Effects of Nonconsecutive Sessions of Transcranial Direct Current Stimulation and Stationary Cycling on Walking Capacity in Individuals With Multiple Sclerosis

Sarvenaz Rahimibarghani, MD; Mohaddeseh Azadvari, MD; Seyede Zahra Emami-Razavi, MD; Mohammad Hossein Harirchian, MD; Shahram Rahimi-Dehgolan, MD; and Hamid R. Fateh, MD

ABSTRACT

BACKGROUND: Exercise has been demonstrated to be safe and well-tolerated in individuals with multiple sclerosis (MS). Physical activity has been shown to enhance the therapeutic effects of transcranial direct current stimulation (tDCS). This study aimed to determine the efficacy of intermittent tDCS combined with riding a stationary bicycle to improve walking capacity in individuals with MS.

METHODS: This double-blind randomized controlled trial enrolled 50 eligible participants. Thirty-nine participants completed the study: 21 in the active group and 18 in the control group. Participants were assigned randomly to exercise on a stationary bike in conjunction with anodal tDCS or to exercise combined with a sham tDCS protocol. Walking capacity tests (2-Minute Walk Test, 5-Meter Walk Test, Timed Up and Go test), manual muscle testing, the Fatigue Severity Scale, and the Multiple Sclerosis Quality of Life–54 were used to determine outcomes.

RESULTS: In terms of observed changes in 2-Minute Walk Test and 5-Meter Walk Test values, the exercise + tDCS group achieved significantly higher posttreatment values than the exercise + sham tDCS group. After the intervention and 1 month later, the intervention group's mean Timed Up and Go test value decreased significantly (P = .002) compared with that of the control group. There was no difference in Fatigue Severity Scale score, Multiple Sclerosis Quality of Life–54 score, or manual muscle testing improvement between the 2 groups.

CONCLUSIONS: Nonconsecutive sessions of anodal tDCS combined with stationary cycling may have a greater effect on the walking capacity of individuals with MS than exercise alone

Int J MS Care. 2022;24(5):202-208. doi:10.7224/1537-2073.2021-004

Multiple sclerosis (MS) is a disease in which the immune system destroys the myelin sheath surrounding axons in the central nervous system. It can result in severe physical disability and psychological complications. Approximately 75% of patients with MS have difficulty walking and are reliant on walking aids and wheelchairs.[1]

Gait issues are regarded as 1 of the most debilitating disorders affecting an individual's personal and professional life.[2] Motor disorders caused by axonal injury are irreversible; however, disability caused by decreased physical activity is reversible.[3,4]

Physical activity and exercise have been shown to be safe and well-tolerated by individuals with MS.[5] In addition, exercise could play a neuroprotective role in this condition.[6] Aerobic activity at low to moderate intensity may improve aerobic capacity, mood, and quality of life (QOL) in patients with mild to moderate MS severity.[7] General guidelines for aerobic exercise training in MS demonstrate that moderate-intensity aerobic exercise 2 to 3 days per week in 10- to 40-minute bouts is more effective than 5 days per week of higher-intensity exercise, which is recommended for advanced aerobic exercise training only.[8] Apart from the necessity of scheduling sessions and intensities appropriately, research indicates that intermittent training causes less fatigue, is much more tolerable, and is preferable to continuous physical activity.[9,10]

Aerobic training can include treadmill exercises, leg ergometry, aquatic therapy, or yoga. As a combination of resistance and aerobic exercises and a repetitive activity, cycling can effectively improve function in patients with MS.[11] Repeated movements increase excitability in the primary motor cortex at the neural

From the Physical Medicine and Rehabilitation Department (SR, MA, SZE-R, SR-D, HRF) and the Iranian Center of Neurological Research, Neuroscience Institute (MHH), Tehran University of Medical Sciences, Tehran, Iran. *Correspondence*: Mohaddeseh Azadvari, MD, Tehran University of Medical Sciences, MS Research Center, Sina Hospital, Hassan Abad Sq, PO Box: 1136746911, Tehran, Iran; email: drazadvari@yahoo.com.

