., USA). The Soterix EasyStrap was customized to allow M1-SO electrode montage with anodal electrode over C3 and cathodal electrode over Fp2 according to the 10–20 EEG system. Rubber electrodes with sponge pad insert (square shape, 5x5 cm^2) were presaturated with saline solution before use to augment the conduction of the mild electrical current across the scalp. The stimulation device was fully

programed by an independent study technician to ensure the blinding of the technician who supervised the treatment sessions.

For the active tDCS condition, the device was programed to deliver the electrical current at 2.5 mA for 20 min, with a current density under the surface electrodes of 0.1 mA/cm^2. For the sham tDCS condition, the device was programed to have a 60-second ramp up/down to the desired current intensity (2.5 mA) delivered at the beginning of the 20-minute period and a 60-second ramp up/down delivered at the end of the 20-minute period, with no current otherwise delivered during the session.[24,25]

At the end of the study, blinding integrity was assessed by participant's guess of assigned condition.

Physical training

All participants completed a total of 10 x 20-minute sessions of daily supervised physical training paired simultaneously with either active or sham tDCS. The physical training program consisted of 20 min of aerobic exercise using a recumbent combination arm/leg elliptical ergometer (PhysioStep LXT-700). According to the recommendation for physical exercise in MS,[26] participants performed the training at moderate intensity corresponding to 60-80% of age-predicted maximum heart rate (HR_{max}). Thus, the heart rate signal was monitored during the entire session by means of a heart rate monitor wristband (Fitbit) and transmitted via Bluetooth connection in real-time for continuous monitoring. Age-predicted maximum heart rate was derived from the equation proposed by Tanaka et al.[27]: $HR_{\max} = 208 - (0.7 \cdot age)$.

Clinical Assessment

Instrumented 10-mwt

Objective walking evaluation was performed using a previously validated wearable inertial sensor[28]. Spatiotemporal parameters of gait were collected using a wireless inertial sensor (G-walk, BTS Bioengineering S.p.A., Italy) that was attached around the participant's waist with a semi-elastic belt (lower lumbar level, centered on the L4–L5 inter-vertebral disc). Per the 10-meter walk test instruction, the participants were directed to walk along a 10-meter hallway at their self-selected speed and as naturally as possible. The sensor, including a tri-axial accelerometer, a gyroscope, and a magnetometer, collected acceleration signals along three orthogonal axes, which were transmitted via Bluetooth to a PC. Postprocessing of these signals allowed obtaining a set of gait spatiotemporal parameters and the following were considered in the analysis[29]:

- Gait speed: the mean velocity of progression (m/s);
- Stride length: the longitudinal distance between two consecutive heel contacts of the same foot (m);
- Gait cycle duration: the time between two consecutive ground contacts of the same foot (s);
- Stance and swing duration: expressed as a percentage of the gait cycle, representing the duration of the phase during which the foot remained in contact with the ground (stance) and not in contact with the ground (% gait cycle);
- Double support duration: the duration of the phase during which both feet were in contact with the ground (% gait cycle).

Instrumented 2-mwt

This test assessed participants' physical endurance – with the same reliability of the 6-minute walk test in people with MS.[30] The objective of this test was to walk as far as possible in 2 min, without running or jogging. The participants were instructed to walk, at maximal gait speed, back and forth along a 30-meter hallway for 2 min. Use of habitual assistive devices was permitted. Gait spatiotemporal parameters, such as gait speed, stride length, and distance traveled, were computed from the acceleration signals collected using the wearable inertial sensor placed around participant's waist as described in the previous paragraph.

