Research Paper

The Combination of Transcranial Direct Current Stimulation and Virtual Reality Training on Fatigue, Balance and Walking in Patients With Multiple Sclerosis

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ABSTRACT

Purpose: Fatigue, imbalance, and walking disorder were commonly observed in patients with multiple sclerosis (MS) as debilitating symptoms. Therefore, the present study aims to examine the effect of transcranial direct current stimulation (tDCS) separately and in combination with virtual reality (VR) training on fatigue, balance, and walking (speed and stride length) in patients with MS.

Methods: The present clinical trial research was conducted with 30 MS patients aged 18-55 years (including 21 women and 9 men). The random assignment of subjects was assessed into one of three groups, tDCS group, VR group, and combined tDCS-VR training group. In the tDCS group, the M1 motor cortex was stimulated by direct electrical current in five sessions, and VR training patients participated in the VR program for six sessions. In the combination intervention, participants were delivered tDCS before each VR session. Fatigue severity scale (FSS), Berg balance scale (BBS), and 25-foot walk test (T25-FW) were used to evaluate the fatigue, balance, and walking speed respectively as pre and post-tests. Statistical analysis of covariance (ANCOVA) was used to compare the results between the three groups.

Results: Our results showed a significant effect of tDCS, VR, and tDCS-VR on fatigue and a significant effect of VR and tDCS-VR on balance and walking speed in patients with MS (P<0.05). In comparing the different interventions performed on the effect on fatigue and balance and walking speed, the improvements were significant in VR and tDCS-VR groups compared to the tDCS group (P<0.05); however, the difference was not significant between VR and tDCS-VR groups (P>0.05).

Conclusion: Despite the positive effect of fatigue, we found VR and tDCS-VR to be a more effective method for treating balance and walking of the patient. The combination effect of tDCS with VR therapy, should be investigated further.

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Highlights

• Walking and balance in multiple sclerosis (MS) patients were improved by virtual reality (VR) training separately and in combination with transcranial direct current stimulation (tDCS).

• In comparing VR training and tDCS combined with VR training, our results showed no significant difference; however, the effect of tDCS combined with VR training should be investigated further.

Plain Language Summary

MS is one of the common non-traumatic brain injuries in young adults characterized by heterogeneous neurological symptoms, including sensory, motor, emotional-behavioral, and cognitive symptoms. Regarding insufficient and limited effects of drug therapy in MS, novel intervention methods, includin tDCS and VR should be considered. The current study was conducted to evaluate the effect of VR training in combination and separately with tDCS on fatigue, balance, and walking disorders in MS patients. Our results showed improvement in fatigue after all interventions and in balance and walking only after VR and tDCS-VR training. VR training separately and in combination with tDCS had a better effect than tDCS, but the difference was not significant between VR training and tDCS combined with VR training.

Introduction

Multiple sclerosis (MS) is a chronic and degenerative neurological disease, with myelin sheath damage in the central nervous system (CNS) [1]. Pathological features of the disease, such as inflammation, demyelination, and destruction of neurons differently appear [2]. The most common non-traumatic CNS injury in young adults with an average age of 20-40 years is MS [3]. The clinical course of the disease is heterogeneous, including mild neurological symptoms to progressive and debilitating forms [3]. Due to the demyelination, patients experience simple or multiple sensory, motor, emotional-behavioral, and cognitive symptoms [4], depending on the location of the lesions [5]. Common symptoms of the disease include muscle weakness, spasticity, fatigue, sensory dysfunctions, balance problems, cognitive disorders, and difficulty in walking [6] Symptoms significantly affect a patient's social communication, quality of life, job, and performance [7].

Fatigue, as one of the common and debilitating symptoms [8], affects about 80% of patients at different stages of the disease [9]. It reduces cognitive and functional abilities, associated with increased need for rest and decreased motivation [10]. Primary and secondary progressive stages of the disease showed more fatigue symptoms compared to relapsing-remitting MS [4]. The pathophysiology of fatigue in MS is not known [11], but it occurs as a result of brain dysfunction (primary fatigue) or following symptoms during the disease (secondary fatigue) [12]. Primary fatigue results from the pathophysiological process of the disease itself, and also secondary fatigue is caused by the complications of the disease, such as endocrine disorders, infections, lack of vitamins, and anemia [8, 10]. People with MS can have limitations in daily activities due to muscle weakness, spasticity, and imbalance. Therefore, it has a bad effect on walking and increases the risk of falling. More than spasticity in MS people, it prevents functional activities, such as moving, which increases disability. Therefore, fatigue has a negative effective (mentally and physically) life and the ability to work in patients with MS by limiting daily activities and coping abilities [13, 14].

