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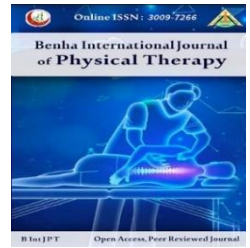

Original research

Cognitive Rehabilitation on The Gait and Balance in Patients with Multiple Sclerosis: A systematic review and metanalysis

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Abstract

Background: Cognitive impairment is a common symptom of multiple sclerosis (MS) and often affects patients' motor functions, particularly gait and balance. **Purposes:** This systematic review aimed to assess the impact of cognitive rehabilitation on gait and balance in patients with MS. **Methods:** A systematic search was conducted across five databases: PubMed, the Cochrane Library, Web of Science, Scopus, and PEDro. Randomized controlled trials (RCTs) investigating the effects of cognitive rehabilitation on gait and balance in adult MS patients were included. The primary outcomes included balance and gait parameters, whereas the secondary outcomes included mobility and patient-reported outcomes. Studies were appraised for methodological quality via the PEDro scale. **Results:** A total of 16 RCTs involving 1,173 participants were included. Despite various cognitive training approaches, no significant improvements were observed in balance control, postural sway, or gait. However, dual-task training increased mobility, as measured by the timed up and go (TUG) test. Patient-reported outcomes, such as the Multiple Sclerosis Walking Scale-12 (MSWS-12), did not significantly improve. The heterogeneity in intervention types and outcome measures across studies may have influenced these findings. **Conclusions:** Cognitive training appears to improve specific mobility parameters in MS patients but does not significantly affect balance. These findings suggest that integrating cognitive training with traditional physical therapies may optimize rehabilitation outcomes. Future research should focus on standardized interventions and longer follow-up periods. Additionally, considering the diverse impacts of MS on individuals, personalized approaches to cognitive training could be beneficial in clinical settings.

Keywords: Cognitive rehabilitation, multiple sclerosis, balance, gait, dual-task training.

INTRODUCTION

Multiple sclerosis (MS) is a complex neurological condition characterized by inflammation and damage to the myelin sheath, the protective covering of nerve fibers in the central nervous system (CNS). This damage disrupts the transmission of nerve signals, leading to a wide range of symptoms, such as fatigue, weakness, numbness, difficulty walking, and vision problems [1]. The clinical symptoms associated with multiple sclerosis (MS) reflect the diverse ways in which the disease can affect the central nervous system. Motor dysfunction often involves weakness, spasticity, or paralysis, whereas cerebellar symptoms such as tremors, dysmetria, and ataxia affect coordination and balance. Brainstem involvement can lead to symptoms such as diplopia (double vision) or nystagmus (involuntary eye movements). Sensory symptoms may include numbness, tingling, or loss of sensation. Urinary and bowel symptoms are common due to dysfunction of the nerves that control these functions. Visual disturbances, such as optic neuritis, are also frequent in MS. Additionally, cognitive impairment is increasingly recognized as a significant aspect of the disease, affecting memory, attention, information processing speed, and executive function [2].

Cognition represents the function of several neural pathways involved in the processing of information in brain cognition, including several correlated and interdependent domains, such as executive function, perceptual–motor function, language, learning and memory, complex attention, and social cognition, as defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) [3]**.** While cognitive impairment is a common feature across various neurological conditions, specific clinical syndromes, the severity of dysfunction, and resulting disability are influenced by several factors. These factors include whether the condition primarily affects cortical or subcortical brain structures, the extent of neural damage, the number of cognitive domains affected, and the individual's cognitive reserve and baseline performance [3].

Cognitive dysfunction affects 40–70% of People with multiple sclerosis [4] and frequently leads to impaired information processing speed and deficits in verbal and visual memory [5]. Cognitive deficits also negatively impact many aspects of quality of life and walking during everyday activities, especially during challenging conditions such as dual tasking [6]**.** These deficits in gait, cognitive function, and dual-tasking are associated with an increased risk of falls and disability [7].