Self-reported questionnaires

MS-related fatigue was self-reported using the Fatigue Severity Scale (FSS) that scored the general impact of fatigue as descriptive clinical measure,[31] and using the 21-item modified form of the Fatigue Impact Scale (MFIS-21) to evaluate changes in the physical, cognitive, and psychosocial aspects of fatigue.[32] The FSS was also used as a descriptive clinical measure at baseline. To assess the effect of the treatment in reducing the impact of MS on walking ability, participants completed the 12-item MS Walking Scale (MSWS-12).[33]

Data analysis

All analyses were completed using the statistical package SPSS version 25 (SPSS, Inc., Chicago, IL). The normal distribution of the variables was assessed by the Kolmogorov-Smirnov test, with all study variables meeting the criteria of normality. Descriptive analyses were generated for all demographic and clinical variables of the groups. Differences between the active and sham groups were tested with t-test (age, weight, height, and FSS),

Fisher's test (sex and MS subtype distribution), and Chi-square test (EDSS).

With normal distribution of the variables (spatiotemporal parameters of gait and scores of the self-reported questionnaires), 2 × 2 general mixed model ANOVAs (*treatment* × *time*) were performed to examine the effects of the between-subjects factor *treatment* (active and sham) and the within-subjects factor *time* (baseline, 10th daily session and follow-up). Changes in gait velocity and stride length over 10 tDCS sessions were submitted to general mixed model ANOVAs with *treatment* (active and sham) as a between-subjects factor and *session* (session 1 to session 10) as a within-subjects factor. When a significant main effect was reached, post hoc tests with Sidak correction for multiple comparisons were conducted to assess treatment or time point differences. The level of significance was set at $P = 0.05$.

Results

A total of 33 participants were screened, and 18 were enrolled in the study to receive the intervention (Fig. 1). One participant did not receive the allocated intervention and two participants discontinued from the study due to personal reasons unrelated to the treatment, with 15 completing all study procedures.

Participants' demographic and clinical features are described in Table 1. At baseline, no significant differences were found in demographic and clinical characteristics between the two groups.