Imbalance is one of the primary symptoms of MS associated with an increased risk of falling [15, 16]. Reduced functional capacity, muscle weakness, fatigue, and spasms, which are common symptoms in these patients, may lead to inappropriate balance [17, 18]. This debilitating symptom has been reported in 75% of patients, which can reduce the mobility and independence of the affected person and ultimately affect his/her quality of life [19]. Balance problems occur at the beginning of the disease and usually increase with the progress of the disease [20].

Walking disorder is also commonly seen in MS patients and is described as the most challenging symptom by 70% of patients [21, 22]. The patterns of walking disorders that are reflected as asymmetry and coordination dysfunction in patients reduce walking speed and

increase energy consumption [23]. Walking disorders appear in different ways, including decreasing the length of the step, reducing the speed, and increasing the width of the step [24]. Walking and balance problems lead to an increase in falling risk, activity limitation, and isolation, which are worsened by the progression of the disease [25].

Pharmacological treatment controls the symptoms and consequences of the disease, but the results are not clinically satisfactory. Alternative therapies have introduced to relieve existing symptoms and to prevent complications of MS [26].

Exercise training and behavioral therapy are both useful for patients with mild disease symptoms [1]. In recent years, in addition to physical exercises, the number of studies on the effectiveness of other non-drug methods, including non-invasive brain stimulation techniques, has increased. One of these effective methods is transcranial direct current electrical stimulation (tDCS), which is easy to use, and is considered a cheap and non-invasive tool for the motor rehabilitation of patients [6, 25]. tDCS produces a low-amplitude direct current that can change cortical excitability without harmful side effects [2, 8]. Stimulation with anodic direct current increases the resting potential of the neuronal membrane, while with cathode current resting potential [26].

tDCS is widely used in the rehabilitation of various neurological diseases, such as stroke, Parkinson's disease, and MS [27]. Navarra-Lopez et al. in their systematic review reported that tDCS along with physical therapy can improve the walking parameters, static and dynamic balance, and lower limb function in stroke [28]. Another study conducted on people with Parkinson's disease in 2020 showed that one session of bilateral and electrical stimulation of the cerebellum can significantly improve balance performance [29].

Among other techniques in rehabilitation, virtual reality (VR), focusing on neural augmentation and motor learning is an effective method that can be used as an alternative to traditional rehabilitation in MS patients [1]. VR provides the user with an alternative and favorable simulation of activity or environment that permits interaction through multiple sensory systems [30]. The environment contains various stimulation which produces a potent signal to reorganize sensorimotor circuits which can affect the motor cortex during motor learning [31]. By the way, repeated and purposeful observation of activities can influence cortico-cortical interactions in the premotor and motor areas [32]. Therefore VR pre-

pares relevant and meaningful stimulation to individual's different brain areas, promoting motor learning and rehabilitation via neuroplasticity. VR not only improves patients' quality of life but also has a role in the return of their brain health [33]. In recent years, VR technology has increasingly become affordable, flexible, and portable, which enables researchers to consider its use in many fields, especially the medical field [34, 35]. In a systematic study and meta-analysis, Zhang et al. confirmed that VR training is effective in the motor function of the upper and lower limbs, walking, balance, and daily activity of stroke patients and improves variables, but without effect on cognition [36]. Moreover, the study conducted by Abou L et al showed positive effects of VR training that improves balance during sitting and standing and a trend of gait improvement in persons with SCI [37]. Another study performed by Wang et al. [38] on the effectiveness of VR on the balance and walking of people with Parkinson's showed a significant effect on balance with no effect on walking [38].

The limited studies evaluated the effects of tDCS and VR on complications, such as fatigue, balance disorder, and walking in people with MS. Therefore, the present study was conducted to evaluate the effect of tDCS and VR on the mentioned symptoms of the disease. In addition, no investigation was found to study the combined effects of VR and tDCS on the mentioned variables. The synergistic effects of these two intervention methods can lead to greater effectiveness and shorter treatment time. Therefore, the secondary goal of this investigation was to compare the therapeutic effects of VR and tDCS separately and in combination on the level of fatigue, balance, and some walking parameters (speed & stride length) of people with MS.