Cognitive rehabilitation, as defined by the Brain Injury Interdisciplinary Special Interest Group (BI-ISIG) of the American Congress of Rehabilitation Medicine, involves systematic, functionally oriented therapeutic activities tailored to the individual's brain-behavior deficits. This approach has demonstrated effectiveness in clinical settings [8]. This therapeutic approach targets the enhancement of cognitive functioning, including attention, learning and memory, problem-solving abilities, and executive function, as well as emotional regulation and expression [9]. Various types of cognitive or cognitive-motor interventions have been proposed in the past to enhance physical functioning potentially. These interventions include cognitive rehabilitation, training of dual-tasking abilities, and the utilization of computer games or virtual reality.

This review aims to determine the effectiveness of cognitive training on balance in patients with MS and to develop standardized clinical guidelines that may direct physical therapy decision making regarding whether to use these methods. To the best of our knowledge, no systematic review has examined the effectiveness of all cognitive rehabilitation interventions on balance and gait in patients with MS.

METHODOLOGY

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) **guidelines** published in 2020 [10]**.** It was registered at the International Prospective Register of Systematic Reviews (PROSPERO) on 12 March 2024 (registration number: CRD42024523540).

Data sources and search strategy

The following databases were searched systematically and comprehensively for relevant studies: PubMed, the Cochrane Library, Web of Science, Scopus, and the Physiotherapy Evidence Database (PEDro) by two authors independently from inception to June 2024.

A search plan for relevant studies used the keywords "Multiple Sclerosis" OR "MS" "Cognitive" "Balance" "Gait" and "Adult" the terms Medical Subject Headings (MeSH), and text words. The detailed search strategy is available in **Appendix I.**

Study Selection

Studies that met the following inclusion criteria were included in this review: peer-reviewed randomized controlled trials (RCTs); adults (>18 years) with a clinical diagnosis of multiple sclerosis with cognitive effects; and interventions involving cognitive rehabilitation training alone or combined with any other intervention, such as cognitive–motor interference., etc., compared with sham training or any control intervention. The outcome measures assessed improvements in gait and balance. Studies published in any language other than English or not peer reviewed will be excluded.

First, the titles and abstracts were filtered to identify the relevant studies. Then, in accordance with the previously determined eligibility criteria, a full-text review of the retained studies was carried out.

A PRISMA flow diagram was used to depict the flow of information through the different phases of this systematic review. It maps out the number of records identified, included, excluded, and the reasons for exclusions [10]**.**

Data Extraction

The data of the included studies were extracted and included the study design, participant characteristics, intervention characteristics, outcome measures, and results**.**

Methodological quality assessment of the studies

A critical assessment of the quality of the included studies was carried out via the PEDro scale [11]. This assessment categorized studies into high- and low-quality groups according to the total score of the scale. Studies with scores of six points or more were deemed high quality (those with scores of six–seven points were good, and those with scores of eight–ten points were excellent), whereas studies with scores less than six points were considered low quality (those with scores of four–five points were fair, and those with scores lower than four points were poor quality).

Data synthesis

To measure the treatment effect, we calculate the effect sizes, expressed as risk ratios (RRs) with 95% CIs for dichotomous outcomes and standard mean differences (SMDs) with 95% CIs for continuous outcomes for each trial when sufficient data are available. Data synthesis will be performed via Review Manager Software (RevMan, version 5.4.1; The Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark, 2021) and Microsoft Excel 2019 (Microsoft Corp., Redmond, WA, USA). A meta-analysis was performed for all outcomes when sufficient data were available. For studies using different measurement scales, we applied the standardized mean difference (SMD). When studies provided median and interquartile range (IQR) data, the median was used to represent the mean, and the standard deviation (SD) was estimated by dividing the IQR by 1.35, following the Cochrane Handbook for Systematic Reviews of Interventions (version 6.2, 2021) [12]. Between-study heterogeneity was assessed via the I^2 test. In the default approach, we employed a fixed-effects model for all analyses. However, if heterogeneity was statistically significant ($p < 0.05$) or I^2 exceeded 50%, we applied the DerSimonian and Laird random effects model [13]. All tests were two-sided with an α-error level set at 0.05.