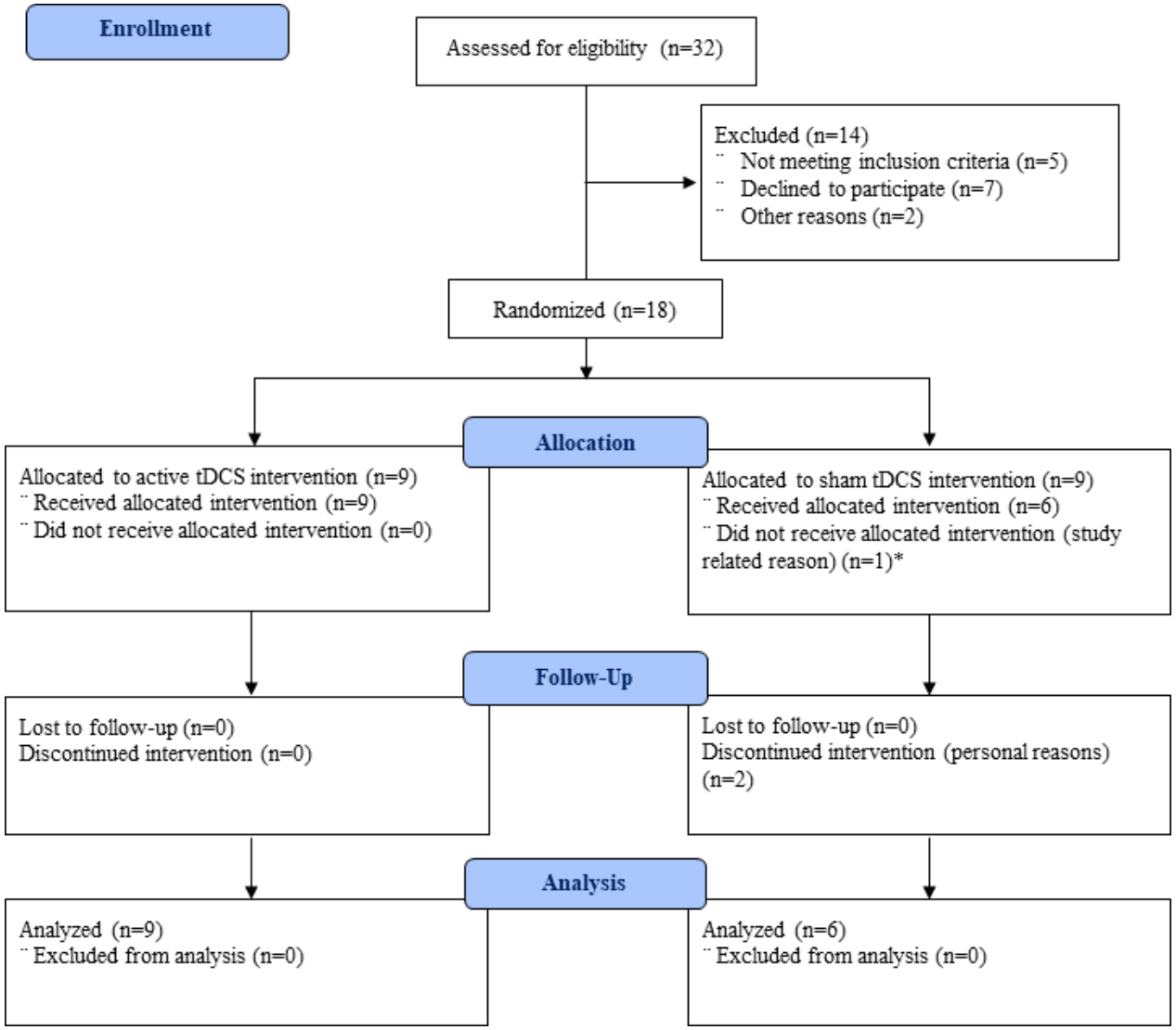

Figure 1. CONSORT flow diagram of the trial. Note: * Ran out of the study time for participating, but they expressed interest in participating

Table 1. Baseline demographic, anthropometric, and clinical characteristics of participants enrolled in active and sham groups. Values are reported as mean ± SD

	Active treatment (n = 9)	Sham treatment (n = 6)	*P*-value
Participants # (M/F)	9 (3/6)	6 (1/5)	0.462
Age (years)	52.1 ± 12.8	53.5 ± 9.8	0.422
Weight (kg)	65.8 ± 14.6	66.2 ± 10.3	0.299
Height (cm)	170.9 ± 12.4	165.3 ± 7.5	0.590
Subtype	2 RRMS, 7 SPMS	3 RRMS, 3 SPMS	0.341
EDSS	5.3 ± 1.1	4.5 ± 1.7	0.855
FSS	5.1 ± 1.5	4.0 ± 1.1	0.265

FSS, Fatigue Severity Scale; RRMS, Relapsing Remitting Multiple Sclerosis; SPMS, Secondary Progressive Multiple Sclerosis.

As shown in Tables 2 and 3, the groups did not differ on any measure of walking performance at baseline (all *P*-values > 0.05).

Safety, tolerability, and blinding

The baseline visit included a 90-second tolerability test for the stimulation (ramp up/down in current), with 2.5 mA tolerated by all participants. Therefore, all tDCS stimulation sessions were delivered at a stimulation intensity of 2.5 mA.

The tDCS intervention was well-tolerated, and there were no side effects that led to session or treatment discontinuation for any participant. None of the reported side effects (e.g., sensations of tingling, itching, and warmth) reached an intensity level of> 7 (rated on a 0- to 10-point scale) for any participant at any session. All reported side effects resolved by the end of the stimulation period.

At study end, tDCS condition assignment (active and sham) was identified correctly by 28% of participants. Specifically, 33% of the participants assigned to the sham group guessed their study condition. The result of the blinding integrity was in agreement with the standards suggested in previous studies for adequate blinding.[34,35]

Instrumented walking assessment

To test for effects on gait spatiotemporal parameters, changes in the instrumented 10-mwt (Table 2) and 2-mwt (Table 3) were compared from baseline to the 10th daily session, and then at a 4-week follow-up to test for any persisting benefits. Active versus sham tDCS resulted in a significant increase in gait velocity and stride length at the 10th daily session, with this benefit persisting at 4 weeks from the treatment end.