Note: Supplementary material for this article is available at IJMSC.org.

level.[12] Furthermore, cycling, similar to walking, results in significant cortical activation.[13]

Motor function rehabilitation is a critical component of MS management that is facilitated by neuroplasticity, the brain's capacity to adapt to injury or disability.[14]

Plasticity seems to mitigate the clinical consequences of central nervous system damage by establishing brain activity patterns and appropriately reorganizing those altered patterns, resulting in improvements in motor performance with practice.[15] Transcranial direct current stimulation (tDCS) modifies synaptic plasticity by altering cortical excitability.[16]

As a type of neuromodulation, tDCS transmits a weak electrical current through the scalp and changes the cortical excitability in the targeted brain area. The electrical current alters the resting membrane potential of nerve cells. Based on the electrode's nature, it increases (anode) or reduces (cathode) the nerve cell's electrical discharge.[17] Anodal tDCS has been shown to increase corticospinal excitability, making it a promising tool for inducing neuroplastic changes.[18] In addition, it is recommended for neurologic rehabilitation as an inexpensive, noninvasive, and safe method.[19]

Previous studies have evaluated the effect of tDCS on gait improvement in MS,[20-23] although they used tDCS for a limited number of consecutive sessions. The purpose of this study was to determine whether 6 weeks of tDCS combined with nonconsecutive cycling sessions improved the walking capacity of individuals with MS.

METHODS

Study Population

From June 2018 to December 2019, this double-blind randomized controlled trial was conducted at the Department of Physical Medicine and Rehabilitation, Tehran University of Medical Sciences. Fifty-seven patients were recruited and diagnosed by an attending neurologist (M.H.H.) using the McDonald diagnostic criteria. Participants were aged 18 to 48 years and had a mild to moderate level of physical disability as measured by the Expanded Disability Status Scale (score >4-6).[24] They had not experienced a relapse in the past 30 days and had a slight increase in muscle tone according to the modified Ashworth scale (score ≤1).[25] Exclusion criteria included severe illness, inability to walk, pregnancy, the use of neuromuscular electrical stimulation or other physiotherapy or occupational therapy methods, underlying conditions that impaired motor function, and missing consecutive sessions. Before the intervention, all research circumstances were described in detail to the participants, and written consent was obtained. The study protocol was approved by the Tehran University of Medical Sciences Ethics Committee.

Interventions

Using the block randomization method, 50 eligible participants were randomly assigned to 1 of 2 groups. Both groups engaged in aerobic exercise on a stationary bicycle (Technogym; Technogym USA Corp) with a load of 30 W/min and moderate-intensity activity as determined by the talk test, indicating that the patients were unable to sing during the activity. Twelve sessions over 6 weeks were scheduled (2 nonconsecutive sessions per week). Sessions lasted approximately 40 minutes and included 10 minutes of cycling followed by 5 minutes of rest. The treatment group received electrical stimulation via 2 sponge surface electrodes (4 × 4 cm [active] and 4 × 9 cm [reference] soaked in 10 mL of sodium chloride) via a 2-channel tDCS device (Neurostim-2, Medina Teb).

The anode electrode was placed in the motor cortex area (C_3) on the dominant hemisphere based on the International 10–20 system. On the opposite shoulder, the cathode was placed extracephalically.[26] In contrast to previous studies that placed the cathode electrode over Fp2, this study placed the cathode on the shoulder, avoiding the cathode-induced decrease in excitability of the right prefrontal cortex.

The current was gradually increased over 30 seconds to 1.5 mA and then was maintained for 20 minutes; the stimulus was gradually decreased over a similar period. The same setup was used in the sham group, but no current was delivered between the rise and fall times.

Measurements

Primary Outcomes

Three methods were used to assess patients' ambulation: the Timed Up and Go (TUG) test, the 2-Minute Walk Test (2MWT), and the 5-Meter Walk Test (5MWT). In the TUG test, the time begins when a patient rises from a chair and ends when the patient sits down after a 3-m walk. The TUG test is an excellent tool for assessing mobility, monitoring disease progression, and identifying fall risk in patients with MS.[27]

In the 2MWT, the patient is instructed to walk as fast as possible for 2 minutes in a 30-m-long straight corridor. Evidence suggests that the 2MWT can be used instead of the 6-Minute Walk Test in routine clinical evaluations of individuals with MS (decreased time and burden associated with regular visits).[28]

In the 5MWT the patient is timed while walking 5 m. This test was developed to determine a person's walking speed. Recent research compared a patient's results on a 5MWT and a 10MWT with the same acceleration and deceleration distance, and the results indicated that there was no significant difference in walking speed.[29]

The 2MWT and the TUG test are both valid and reliable measures of walking capacity and overall mobility in individuals with mild MS.[30]

TABLE 1. Demographic and Baseline Characteristics (Preintervention)