RESULTS

A systematic search yielded 1581 records, which resulted in 1045 records after removing duplicates. Among these, 31 full-text articles were assessed for eligibility, and 16 studies met the inclusion criteria [7,14,23–28,15–22] **(Figure 1).** Fifteen studies were excluded, and the reasons for exclusion are detailed in **Appendix 2.**

All included studies were randomized controlled trials (RCTs) involving 1173 participants diagnosed with multiple sclerosis (MS), with an average age range of 32-54 years. According to the physiotherapy evidence database (PEDro) quality assessment scale, five of the included studies were classified as having excellent quality[7,14,21,25,29], nine studies had good quality[15–20,22,26,28], and two studies were deemed to have fair quality[23,27]. The details of the risk of bias assessment are presented in Table 1.

Twelve studies applied dual-task intervention (cognitive–motor exercise or motor–motor exercise) for cognitive rehabilitation [7,14,25,27,15–21,24], three studies utilized a single cognitive task [22,23,28], and one study applied multitask training [26].

The control groups in the included studies received motor training alone (11 studies) [7,16,17,20–23,25,29], continued their routine exercises (three studies) [14,15,19], or practiced Jacobson's progressive relaxation exercises (two studies) [26,27].

The duration of application varied from four to 24 weeks, with frequencies ranging from two to five sessions per week, each lasting between 30 and 60 minutes. The follow-up periods ranged from four weeks to six months [14,17,20–22,24,30] **Table 2.**

Outcome measures across studies included balance, postural sway, gait endurance, and speed as primary outcomes and mobility and patient-reported outcomes as secondary outcomes. Whenever possible, data were pooled across the type of cognitive training to single cognitive task training or dual-task training.