For the spatiotemporal parameters assessed during the 10-mwt, there were a significant effects of time on stride length ($F_{2,\ 26} = 24.62$, $P = 0.001$, $\eta^2 = 0.247$), gait velocity ($F_{2,\ 26} = 18.18$, $P = 0.001$, $\eta^2 = 0.236$), gait cycle duration ($F_{2,\ 26} = 10.32$, $P = 0.001$, $\eta^2 = 0.255$), and cadence ($F_{2,\ 26} = 7.52$, $P = 0.003$, $\eta^2 = 0.221$). Significant time × treatment interactions was found in stride length ($F_{2,\ 26} = 25.13$, $P = 0.001$, $\eta^2 = 0.261$), gait speed ($F_{2,\ 26} = 16.671$, $P = 0.001$, $\eta^2 = 0.241$), gait cycle duration ($F_{2,\ 26} = 6.95$, $P = 0.004$, $\eta^2 = 0.220$), and cadence ($F_{2,\ 26} = 8.94$, $P = 0.001$, $\eta^2 = 0.263$). Post hoc evaluation demonstrated a significant increase in gait velocity, stride length, and cadence at the 10th daily session and 4-week follow-up visit compared to baseline in the active tDCS group (all *P*-values = 0.001).

For the distance covered during the 2-mwt, there was a significant effect of the time ($F_{2,\ 26} = 6.27$, $P = 0.006$,

Table 2. Spatiotemporal parameters calculated from the 10-mwt at baseline, after 10 daily sessions and follow-up visit. Values are reported as mean ± SD

	Active treatment (*n* = 9)			Sham treatment (*n* = 6)			Interaction *P*-value Time x Treatment
	Baseline	10th day	Follow-up	Baseline	10th day	Follow-up	
Gait speed (m/s)	0.87 ± 0.32	1.20 ± 0.32*	1.18 ± 0.3*	0.95 ± 0.33	0.96 ± 0.35	0.96 ± 0.33	<0.001
Stride length (m)	1.04 ± 0.17	1.36 ± 0.15*	1.35 ± 0.13*	1.09 ± 0.21	1.07 ± 0.15	1.11 ± 0.21	< 0.001
Gait cycle duration (s)	1.28 ± 0.29	1.14 ± 0.22*	1.14 ± 0.26*	1.25 ± 0.30	1.24 ± 0.21	1.24 ± 0.31	0.004
Cadence (steps/min)	99. 83 ± 18.35	107.61 ± 22.16*	108.61 ± 25.34*	104.89 ± 22.00	104.86 ± 20.92	104.30 ± 20.39	0.001
Stance phase (% gait cycle)	60.34 ± 2.78	59.73 ± 2.38	59.81 ± 2.28	60.60 ± 2.55	60.45 ± 2.20	60.35 ± 1.89	0.610
Double support phase (%gait cycle)	20.18 ± 4.79	18.44 ± 4.60	20.70 ± 6.46	22. 32 ± 5.02	21.63 ± 3.89	21.59 ± 6.79	0.781

*indicates a significant difference from baseline ($P < 0.05$).

Table 3. Results of RM-ANOVA for spatiotemporal parameters calculated from the 2-mwt. Values are reported as mean ± SD

	Active treatment (n = 9)			Sham treatment (n = 6)			Interaction P-value Time x Treatment
	Baseline	10th day	Follow-up	Baseline	10th day	Follow-up	
Distance covered (m)	118.53 ± 47.52	133.06 ± 49.2*	143.82 ± 55.5*	117.38 ± 66.71	116.95 ± 67.55	115.78 ± 67.21	0.002
Gait speed (m/s)	1.07 ± 0.43	1.24 ± 0.44*	1.28 ± 0.52*	1.09 ± 0.66	1.07 ± 0.66	1.08 ± 0.62	0.016
Stride length (m)	1.23 ± 0.37	1.35 ± 0.46*	1.41 ± 0.47*	1.17 ± 0.37	1.13 ± 0.34	1.15 ± 0.26	0.040

*Indicates a significant difference from baseline ($P < 0.05$).