Characteristic	TE group (n = 21)	E group (n = 18)	*P* value
Sex, No (%)			
Female	13 (61.9)	11 (61.1)	.55
Male	8 (38.1)	7 (38.9)	
Age, mean ± SD, y	40.0 ± 7.1	39.8 ± 6.6	.93
EDSS score, mean ± SD	4.76 ± 0.77	4.76 ± 0.88	.99
Type of MS, No. (%)			
PPMS	6 (28.6)	10 (55.6)	.12
RRMS	3 (14.3)	4 (22.2)	
SPMS	12 (57.1)	4 (22.2)	
Manual muscle testing, No. (%)			
No weakness	1 (4.8)	1 (5.6)	.84
Proximal weakness[a]	9 (42.8)	5 (27.8)	
Proximal and distal weakness[a]	11 (52.4)	12 (66.7)	
2MWT, mean ± SD, m	58.21 ± 3.40	56.52 ± 4.07	.75
5MWT, mean ± SD, s	8.63 ± 0.80	9.60 ± 1.24	.51
TUG test, mean ± SD, s	15.84 ± 1.75	14.93 ± 1.56	.70
FSS score, mean ± SD	46.24 ± 8.1	43.96 ± 10.1	.38
MSQOL-54 physical health composite score, mean ± SD	50.16 ± 2.20	46.39 ± 2.30	.25
MSQOL-54 mental health composite score, mean ± SD	44.40 ± 2.90	45.35 ± 2.20	.83
MS duration, mean ± SD, y	11.72 ± 3.70	9.32 ± 4.1	.41

2MWT, 2-Minute Walk Test; 5MWT, 5-Meter Walk Test; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; MS, multiple sclerosis; MSQOL-54, Multiple Sclerosis Quality of Life–54; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS; TUG, Timed Up and Go.
[a]Proximal muscles: hip (flexors, extensors, adductors, abductors), knee (extensors and flexors); distal muscles: ankle dorsiflexors, plantar flexors (manual muscle test ≤4).

Secondary Outcomes

Manual muscle testing was scored on a scale from 0 (inability to move muscles) to 5 (overcoming the maximum resistance). The resident assessed the strength of the lower extremity's proximal and distal muscles. Proximal muscles are those in the hip (flexors, extensors, adductors, abductors) and knee (extensors, flexors), and distal muscles are the ankle dorsiflexors and the plantar flexors. Clinical strength assessment is reliable and valid for individuals with MS and may assist clinicians in tracking changes over time.[31]

The Fatigue Severity Scale (FSS) was translated into Persian and validated. It consists of 9 statements describing fatigue symptoms. A low score indicates less fatigue, whereas a high score indicates more severe fatigue.[32]

The Multiple Sclerosis Quality of Life–54 (MSQOL-54) asks 52 questions about health perception and satisfaction that are divided into 12 multi-item subscales and 2 single-item subscales: physical function, role limitation due to physical problems, role limitation due to mental problems, social function, stress about one's health, sexual function, satisfaction with sexual function, pain, energy, health perception, overall QOL, health changes, cognitive function, and mental well-being.[33] All parameters were assessed before the interventions, after the final intervention, and 1 month after the final intervention session.

Randomization and Blinding

Patients were assigned by block randomization to 1 of 2 groups: exercise combined with anodal tDCS (TE group) or exercise combined with sham tDCS (E group). Random allocation software was used to determine the patient distribution. The randomization process was performed by an independent researcher (H.R.F.) who had no contact with the patients. The participants, the researcher who evaluated them, and the intervention technician were all masked to the protocol assignment. At the conclusion of the study, blinding integrity was

TABLE 2. Comparison of the Groups in Terms of Mean Differences in 2MWT, 5MWT, and TUG Test Outcomes

Outcome	TE group	E group	*P* value	Cohen *d*
2MWT, mean ± SD, m				
Preintervention	58.21 ± 3.40	56.52 ± 4.07	.75	
Postintervention	68.83 ± 5.90	62.57 ± 5.67		
Relative change, %[c]	23.2	8.3	.02[ab]	0.72
P value[d]	.003[b]	.12		
Follow-up (4 wk)	61.2 ± 5.20	55.29 ± 4.01		
Relative change, %[c]	13.8	−2.3	.002[ab]	1.11
P value[d]	.002[b]	.73		
5MWT, mean ± SD, s				
Preintervention	8.63 ± 0.80	9.60 ± 1.24	.516	
Postintervention	7.36 ± 0.60	8.97 ± 1.04		
Relative change, %[c]	−13.6	−6.7	.08[e]	0.48
P value[d]	.002[b]	.03[b]		
Follow-up (4 wk)	8.21 ± 0.60	9.61 ± 1.34		
Relative change, %[c]	−8.9	3.3	.001[be]	0.45
P value[d]	.15	.90		
TUG test, mean ± SD, s				
Preintervention	15.84 ± 1.75	14.93 ± 1.56	.701	
Postintervention	12.72 ± 1.05	13.52 ± 1.16		
Relative change, %[c]	−16.9	−8.5	.02[ab]	0.58
P value[d]	.001[b]	.002[b]		
Follow-up (4 wk)	14.23 ± 1.45	14.45 ± 1.36		
Relative change, %[c]	−9.6	−3.4	.002[ab]	0.90
P value[d]	.002[b]	.03[b]		