Materials and Methods

The participants included 30 patients with MS aged 18-55 years. Patients whose disease was confirmed by neurologists participated in the present study voluntarily and purposefully. The inclusion criteria included a patient with expanded disability status scale (EDSS) ≤6 (EDSS is used to quantify disability and monitor its alterations during the time in MS) and not having any type of severe visual impairment, no history of concussion, ability to walk independently with or without an assistive device and not having any attack during last month. By the way, the exclusion criteria included patients with any severe systemic disorder, such as epilepsy or psychiatric disease, which prevented the use of VR modality and electrical stimulation. Participants entered the study after completing the written informed consent form and

had the option to withdraw from the research at any time. The patients were brain type of MS with their routine MS drug therapy without participating in other rehabilitation interventions. Table 1 presents the demographic information of the subjects.

The present study is a clinical trial study, with pre and post-assessment. The subjects were randomly allocated (by choosing a number from the box) to one of three groups according to the study inclusion/exclusion criteria, tDCS-VR group (n=10), VR group (n=10), and tDCS group (n=10).

The pre-test performed before the intervention included the fatigue severity scale (FSS), modified fatigue effect scale (MFIS), balance sheet scale (BBS), and 25-foot walk test (T25-FW). Immediately after the intervention, these evaluations were repeated as post-test. The intervention stages are shown in Figure 1. The researcher administering all tests was blinded to the test condition.

tDCS

A device (ActivaDose) was used to administer tDCS by a trained therapist. At first, we placed the anode and cathode electrodes in 5×5 cm sponge pads, and the pads were dipped in salt solution. We placed the anode electrode on the motor cortex M1 (C3) on the left side and the cathode on the right forehead according to the international 10-20 system [38]. Then, the stimulation protocol [38] consisting of electrical stimulation of the brain with a direct current of 2 mA, 20 minutes daily for 5 consecutive days was used. As a sham intervention, the current was turned off after 60 s of the onset of stimulation.

VR

The VR protocol was implemented using the VR BOX headset and based on the defined protocol [17, 39] and Costa (2020) [40]. Patients performed the VR program three sessions per week for two weeks. The duration of each session was 20 minutes.

We used the VR BOX headset to implement the VR protocol. In this way, we first put the Android phone inside the headset compartment and then put it on the patient's face.

The combined protocol was as follows: We placed the anode and cathode electrodes on the M1 motor cortex and on the forehead, respectively. We applied direct electrical stimulation of the brain for two weeks and three seasons every week with a current intensive of 2MA

and 20 minutes. After fixing the electrodes in the desired place using a strap, we placed the VR headset on the patient's face and applied two stimuli simultaneously. VR was also performed for six sessions, three times a week, and for 20 minutes.

The games include Slalom ski, penguin slide, and marble balance:

Slalom ski: This game requires the patient to pass between two flags placed along the track.

Penguin slide: In this game, patients must move from the ice platform to the fishing points outside the platform without falling.

Marble balance: In this game, the patient has to put the ball in a hole. Accordingly, he/she should shift his/her body weight to the direction where he/she wants the ball to be placed. If successful, the patient is transferred to the next stage, which is more difficult.

It should be noted that the VR group was also considered as a sham group and thus therefore simultaneously received sham stimulation by electrodes located according to the mentioned protocol.

During the combined VR+tDCS protocol, the anode and cathode electrodes were placed on the M1 motor cortex and the forehead, respectively, and at the same time, the VR headset was placed on a patient's face, and both types of intervention were performed simultaneously (tDCS with intensity of 2 mA that simultaneously applied using VR for 20 minutes for two weeks and three sessions each per week).

Tools

FSS: FSS is a 9-item scale that mainly focuses on the physical aspect of fatigue. Each item has a 7-point Likert scale, ranging from 1 (completely disagree) to 7 (completely agree). Therefore, the total score can be from 9 to 63. Having a FSS <4, 4> FSS <5, and FSS >5 is classified as mild, moderate, and severe fatigue, respectively. In the Iranian version of the instrument, Cronbach's α coefficient and intra-class correlation coefficient (ICC) were reported as 0.96, and 0.93 respectively. A validity of 85% was shown in the researchers' results [40].

MFIS: MFIS is a 21-item scale that assesses cognitive and psychosocial in addition to physical dimensions with a 5-point Likert scale, ranging from zero (never) to four (almost always). The range of total score is from 0 to 84.