$\eta^2 = 0.325$) and a time × treatment interaction ($F_{2,\ 26} = 8.02$, $P = 0.002$, $\eta^2 = 0.382$). Accordingly, the post hoc analysis indicated that, compared to the sham group, a significant improvement in the distance covered occurred in the active group (baseline vs. 10th daily session, $P = 0.004$; baseline vs. follow-up, $P = 0.001$). There was a significant effect of time on gait speed ($F_{2,\ 26} = 3.6$, $P = 0.042$, $\eta^2 = 0.217$) and the stride length ($F_{2,\ 26} = 4.39$, $P = 0.040$, $\eta^2 = 0.209$). Moreover, time × treatment interactions were found for gait speed ($F_{2,\ 26} = 4.88$, $P = 0.016$, $\eta^2 = 0.273$) and stride length ($F_{2,\ 26} = 4.39$, $P = 0.040$, $\eta^2 = 0.210$). The post hoc analysis showed a significant differences for both parameters in the active tDCS group at the 10th daily session (gait speed, $P = 0.001$; stride length, $P = 0.003$) and the follow-up visit (gait speed, $P = 0.003$; stride length, $P = 0.015$) compared to baseline, but not in the sham group (all P-values> 0.05).

Earliest benefits of tDCS were detected by the fourth of the 10 treatment sessions compared to the baseline assessment. There was a significant main effect of session ($F_{10,\ 127} = 4.17$, $P = 0.001$, $\eta^2 = 0.214$) and a significant treatment × session interaction ($F_{10,\ 127} = 5.94$, $P = 0.001$, $\eta^2 = 0.210$), showing that changes in gait velocity and stride length significantly increased across the 10 treatment sessions. Moreover, the post hoc analysis showed that gait velocity and stride length significantly increased compared to baseline assessment from the 4th to 10th tDCS session (Figure 2).

Self-reported outcomes

Self-reported benefit corresponded to the objective measures. Table 4 provides the descriptive data for self-reported questionnaire scores.

There was a significant time × treatment interaction in MSWS-12 total score ($F_{2,\ 26} = 7.06$, $P = 0.004$, $\eta^2 = 0.354$). The post hoc analysis revealed a significant reduction of the MSWS-12 total score within the active tDCS group at the 10th daily session ($P = 0.001$) and at the follow-up visit ($P = 0.014$), compared to baseline. While no significant change was found in the MFIS-21 total score, there was a significant positive change in the physical fatigue subscale for the active group, with a significant time × treatment interaction for the physical subscale ($F_{2,\ 26} = 5.11$, $P = 0.013$, $\eta^2 = 0.254$). The post hoc analysis showed a significant reduction on the MFIS-21 physical subscale in the active tDCS group at the 10th daily session compared to baseline ($P = 0.001$).

Discussion

Impaired gait constitutes a crucial functional limitation in patients with MS. We found that 10 sessions of aerobic exercise paired with anodal tDCS applied to the left M1 cortex enhanced acute positive effects on gait function in patients with MS. Following treatment, the active tDCS group increased the walking distance covered during the 2-mwt after 10 sessions, with similar results for gait speed and stride length assessed during the 10-mwt. There was a clear trend of increase in gait speed and stride length across the 10 treatment sessions in the active tDCS group, with significant measurable differences by the fourth treatment session. Importantly, the improvements of the active group in gait speed, stride length, and cadence and the ability to walk for a farther distance were maintained over a period of up to 4 weeks after the treatment end.

The 33.0% improvement in gait velocity during the 10-mwt and 12.3% in the distance covered for the 2-mwt are well withinthe range of the meaningful clinically important difference for adults with motor disorders (e.g., >12-20%).[36,37,38] Additionally, the improvement measured by the advanced technology for motion analysis had a direct correspondence with self-reported benefits, especially for reports of distance traveled and the smoothness of walking.