2MWT, 2-Minute Walk Test; 5MWT, 5-Meter Walk Test; MD, mean difference; TUG, Timed Up and Go.

[a]Between-group analysis *t* test.

[b]Statistically significant.

[c]Calculated as ([Baseline – After Month] / Baseline) * 100.

[d]Within-group comparison using repeated-measures analysis.

[e]Mann-Whitney *U* test.

established by documenting patients' perceptions of their treatment group.

Safety and Adverse Events

There were no significant adverse events associated with tDCS, although some participants experienced a brief tingling sensation.

Statistics

A statistical software program (Stata 14; Stata Corp) was used for statistical analysis. In all statistical analyses, $P < .05$ was considered significant. Demographic and baseline variables are shown as mean ± SD, and order variables are given as number (percentage). The data were analyzed using modified intention-to-treat and a subset of full intention-to-treat; only individuals with data loss at a specific time point were excluded from statistical analysis. The Shapiro-Wilk test was used to assess the normality of the data. If the normality hypothesis was met, the available items were analyzed using repeated analysis of variance; otherwise, the Friedman test was used. A *t* test was used when the variables had a normal distribution; otherwise, the Mann-Whitney *U* test was used.

RESULTS

Of 57 participants assessed for eligibility, 5 did not meet the inclusion criteria and 2 declined to participate. The study enrolled 50 individuals to receive the intervention. Twenty-five patients were scheduled for tDCS plus exercise (TE group) and 25 for a control exercise program (E group). Three patients in the TE group and 4 in the E group did not complete the sessions due to a new relapse, an ankle sprain at work, or personal issues. One patient in the TE group did not return for the fourth follow-up week, and 3 patients in the E group refused to be reexamined. Thus, only 21 participants in the TE group and 18 in the E group completed the final follow-up (**FIGURE S1,** which is published in the online version of this article at IJMSC.org). The demographic characteristics and baseline clinical variables in both groups are summarized in **TABLE 1**.

Both groups shared similar characteristics regarding sex, age, clinical type of MS (relapsing-remitting,

primary progressive, or secondary progressive), disease duration, disability level, and muscle strength. There were no significant differences in the mean pretreatment MSQOL-54, TUG test, FSS, 2MWT, and 5MWT scores between the 2 groups (Table 1).

The 2MWT distance improved in both groups after the intervention (**TABLE 2**). At the first follow-up visit there was a 23.2% change (P = .003) in the TE group vs an 8.3% change (P = .12) in the E group. At the second follow-up visit the E group changed to −2.3% (P = .73). In week 4, the TE group maintained a significant improvement (13.8%; P = .002) compared with baseline. As expected, all changes were significantly greater in the TE group than in the control group, as indicated by Cohen d values of 0.72 (P = .02) and 1.11 (P = .002), respectively, for the first and second follow-up visits. Both groups demonstrated a statistically significant decrease in 5MWT time (relative to baseline: change of −13.6% in the TE group and −6.7% in the E group). However, the difference between the 2 groups was not significant (P = .08).

Clinical improvement in the TE group reached changes of −8.9% compared to baseline at the second follow-up visit; and there was no significant improvement (P = .15). In group E, an inverse trend was observed, and participants had higher 5MWT scores than at baseline (3.3%; P = .90). After 1 month, the TE intervention was significantly superior to the control (P = .001). As a result, we can conclude that the TE intervention was more effective at both time points (Cohen d = 0.48 for the first follow-up and 0.45 for the second follow-up). The TUG test time was significantly better in the TE group than in the E group (−16.9% vs −8.5%), with a Cohen d of 0.58 and a P = .02 difference between the 2 groups. One month after the initial results, the improvement trajectory remained significant in the TE and E groups (changes of −9.6% and −3.4%, respectively). Within-group improvements were also statistically significant; the TE intervention was superior (Cohen d = 0.90; P = .002). Finally, both groups had minor improvements in baseline FSS and MSQOL-54 scores after the sessions and 1 month later (**TABLE S1**).