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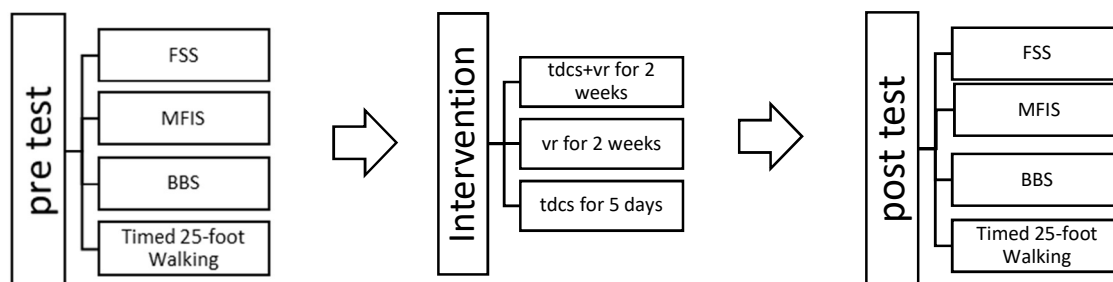
Intervention Stage

Figure 1. Intervention stages

A correlation of r=68%, P<0.0001 was reported between the two tests of fatigue intensity scale and modified fatigue effect [41]. A high Cronbach's score and ICC were reported in the Persian version of MFIS [41].

Berg balance scale (BBS): BBS contains 14 common functional activities that are performed repeatedly in a day in a 4-point Likert scale, ranging from 0 to 4 (0 indicating the lowest level of performance and 4 indicating the highest level of performance). Persian version of the test showed very high inter-rater and test re-test reliability (ICC=0.93 and 0.95, respectively) in the elderly [42, 43].

T 25-F W: T 25-F W as one of the three components of patients with MS function evaluates walking speed. Walking speed in meters per second is obtained by dividing the measured distance of 25 feet by the time. The reliability and validity of the T25-FW is reported as 97% [44].

Statistical analysis

The first normality of data was checked. The dependent t-test was used to compare within-group variables. Then analysis of covariance (ANCOVA) was employed to determine differences between the post-test scores of three groups, using baseline values as covariates while Turkey's method was used as a post-test. P<0.05 was regarded as statistically significant. SPSS software, version 19, was used for statistical analysis.

Results

All participants completed all stages, and also no drop was observed in the number of samples in the present study. Table 1 presents the demographic characteristics and disability score (Mean±SD) of the groups. Descriptive finding and comparison of within-group assessments were shown in Table 2.

The one-way analysis of covariance (ANCOVA) was used to compare the adjusted mean of the dependent variables in the 2×3 design (three groups in two stages). A significant difference was observed between the post-test-adjusted mean of all dependent variables (P<0.05) (Table 3).

According to Turkey's post hoc test results of the mean intensity of fatigue, both the VR and the tDCS-VR group significantly had lower scores than the tDCS group (P<0.001); however, the mean fatigue intensity between the VR and the tDCS-VR group was not significant (P=0.990) (Table 4).

Regarding the post hoc results of the balance test, the VR and tDCS-VR groups were significantly better than the tDCS group (P<0.001). No significant difference was observed between the mean balance of the VR group and the tDCS-VR group (P=0.995) (Table 4).

According to the mean walking speed, the VR and the tDCS-VR groups were significantly better than the tDCS group (P<0.001). While the difference between the mean walking speed of the VR and the tDCS-VR groups was not significant (P=1.000).

Moreover, in the mean modified fatigue, the VR group significantly showed lower scores than the tDCS and tDCS-VR groups (P=0.037), therefore it can be said that the VR intervention significantly reduced the modified fatigue compared to the other two interventions.

Discussion

The present study was conducted to investigate the effects of VR and tDCS separately and in combination on fatigue; balance and walking speed of MS patients. The results showed a significant effect of tDCS, VR, and tDCS-VR on fatigue and a significant effect of VR

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Table 1. Demographic characteristic and disability score of groups

Variables	Mean±SD/ No.		
	VR (n=10)	tDCS (n=10)	VR and tDCS (n=10)
Sex (male/female)	3/7	3/7	3/7
Age (y)	40.0±10.57	36.7±8.40	39.9±12.38
Weight (kg)	75.2±5.63	74.2±2.04	72±3.23
EDSS	6.2±0.26	6.05±0.24	6.3±0.025

PHYSICAL TREA†MENTS

Abbreviations: EDSS: Expanded disability status scale; VR: Virtual reality; tDCS: Transcranial direct current stimulation.