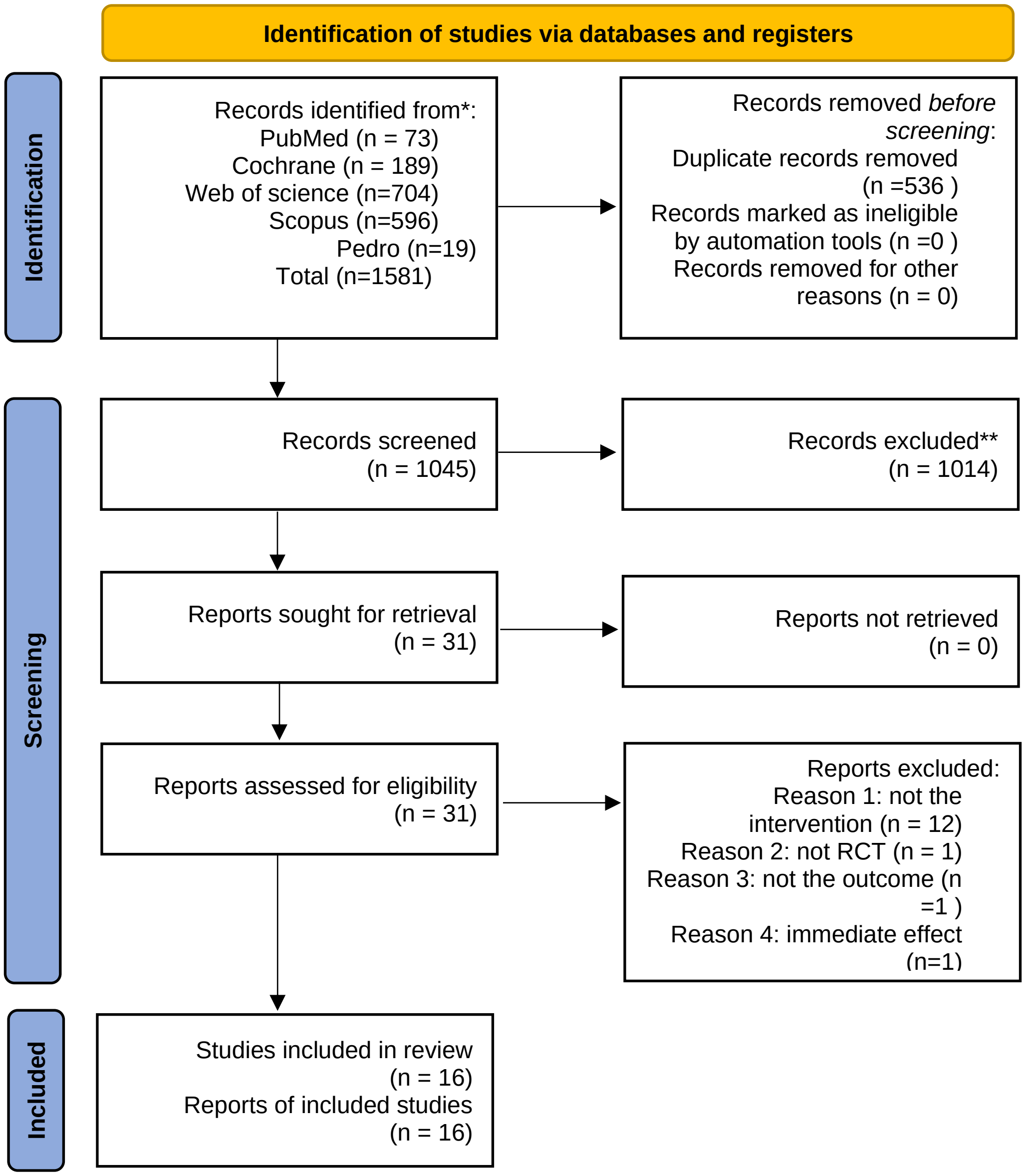

Figure (1). PRISMA flow chart

Table 2: Quality assessment of included studies:

PEDro Scale Item	Hoang et al., 2016	Monjezi et al., 2017	Peruzzi et al., 2017	SosNOff et al., 2017	Jonsdottir et al., 2018	Felippe et al., 2019	Veldkamp et al., 2019	Mohammadzadeh et al., 2020	Ozkul et al., 2020	Azimian et al., 2021	Molhemi et al., 2021	Argento et al., 2023	Galperin et al., 2023	Ozkul et al., 2023	Hoang et al., (2024	Tramontaon et al., 2024
Eligibility criteria were specified	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Random allocation	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Concealed allocation	YES	NO	YES	YES	YES	NO	YES	NO	NO	YES	YES	NO	YES	YES	YES	YES
Baseline similarity	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Blinding of subjects	NO	YES	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO
Blinding of therapists	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Blinding of assessors	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	YES	YES	YES
Adequate follow-up	YES	NO	NO	NO	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES
Intention-to-treat analysis	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	NO	YES	NO	YES	YES
Between-group statistical comparisons	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Point estimates and variability	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Total Score	**7**	**6**	**6**	**6**	**9**	**6**	**6**	**7**	**5**	**7**	**8**	**5**	**8**	**7**	**8**	**8**

Table 2: Characteristics of included studies

Study	Participants				Intervention			Outcome Measures	Results
	N (completers)		Age	MS Type	Study	Control	Duration		
	SG	CG							
Hoang et al. 2016	28 (23)	22 (21)	52.52±11.85	Any	CR in form of Interactive exergames	Usual care	Thirty min session, 2 times / week, 12 weeks	- CRST - SST - Postural sway - TUG - 10MWT - 6MWT - 9-HPT	- Significant differences were observed favouring the SG concerning CRST (P = 0.031), SST (P = 0.011), CRST decision time (P = 0.041), and movement time (P = 0.039), sway with eyes open (P = 0.04), 10MWT (P = 0.023), TUG in DT (P = 0.036) and 9-HPT (P = 0.001). - No differences were observed between groups regarding swaying with eyes closed, 6MWT, TUG in single task.
Monjezi et al., 2017	23 (19)	24 (19)	36±8	RRMS	DT balance training	ST balance training	Forty-five min session, 3 times / week, 4 weeks	- 10MWT - TUG - ABC - BBS - FGA	- No differences were noted between groups in all outcomes.

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Peruzzi et al., 2017	16 (14)	15 (11)	42.89±10.81	RRMS	TT + VR	TT	Forty-five min session, 3 times / week, 6 weeks	- Gait kinematics in ST & DT - 6MWT - TUG - BBS - FSST - LE ROM - LE Muscle Power	- The most affected knee and hip showed statistically significant improvement in the range of motion whether in ST (P = 0.022 and 0.009) or DT (P = 0.009 and 0.012), in addition the most affected hip showed similar results in terms of generated torque in both ST (P = 0.011) and DT (P = 0.031). - No differences were observed in all other outcomes.
Sosnoff et al., 2017	10 (8)	10 (6)	51.94±12.12	Any	DT training including same program of CG plus cognitive tasks	ST training including balance and gait training	One hour session, 2 times / week, 12 weeks	- Gait velocity in ST and DT - BBS	- No differences were observed between groups regarding balance and gait velocity.
Jonsdottir et al., 2018	28 (26)	14 (12)	53.07± 9.65	Any	DT training through treadmill	Strengthening exercises	Thirty min session, 4-5 times / week, 4 weeks	- 2MWT - 10MWT - TUG - BBS - DGI	- Statistically significant differences were observed favouring the DT group in terms of 2MWT (P = 0.0006), gait speed (P = 0.01), and TUG (P = 0.009). - BBS and DGI results were similar in both groups.