The manual muscle test did not significantly improve (<5% within groups). Postintervention and 4-week follow-ups are depicted in **FIGURE S2**.

DISCUSSION

Multiple sclerosis is becoming more prevalent in Iran. Most people with MS are aged 20 to 50 years, and nearly two-thirds of them experience walking difficulties within 10 years of diagnosis.[34] The development of various rehabilitation techniques to reduce gait disturbance could be considered a critical public health priority. The purpose of this study was to evaluate the therapeutic effects of intermittent exercise alone and combined with electrical stimulation delivered via a 2-channel tDCS device and ensure that efficacy remained stable during a 1-month follow-up period. Current research has successfully demonstrated an increase in walking capacity (2MWT, 5MWT, TUG test). However, combined therapy did not outperform exercise alone in terms of fatigue, muscle strength, or QOL.

In the present trial, combining tDCS and exercise resulted in a more significant improvement in 2MWT, TUG test, and 5MWT values compared with exercise alone. Within 1 month of follow-up, this improvement remained relatively consistent. The present findings corroborate a recent study that suggested that combining multiple sessions of tDCS with exercise training can enhance the benefits of physical activity.[23] The major difference is that the present study focused on consecutive sessions over a shorter period vs nonconsecutive sessions over a more extended period.

Among the walking speed parameters, the 2MWT showed the most significant improvement. From the patient's and therapist's perspectives, the clinically significant values for the 2MWT were 9.6 m and 6.8 m, respectively (P < .05).[35] In the present study, the TE group showed a clinical improvement of 10.6 m.

Although a valid and reliable test in the MS population, the TUG test results in this study are insufficiently sensitive to detect clinically significant changes after rehabilitation.[36] In addition, there was little agreement among other studies regarding minimally important improvements to the 10MWT and 5MWT.[37]

Most patients reported only minor changes in QOL after the intervention. Most participants had mild to moderate disability: they were able to perform most activities independently but with some difficulty. This implies that rehabilitation affects the QOL of more severely disabled patients, particularly the mental QOL associated with emotional difficulties in daily life.[38] Although anodal tDCS stimulation of the primary motor cortex and the dorsolateral prefrontal cortex (DLPFC) both improve QOL, the effect of DLPFC stimulation is superior to that of primary motor cortex stimulation.[39]

Although previous research has demonstrated improved FSS scores after tDCS application, there were no significant differences between the present study groups. Previously published studies used different montages, such as the DLPFC, or compound montages that included primary motor cortex, DLPFC, and bilateral cortical stimulation.[39-41] This could account for the improvement in fatigue score. In addition, fatigue-related MS is a multifaceted condition characterized by physical, cognitive, and psychosocial fatigue. The FSS, on the other hand, is a 1-dimensional questionnaire that assesses the severity of fatigue rather than the nature of the involvement.[42]

In the present study, the difference in muscle strength between the 2 groups was relatively similar. However, there is evidence to support the use of clinical strength assessment in the MS population,[31] as specific

PRACTICE POINTS

- Transcranial direct current stimulation (tDCS) is a low-cost, noninvasive neuromodulation technique. Multiple sessions of anodal tDCS over the primary motor cortex area may be a complementary approach to improving walking speed in patients with multiple sclerosis.
- The combination of tDCS and exercise on a stationary bicycle resulted in a more significant improvement in performance on the 2-Minute Walk Test than exercise alone.
- Adding brain stimulation to exercise may result in greater benefits for patients with multiple sclerosis.

instruments, such as isokinetic dynamometers, can precisely measure mechanical muscle function.[43] Most studies demonstrate that tDCS affects muscle strength by using such objective tools.[44]

As previously stated, the walking speed parameters improved after the intervention. Electrical stimulation of the frontal and parietal cortex can generally increase walking speed, as suggested previously.[45] Most trials have demonstrated that tDCS has both immediate and long-term beneficial effects on motor function.[46] However, the magnitude of the effect may be influenced by many technical variants, including differences in current densities, electrode sizes, and extracephalic montage for the reference electrode.

One possible explanation for the present study's improvement in walking speed is that anodal stimulation was applied over the primary motor cortex and the cathode electrode was placed on the shoulder. By avoiding the cathodal counter effect on the right prefrontal cortex, this montage increased cortical excitability.[26] In addition, receiving transcranial electrical stimulation simultaneously with training can enhance the effect of exercise and improve functional ambulation.