These findings demonstrated that multiple tDCS sessions had a cumulative effect, and repeated treatments are needed to induce reliable and persisting changes. Our results are in line with recent reports that proposed NIBS,

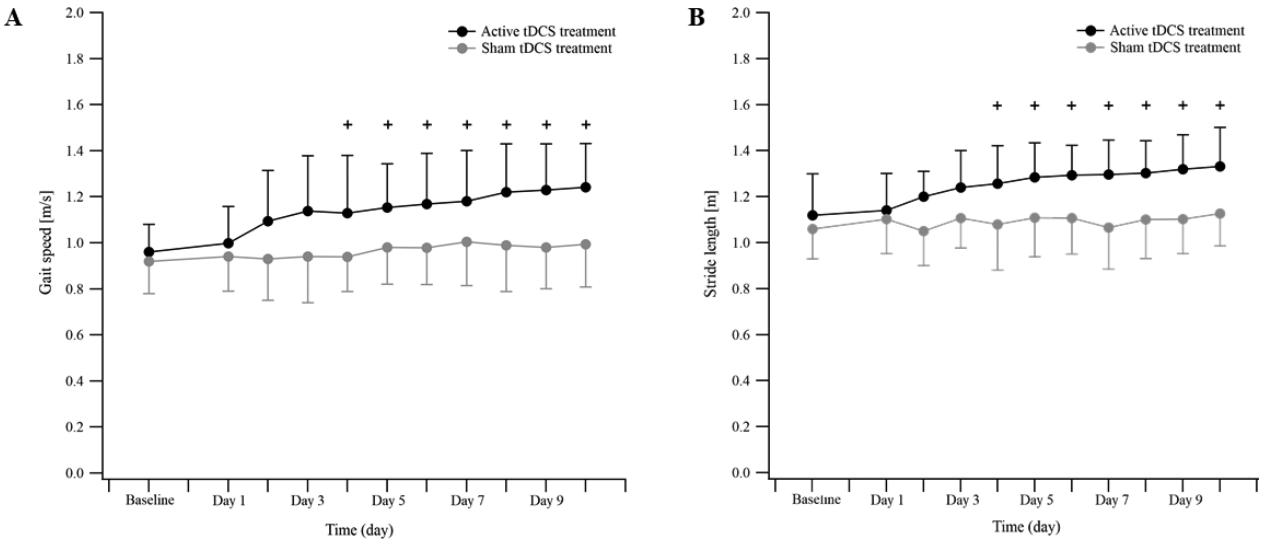

Figure 2. Trends in gait velocity (A) and stride length (B) over 10 tDCS sessions. Changes in gait velocity and stride length over 10 treatment sessions in both stimulation groups (active, $n = 9$, and sham, $n = 6$). Active stimulation is represented by a black solid line and sham stimulation is represented by a gray solid line. Values at baseline represent the gait velocity measured before the beginning of stimulation treatment. The symbol + indicates a significant difference compared to the baseline ($P < 0.05$)

Table 4. Results of RM-ANOVA analysis for the self-report questionnaire scores. Values are reported as mean ± SD

	Active treatment ($n = 9$)			Sham treatment ($n = 6$)			Interaction *P*-value
	Baseline	10th day	Follow-up	Baseline	10th day	Follow-up	Time x Treatment
12-MSWS	42.7 ± 8.9	37.8 ± 9.7*	38.2 ± 9.2*	42.3 ± 8.8	39.8 ± 9.8	39.5 ± 9.9	0.004
MFIS-21	43.8 ± 14.7	31.4 ± 13.8	36.3 ± 15.7	42.7 ± 22.3	41.1 ± 25.9	36.5 ± 25.9	0.181
Physical subscale	24.0 ± 6.9	16.9 ± 5.8*	20.6 ± 8.1	20.7 ± 6.1	21.8 ± 8.7	18.7 ± 7.2	0.013
Cognitive subscale	15.0 ± 8.2	11.0 ± 8.3	11.3 ± 8.2	18.5 ± 14.2	17.50 ± 13.2	16.2 ± 14.2	0.674
Psychosocial subscale	4.8 ± 2.2	3.6 ± 2.2	4.4 ± 2.5	3.5 ± 2.6	3.5 ± 2.8	3.3 ± 2.5	0.324