Felippe et al., 2019	13	14	36.55±15.65	RRMS	CR + MR	Usual care	One hour session, 2 times / week, 24 weeks	- TUG	- Statistically significant differences were observed favouring the SG regarding TUG time and cadence in single task (P =0.033 and 0.029), dual task (P = 0.033 and 0.038) and cognitive tasks time only (P = 0.033).
Veldkamp et al., 2019	24 (20)	23 (20)	52.4± 9.16	Any	DT training via an interactive tablet-based application	Single mobility training	Forty-five min session, 20 times / 8 weeks	- T25FW - TUG - DGI - 2MWT - MSWS-12 - FESI	- No differences were observed in the between groups comparison in all motor outcomes.
Mohammadzadeh et al., 2020	11	11	40.32±9.12	Any	MP for 20 min + OT exercises same as control	OT exercises including balance, strengthening, stretching and gait training	One hour session, 3 times / week, 6 weeks	- 6MWT - 25FWT - BI	- Significant differences were observed favouring the SG regarding 6MWT (P = 0.0468) and 25FWT (P = 0.00025) however, no difference existed between groups regarding BI.

Ozkul et al., 2020	17 (13)	17 (13)	31.5± 10.11	RRMS	Immersive VR with interactive balance games for 20 min + Pilates training for 30 min	Relaxation exercises for 20 min	Two times / week, 8 weeks	- BBS - Posturography using Biodex - TUG	- Statistically significant differences were observed favouring the SG regarding postural sway with eyes closed (P = 0.048), postural sway on the right lower limb (P < 0.001), TUG and cognitive TUG (P < 0.001). - No differences existed between groups regarding all other posturography parameters and BBS.
Azimian et al., 2021	36	35	43.44±9.85	Any	CR + OT	OT	One hour session, 3 times / week, 4 weeks	- BEST	There were statistically significant differences in favour of the CR group compared to control regarding BEST (P <0.001)
Molhemi et al., 2021	19	20	39.26±8.63	RRMS, SPMS	VR interactive exergames + conventional PT program	Conventional PT program including gait and balance training	Forty-five min session, 3 times / week, 6 weeks	- LOS - TUG - 10MWT - FESI - BBS - MSWS-12 - ABC - Rate of Falls	- Only cognitive 10MWT and TUG showed statistically significant differences favouring the SG (P= 0.03 and 0.01) respectively.
Argento et al., 2023	16	16	49.25±10.13	RRMS, SPMS	CR	MR	Forty-five min session, 2 times /week, 12 weeks	- T25FW - 9HPT - 6MWT - TS - BBS	- Only TS showed a statistically significant difference favouring SG (P = 0.019).

Galperin et al., 2023	60 (53)	64 (51)	49.0± 9.8	RRMS	TT + VR	TT	Three times / week, six weeks	- Gait kinematics in UW & DTW - T25FW - 6MWT - UW - DTW - MSWS-12	No significant differences between groups were observed.
Ozkul et al., 2023	14 (13)	14 (13)	35.31±11.66	RRMS	DT training during the first two weeks then MT in the last four weeks	ST training	One hour session, 2 times / week, 6 weeks	- Posturography using Biodex - TUG - 9-HPT	- Only TUG revealed significant difference favouring the SG (P = 0.002)
Hoang et al 2024	235 (223)	234 (230)	52.6± 11.2	Any	CR in form of Interactive exergames	usual care	Two hours session / week, 24 weeks	- Rate of fall (6 & 12 mon) - CRST - SST - Postural sway - MBI - 10MWT - Knee ext. & Hip flex. Strength	- Statistically significant differences were observed favouring the SG regarding CRST and inhibitory CRST movement time (P = 0.002 and 0.003) and total response time (P = 0.01 and 0.001) however all other outcome measures showed no differences.
Tramontano et al., 2024	21 (20)	18 (16)	50.95±9.77	RRMS	DT (20 min MR + CR) + 30 min conventional neuromotor therapy	CTg 20 min of dynamic postural stability training + 30 minutes of conventional neuromotor therapy	Fifty min session, 3 times / week, 4 weeks	- Mini-BEST - POMA - MBI - 10MWT - Fo8WT - Gait kinematics	- F08WT and 10MWT showed statistically significant differences favouring the DT (P = 0.021 and 0.023) respectively. - All other outcome measures revealed no differences between groups.