The present study's strength is that it examines an affordable combination therapy for rehabilitating patients with MS who have difficulty walking. Moreover, scheduling the sessions in nonconsecutive order and extending them to 6 weeks was feasible and tolerable. As a result, patient compliance was increased, and they were motivated to adhere to protocols on a consistent and prolonged basis.

Limitations of the Study

This study had several limitations. One limitation of any study of MS is the disease's dynamic nature, which can be influenced by various factors, including changes in mood, temperature, and seasonal climate. Another limitation is the high cost of the objective tests used to analyze movement. Finally, the use of more precise parameters or larger sample sizes could have resulted in more accurate data. Long-term follow-up is necessary to determine the persistence of the effects of such interventions.

Conclusions

Intermittent use of tDCS and exercise programs can improve the walking speed of individuals with MS. Both interventions seem to have comparable effects on muscle strength, fatigue, and overall QOL. The effectiveness of advanced neuromodulation technology shows that it can improve rehabilitation benefits. □

ACKNOWLEDGMENTS: We appreciate the cooperation of the Tehran University of Medical Sciences hospital staff and express our gratitude to the study participants and our technician, who treated the patients with dignity and respect. Our special thanks go to Dr Maryam Barangi.

FINANCIAL DISCLOSURES: The authors have disclosed no relevant financial relationships.

FUNDING/SUPPORT: None.

REFERENCES

1. Blake DJ, Bodine C. An overview of assistive technology for persons with multiple sclerosis. *J Rehabil Res Dev*. 2002;39(2):299-312.
2. Stevens V, Goodman K, Rough K, Kraft GH. Gait impairment and optimizing mobility in multiple sclerosis. *Phys Med Rehabil Clin N Am*. 2013;24(4):573-592. doi:10.1016/j.pmr.2013.07.002
3. Ghasemi N, Razavi S, Nikzad E. Multiple sclerosis: pathogenesis, symptoms, diagnoses and cell-based therapy. *Cell J*. 2017;19(1):1-10. doi:10.22074/cellj.2016.4867
4. Oh J, Vidal-Jordana A, Montalban X. Multiple sclerosis: clinical aspects. *Curr Opin Neurol*. 2018;31(6):752-759. doi:10.1097/WCO.0000000000000622
5. Dalgas U. Exercise therapy in multiple sclerosis and its effects on function and the brain. *Neurodegener Dis Manag*. 2017;7(6s):35-40. doi:10.2217/nmt-2017-0040
6. Ochi H. Sports and physical exercise in multiple sclerosis. *Brain Nerve*. 2019;71(2):143-152. doi:10.11477/mf.1416201233
7. Alphonsus KB, Su Y, D'Arcy C. The effect of exercise, yoga and physiotherapy on the quality of life of people with multiple sclerosis: systematic review and meta-analysis. *Complement Ther Med*. 2019;43:188-195. doi:10.1016/j.ctim.2019.02.010
8. Kim Y, Lai B, Mehta T, et al. Exercise training guidelines for multiple sclerosis, stroke, and Parkinson disease: rapid review and synthesis. *Am J Phys Med Rehabil*. 2019;98(7):613-621. doi:10.1097/PHM.0000000000001174
9. Karpatkin H, Rzetelny A. Effect of a single bout of intermittent versus continuous walking on perceptions of fatigue in people with multiple sclerosis. *Int J MS Care*. 2012;14(3):124-131. doi:10.7224/1537-2073-14.3.124
10. Halabchi F, Alizadeh Z, Sahraian MA, Abolhasani M. Exercise prescription for patients with multiple sclerosis; potential benefits and practical recommendations. *BMC Neurol*. 2017;17(1):185. doi:10.1186/s12883-017-0960-9
11. Hochman L. *Effects of Functional Electrical Stimulation Cycling versus Cycling Only on Walking Performance and Quality of Life in Individuals with Multiple Sclerosis: A Randomized, Clinical Pilot Study*. Dissertation. Nova Southeastern University; 2017.
12. Patel V, Craig J, Schumacher M, Burns MK, Florescu I, Vinjamuri R. Synergy repetition training versus task repetition training in acquiring new skill. *Front Bioeng Biotechnol*. 2017;5:9. doi:10.3389/fbioe.2017.00009