Abbreviations: 12-MSWS, 12-item MS Walking Scale; FSS, Fatigue Severity Scale; MFIS-21, 21-item Modified form of the Fatigue Impact Scale.
*Indicates a significant difference from baseline ($P < 0.05$).

and tDCS paired with exercise training specifically, to augment or potentiate the benefits induced by physical activity in Parkinson's disease,[39] cerebellar ataxia,[40] and cerebral palsy.[41]

Two previous studies have tested anodal tDCS to treat walking impairment in patients with MS,[18,19,21] evaluating outcomes after only one session of tDCS paired with a motor activity[18] or using tDCS only (without paired activity) for five sessions.[21] Most recently, the timing window of tDCS application was assessed using the 6-minute walk test in 12 patients with MS either before or during stimulation.[18] The authors found a decrease in distance walked in the "during" group and an increase in gait velocity in the "before" group.[18] A previous study using tDCS alone found an increase in gait velocity in the active versus the sham group following seven sessions,[19] but without any corresponding change in self-reported outcomes (MSWS-12 score). Taken together, the present findings suggest that tDCS should be paired with simultaneous exercise or motor training and should include extended treatment with multiple sessions to lead to measurable benefits.

In previous tDCS studies in patients with MS, using different protocols and electrode montages,[42] the self-reported fatigue and, in particular, its physical aspect also decreased following active tDCS compare to sham. Given the relationship between the perceived MS fatigue and motor performance,[43,44] lowering fatigue may serve to mediate and improve the execution of a sustained motor task or possibly to avoid motor performance exhaustion or disruption.

To date, few studies have sought to characterize any persisting effects following tDCS treatments. Similar to

our findings, these studies have found continuing and durable motor benefits after repeated tDCS treatment on motor outcomes in patients with stroke,[45] cerebellar ataxia,[40] cerebral palsy,[41] and Parkinson's disease.[39] The presence of durable effects may be related to the promotion of neuroplasticity-mediated changes.[11,46]

This was a pilot study with limitations including its relatively small sample size. Our electrode montage placed the anode over the left primary motor cortex (C3) and the cathode over the supraorbital area (Fp2). While anodal stimulation is considered to target the region of interest, there is important consideration for the potential effects of the current delivered through the cathode.[47,48] Therefore, these findings may have reflected, at least in part, the stimulation of multiple brain areas that contributed to the locomotion control maximizing the benefits. To date, the specific motor electrode montages have varied across studies aimed at improving motor performance and symptoms, but the optimal electrode placement is still an aspect that remains to be determined. Even if some studies conceptualized experimental alternative motor electrode montages varying the position of the cathode, evidence is still mixed concerning whether these variations can enhance the neuromodulatory effects.[49,50]

In addition to the electrode montage, dosing parameters for tDCS, such as optimal intensity, timing, and duration of stimulation, still remain largely undefined. As a result, there is a general lack of standardization of the stimulation methodologies and dosing features, making comparison across studies difficult.

Future studies are required to confirm the observed benefits and explore both individual differences in treatment response and comparison on dosing approaches.

Conclusion

Repeated sessions of anodal tDCS over the left M1 cortex paired with aerobic exercise can lead to improvements in gait velocity, step length, and walking endurance in patients with MS. The benefit is cumulative with a strong and persisting effect following treatment. The pairing of tDCS with aerobic physical activity has the potential role for the rehabilitation of walking problems in MS.

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Conflict of Interest

None of the authors disclose any conflict of interest concerning this manuscript.

Author Contributors

CC and MS recruited patients. CC and GP collected data. LK screened and cleared the study participants. MM assessed and cleared study participants' ability to exercise safely. GP, GC, EC, MM, MP, and LC conceptualized and designed the study. GP and LC analyzed and interpreted the data, and drafted the manuscript for intellectual content. All the authors revised the manuscript critically for important intellectual content.

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