Table 2. Descriptive finding and comparison of within-group assessments in three groups

Variables	Groups	Pre-test	Post-test	t	P
FSS	VR	47.1±4.81	28.9±4.06	8.38	0.0001
	tDCS	47.11±3.47	45.1±2.92	2.73	0.02
	tDCS-VR	48.8±4.73	29.9±2.46	10.04	0.0001
MFIS	VR	59.5±7.16	50.8±7.68	2.46	0.03
	tDCS	61.3±5.43	59.2±5.41	2.16	0.06
	tDCS-VR	61.2±7.91	51.7±7.3	2.36	0.04
Balance (BBS)	VR	41.3±2.58	45.5±2.32	-3.64	0.005
	tDCS	41.5±2.36	39.5±2.77	1.79	0.1
	tDCS-VR	42.7±1.56	45.9±2.76	-2.58	0.02
Walking (T 25-F W)	VR	4.82±0.5	3.76±0.23	8.95	0.0001
	tDCS	4.89±0.46	4.77±0.33	0.88	0.39
	tDCS-VR	4.83±0.46	3.58±0.35	6.48	0.0001

PHYSICAL TREA†MENTS

Abbreviations: VR: Virtual reality; tDCS: Transcranial direct current stimulation; FSS: Fatigue severity scale; MFIS: Modified fatigue impact scale; BBS: Berg balance scale.

Table 3. Covariance statistics for comparison of three groups

Variables		Sum of Squares	df	F	Sig.	Effect Size
FFS	Base line	0.44	1	0.004	0.949	0.00
	Intervention	163.68	2	75.85	0.000	0.854
MFIS	Base line	2.01	1	0.041	0.841	0.002
	Intervention	427.37	2	4.370	0.023	0.252
Balance	Base line	15.46	1	3.082	0.091	0.106
	Intervention	269.22	2	26.832	0.001	0.674
Walking	Base line	0.208	1	2.245	0.146	0.079
	Intervention	8.56	2	46.186	0.001	0.780

FSS: Fatigue severity scale; MFIS: Modified fatigue impact scale.

PHYSICAL TREA†MENTS

Table 4. Tukey's post hoc test results to compare the research groups in the post-test stages

	Group I	Group J	Difference of Means (I-J)	Meaningful
FSS	tDCS-VR	VR	1	0.76
		tDCS	-15.20	0.0001*
	VR	tDCS	-16.20	0.0001*
MFIS	tDCS-VR	VR	0.90	0.95
		tDCS	-7.5	0.05*
	VR	tDCS	-8.40	0.02*
BBS	tDCS-VR	VR	0.40	0.92
		tDCS	6.40	0.0001*
	VR	tDCS	6.00	0.0001*
Walking (T 25-F W)	tDCS-VR	VR	-0.09	0.79
		tDCS	-1.19	0.0001*
	VR	tDCS	-1.10	0.0001*

PHYSICAL TREA†MENTS

Abbreviations: VR: Virtual reality; tDCS: Transcranial direct current stimulation; FSS: Fatigue severity scale; MFIS: Modified fatigue impact scale; BBS: Berg balance scale.

*Significant at P≤0.05.

and tDCS-VR on balance and walking speed in patients with MS. In comparing the effect of different interventions on fatigue, balance, and walking speed, the VR and tDCS-VR groups significantly showed better results, but no significant difference was observed between VR and tDCS-VR groups. A significant difference of the modified fatigue was observed between the VR with the other groups.

Fatigue: Our study showed that all three groups (including AtDCS, VR, and tDCS-VR) had a significant decrease in the intensity of fatigue in the post-test compared to the pre-test. The participants in the tDCS group improved severe fatigue symptoms and 8 of them improved the modified fatigue. In the present study, anodic stimulation was used by placing the stimulating electrode on the left M1 region and the cathode on the right frontal region. In previous studies, different areas have been used to reduce fatigue, such as [45] dorsolateral prefrontal cortex (DLPFC), parietal P4 [46] and S1 [47] and M1 [48]. Anodic stimulation can improve fatigue caused by MS by several mechanisms, including the antidepressant effects of AtDCS [49], and the neurochemical effects of anodic stimulation leading to facilitating the entry and exit of the motor system. These effects occur by increasing substances, such as myoinositol following tDCS and rTMS stimulation [50] inside the brain, which increases force production and its stability, or by decreasing mediators, such as gamma-aminobutyric acid (GABA), which compensates for impaired brain function [51]. Another mechanism for reducing fatigue during anodic stimulation is an increase in neuronal and axonal excitability in the cortex [52] which according to the pathophysiology of MS disease can be effective in axonal transmission. It can also be effective in facilitating thalamocortical afferents [53]. Resting-state MRI analysis showed that anodic stimulation strengthens neuronal connections, leading to recovery from fatigue [54, 55]. M1 stimulation increases cortical excitability and recruitment of more motor units and reduces supra-spinal fatigue [56]. In a review performed [57], the effectiveness of VR on functional mobility, balance, fatigue and quality of life in people with MS has been observed compared to regular exercises [58], which is consistent with our study. Previous studies have shown that the use of VR without accompanying physical exercises can be effective in improving the debilitating effects of MS disease [59]. Compared to physical exercises improving muscle resistance, heart rate and respiratory frequency plays a crucial role in the treatment of fatigue; VR is more adaptable to the patient's conditions. The possibility of performing at home and high attractiveness in patients create more motivation.