13. Storzer L, Butz M, Hirschmann J, et al. Bicycling and walking are associated with different cortical oscillatory dynamics. *Front Hum Neurosci*. 2016;10:61. doi:10.3389/fnhum.2016.00061
14. Lipp I, Tomassini V. Neuroplasticity and motor rehabilitation in multiple sclerosis. *Front Neurol*. 2015;6:59. doi:10.3389/fneur.2015.00059
15. Tomassini V, Matthews PM, Thompson AJ, et al. Neuroplasticity and functional recovery in multiple sclerosis. *Nat Rev Neurol*. 2012;8(11):635-646. doi:10.1038 /nrneurol.2012.179
16. Stagg, CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. *Neuroscientist*. 2011;17(1):37-53. doi:10.1177/1073858410386614
17. Niérat MC, Similowski T, Lamy JC. Does trans-spinal direct current stimulation alter phrenic motoneurons and respiratory neuromechanical outputs in humans? a double-blind, sham-controlled, randomized, crossover study. *J Neurosci*. 2014;34(43):14420-14429. doi:10.1523 /JNEUROSCI.1288-14.2014
18. Nitsche MA, Doemkes S, Karaköse T, et al. Shaping the effects of transcranial direct current stimulation of the human motor cortex. *J Neurophysiol*. 2007;97(4):3109-3117. doi:10.1152 /jn.01312.2006
19. Mortezanejad M, Ehsani F, Masoudian N, Zoghi M, Jaberzadeh S. Comparing the effects of multi-session anodal trans-cranial direct current stimulation of primary motor and dorsolateral prefrontal cortices on fatigue and quality of life in patients with multiple sclerosis: a double-blind, randomized, sham-controlled trial. *Clin Rehabil*. 2020;34(8):1103-1111. doi:10.1177 /0269215520921506
20. Workman CD, Kamholz J, Rudroff T. Transcranial direct current stimulation (tDCS) to improve gait in multiple sclerosis: a timing window comparison. *Front Hum Neurosci*. 2019;13:420. doi:10.3389/fnhum.2019.00420
21. Oveisgharan S, Karimi Z, Abdi S, Sikaroodi H. The use of brain stimulation in the rehabilitation of walking disability in patients with multiple sclerosis: a randomized double-blind clinical trial study. *Iran J Neurol*. 2019;18(2):57-63.
22. Pilloni G, Choi C, Coghe G, et al. Gait and functional mobility in multiple sclerosis: immediate effects of transcranial direct current stimulation (tDCS) paired with aerobic exercise. *Front Neurol*. 2020;11:310. doi:10.3389 /fneur.2020.00310
23. Pilloni G, Choi C, Shaw MT, et al. Walking in multiple sclerosis improves with tDCS: a randomized, double-blind, sham-controlled study. *Ann Clin Transl Neurol*. 2020;7(11):2310-2319. doi:10.1002/acn3.51224
24. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33(11):1444-1452. doi:10.1212 /wnl.33.11.1444
25. Bohannon R, Smith M. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther*. 1987;67(2):206-207. doi:10.1093/ptj/67.2.206
26. Angius L, Pageaux B, Hopker J, Marcora SM, Mauger AR. Transcranial direct current stimulation improves isometric time to exhaustion of the knee extensors. *Neuroscience*. 2016;339:363-375. doi:10.1016/j .neuroscience.2016.10.028
27. Kalron A, Dolev M, Givon U. Further construct validity of the timed up-and-go test as a measure of ambulation in multiple sclerosis patients. *Eur J Phys Rehabil Med*. 2017;53(6):841-847. doi:10.23736/S1973-9087.17.04599-3
28. Gijbels D, Eijnde BO, Feys P. Comparison of the 2- and 6-minute walk test in multiple sclerosis. *Mult Scler*. 2011;17(10):1269-1272. doi:10.1177/1352458511408475
29. Ng SS, Au KK, Chan EL, et al. Effect of acceleration and deceleration distance on the walking speed of people with chronic stroke. *J Rehabil Med*. 2016;48(8):666-670. doi:10.2340 /16501977-2124
30. Valet M, Lejeune T, Devis M, van Pesch V, El Sankari S, Stoquart G. Timed up-and-go and 2-minute walk test in patients with multiple sclerosis with mild disability: reliability, responsiveness, and link with perceived fatigue. *Eur J Phys Rehabil Med*. 2019;55(4):450-455. doi:10.23736/S1973-9087.18.05366-2