Abbreviations: 2MWT: Two Minutes Walking Test; 6-MWT: 6-Minute Walk Test; 9HPT: 9-Hole Peg Test; 10-MWT: 10-Meter Walk Test; ABC: Activities-specific Balance Confidence Scale; BBS: Berg Balance Scale; BEST: Balance Evaluation System Test; BI: Barthel Index; CG: Control Group ; CR: Cognitive Rehabilitation; CRR: Correct Response Rate; CSRT: Choice Stepping Reaction Time; CTg: Conventional Therapy group; DGI: Dynamic Gait Index; DT: Dual-Task; DTG: Dual-Task Group; DTW: Dual-Task Walking ; FESI: Fall Efficacy Scale-International; FGA: Functional Gait Assessment; Fo8WT: Figure-of-8 Walk Test; FSST: Four Square Step Test; LE: Lower Extremit; LOS: Limits Of Stability; MBI: Modified Barthel Index; MP: Mental Practice; MR: Motor Rehabilitation; MS: Multiple Sclerosis; MSWS-12: Multiple Sclerosis Walking Scale-12; MT: Multi-Task; N: Number; OT: Occupational therapy; POMA: Tinetti Performance-Oriented Mobility Assessment; PT: Physical Therapy; ROM: Range Of Motion; RRMS: Relapsing and Remitting Multiple Sclerosis; SG: Study Group; SPMS: Secondary-Progressive Multiple Sclerosis; SST: Stroop Stepping Time; ST: Single Task; T25-FWT: Timed 25-Foot Walk Test; TS: Tinetti Scale; TT: Treadmill Training; TUG: Time Up and Go;UW: Usual Walk; VR: Virtual Reality.

Primary outcomes:

Effect of cognitive training on balance

Nine included studies examined the effect of cognitive training on balance control via the Berg Balance Scale (BBS) [16–18,21,23,25,27], Balance Evaluation System Test (BEST) [22], or MINI Balance Evaluation System Test (MINI BEST) [29].

Pooled statistical analysis of eight studies revealed no significant difference between groups regarding balance control in single cognitive task training (SMD = 0.14 [-0.88, 1.16], P = 0.79) [22,23] (**Figure 2**). or in dual-task training (SMD =0.23 [-0.05, 0.52], P = 0.1) [16,17,21,25,27,29] (**Figure 3**).

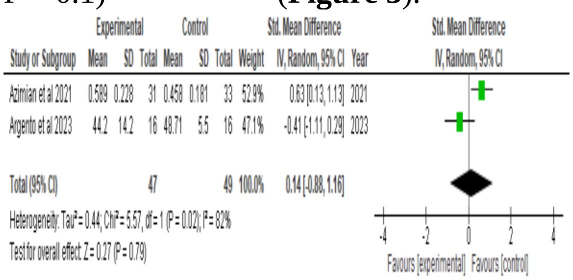

Fig. (2): Forest plot comparing cognitive training and control, outcome: Balance control via BBS and BEST for single CR training.

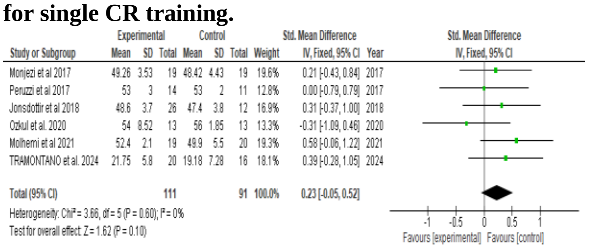

Fig. (3): Forest plot of comparing between dual-task group (DTG) and control, outcome: Balance control via BBS and MINI BEST.