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On the other hand, the results of our study showed that in the post-test, the VR + tDCS group and the VR group had less fatigue than the tDCS group. Similarly, no improvement in fatigue symptoms was reported in active tDCS compared to sham+video game effect in a case report of MS patients.

The results showed that the VR+tDCS group as well as the VR group had better balance and showed a significant reduction in walking time from pre-test to post-test; while the tDCS groups did not show any significant change. Also, no significant difference was observed between the two VR+tDCS group and the VR group. The effectiveness of VR in the balance and gait of patients with MS compared to conventional mediated treatments has been proven due to their cost-effectiveness and attractiveness during review studies and meta-analysis [19, 60].

VR can provide a multiple sensory environment to the MS patient, which can cause neuroplasticity in the motor sensory cortex, and may be effective in the patient's motor rehabilitation [61]. A similar effect of VR training and tDCS in promoting neuroplasticity of the cortex in neurologic patients has been shown by functional magnetic resonance imaging (fMRI) [62, 63].

Since several exergames, such as Xbox Kinect or Nintendo Wii sports games require fast hand-eye, and foot-eye coordination, VR training can improve cognitive-motor skills, including hand-eye coordination, and eye-foot coordination, and increase manual dexterity and the ability to perform movements like walking.

Therefore, we tried to use games in the present study in which coordination can play a significant role in playing them. For example, in the game of boxing, two-handed and hand-eye coordination, soccer game, eye-foot coordination, tennis game, eye-hand coordination, golf game, two-handed coordination, American football game, hand-eye coordination, and in skiing game, eye-foot coordination, eye-hand coordination, and bimanual coordination are essential.

To the best of our knowledge, except for a case study [39], this is the first randomized controlled study to apply a combined tDCS-VR method to MS patients. Although the facilitating effect of brain stimulation on the effectiveness of VR therapy has been reported in some previous studies [64, 65], we did not find a significant difference between the two groups of VR + tDCS combination with VR+sham, indicating that tDCS did not enhance the positive effect of VR on balance and walking speed.

Consistent with our study, in some studies, the addition of tDCS did not strengthen the effect of VR [66]. The lack of difference between VR+ sham and VR+ anodal tDCS in the investigation conducted by Monte-Silva et al on stroke patients was explained by the ceiling effect [67]. The other reason may be that our tDCS protocol did not completely target the cortex area involved in balance and walking. Future studies are needed to evaluate the combined effect of placing anodal electrodes in other areas like Cz to stimulate the bilateral motor cortex.

Conclusion

Our results showed that VR separately and in combination with tDCS can improve fatigue, and balance and walking speed in patients with MS. However, we found more excessive effect in tDCS combined with VR therapy. Our results indicate that the effect of tDCS with VR therapy should be investigated further.

Considering that VR exercises and tDCS are a new training method of interventions for treating movement problems. And by creating an attractive and fresh environment, in addition to being a training environment, it makes people with MS cheerful and play a challenging environment by using games. It is suggested that according to the positive effects of VR and tDCS on significant or positive improvement in various parameters of this study, continuous use in the exercises of people with MS is suggested.

Also, due to the ease of using these exercises and the ability to do them at home and in rehabilitation centers, it is recommended to use these exercises at home and in rehabilitation centers.

It is recommended that evaluations be conducted for more accurate tests and instruments. For example, checking balance with Biodex and walking with quinoa, like examining plasticity by imaging the brain.

Considering that people with MS were used in this study, if possible, it should be tested for other people who have movement problems.

In this research, due to the limitations of the subject and the researcher, limited variables were measured. It is recommended to examine other movement variables related to MS, such as coordination and reaction time.

Ethical Considerations

Compliance with ethical guidelines

Funding

Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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