31. Mañago MM, Hebert JR, Schenkman M. Psychometric properties of a clinical strength assessment protocol in people with multiple sclerosis. *Int J MS Care*. 2017;19(5):253-262. doi:10.7224/1537-2073.2016-078
32. Shahvaroughi-Farahani A, A'zimiyan M, Fallah-Pour M, Karimlou M. Fatigue severity scale (FSS): evaluation of reliability of the Persian version among persons with multiple sclerosis. *J Rehab*. 2010;10(4). http://rehabilitationj.uswr .ac.ir/article-1-422-en.html
33. Masoodi R, Mohammadi E, Nabavi S, Ahmadi F. The effect of Orem-based self-care program on physical quality of life in multiple sclerosis patients. *J Shahrekord Univ Med Sci*. 2008;10(2):21-29. http://78.39.35.44/article-1-5-en .html
34. Sahraian MA, Sahebkar M, Dehghani R, Derakhshan-Jazari M, Kazami-Moghaddam V, Kouchaki E. Multiple sclerosis—a disease on a dramatically rising trend in Iran: review of possible reasons. *Iran J Neurol*. 2017;16(1):34-40.
35. Baert I, Freeman J, Smedal T, et al. Responsiveness and clinically meaningful improvement, according to disability level, of five walking measures after rehabilitation in multiple sclerosis: a European multicenter study. *Neurorehabil Neural Repair*. 2014;28(7):621-631.
36. Baert I, Smedal T, Kalron A, et al. Responsiveness and meaningful improvement of mobility measures following MS rehabilitation. *Neurology*. 2018;91(20):e1880-e1892. doi:10.1212/WNL .0000000000006532
37. Kieseier BC, Pozzilli C. Assessing walking disability in multiple sclerosis. *Mult Scler*. 2012;18(7):914-924. doi:10.1177/1352458512444498
38. Fanciullacci C, Straudi S, Basaglia N, Chisari C. The role of psychological well-being in multiple sclerosis rehabilitation. *Eur J Phys Rehabil Med*. 2017;53(1):105-113. doi:10.23736 /S1973-9087.16.04158-7
39. Mortezanejad M, Ehsani F, Masoudian N, Zoghi M, Jaberzadeh S. Comparing the effects of multi-session anodal trans-cranial direct current stimulation of primary motor and dorsolateral prefrontal cortices on fatigue and quality of life in patients with multiple sclerosis: a double-blind, randomized, sham-controlled trial. *Clin Rehabil*. 2020;34(8):1103-1111. doi:10.1177 /0269215520921506
40. Charvet LE, Dobbs B, Shaw MT, Bikson M, Datta A, Krupp LB. Remotely supervised transcranial direct current stimulation for the treatment of fatigue in multiple sclerosis: results from a randomized, sham-controlled trial. *Mult Scler*. 2018;24(13):1760-1769. doi:10.1177 /1352458517732842
41. Chalah MA, Grigorescu C, Padberg F, Kümpfel T, Palm U, Ayache SS. Bifrontal transcranial direct current stimulation modulates fatigue in multiple sclerosis: a randomized sham-controlled study. *J Neural Transm (Vienna)*. 2020;127(6):953-961. doi:10.1007/s00702-020-02166-2
42. Beckerman H, Eijssen IC, van Meeteren J, et al. Fatigue profiles in patients with multiple sclerosis are based on severity of fatigue and not on dimensions of fatigue. *Sci Rep*. 2020;10(1):4167. doi:10.1038/s41598-020-61076-1
43. Jørgensen M, Dalgas U, Wens I, Hvid LG. Muscle strength and power in persons with multiple sclerosis: a systematic review and meta-analysis. *J Neurol Sci*. 2017;376:225-241. doi:10.1016/j.jns.2017.03.022
44. Machado, S. Jansen P, Almeida V, Veldema J. Is tDCS an adjunct ergogenic resource for improving muscular strength and endurance performance? a systematic review. *Front Psychol*. 2019;10:1127. doi:10.3389/fpsyg.2019.01127
45. Jor'dan, AJ, Poole VN, Iloputaife, I, et al. Executive network activation is linked to walking speed in older adults: functional MRI and TCD ultrasound evidence from the MOBILIZE Boston study. *J Gerontol A Biol Sci Med Sci*. 2017;72(12):1669-1675. doi:10.1093/gerona/glx063
46. Brunoni AR, Fregni F, Pagano RL. Translational research in transcranial direct current stimulation (tDCS): a systematic review of studies in animals. *Rev Neurosci*. 2011;22(4):471-481. doi:10.1515/RNS.2011.042