Effect of cognitive training on postural sway:

Three studies examined the effect of dual-task cognitive training on postural sway[14,15,27]. Pooled statistical analysis revealed no significant difference between groups regarding postural sway while standing on the floor with the eyes open (SMD = -0.24 [-0.87, 0.39], P = 0.46) (**Figure 4**).

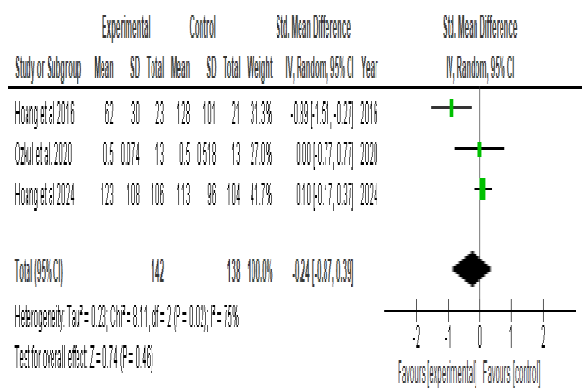

Fig. (4): Forest plot of comparing between dual-task group (DTG) and control, outcome: Postural Sway eye open stand on floor.

Effect of cognitive training on gait speed:

Eight included studies examined the effect of dual-task cognitive training on gait speed via a 10-meter walk test (10-MWT) [7,14–18,20,25].

Pooled statistical analysis of seven studies revealed no significant difference for the dual-task group regarding the 10-MWT in dual-task cognitive training (SMD = 0.25 [0.07, 0.43], P = 0.004) [7,14–18,25] (**Figure 5**).

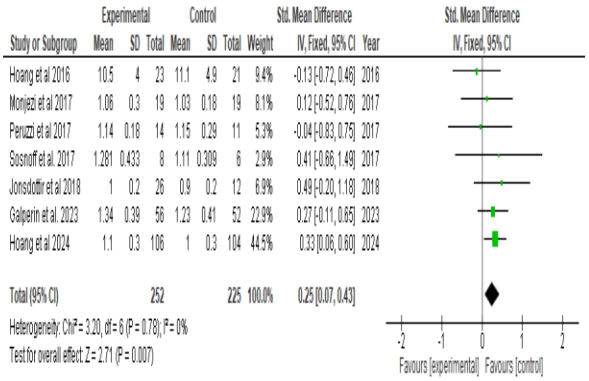

Fig. (5): Forest plot of comparing between dual-task group (DTG) and control, outcome: Gait speed via 10-MWT.

Effect of cognitive training on Gait endurance:

Six studies examined the effect of dual-task cognitive training on gait endurance via a 6-minute walk test (6-MWT) or 2-minute walk test (2-MWT) [7,14–16,20,25]. Pooled statistical analysis of five studies revealed no significant difference between groups regarding gait endurance (SMD = 0.03 [-0.18, 0.24], P = 0.75) [14–16,20,25] (**Figure 6**).

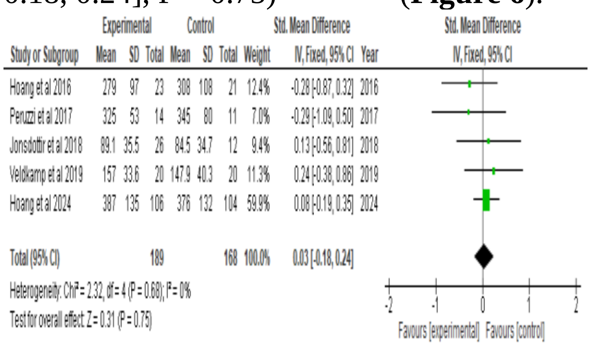

Fig. (6): Forest plot of Comparing between dual-task group (DTG) and control, outcome: Gait endurance 6-MWT/ 2-MWT.

Secondary outcomes:

Effect of cognitive training on mobility:

Nine included studies examined the effect of dual-task cognitive training on mobility via the Time Up and Go (TUG) test [15–17,19–21,25–27].

Pooled statistical analysis of seven studies revealed a significant difference in favor of the dual-task training group (SMD =-0.90 [-1.46, -0.35], P = 0.001) [15–17,20,21,25,27] (**Figure 7**).

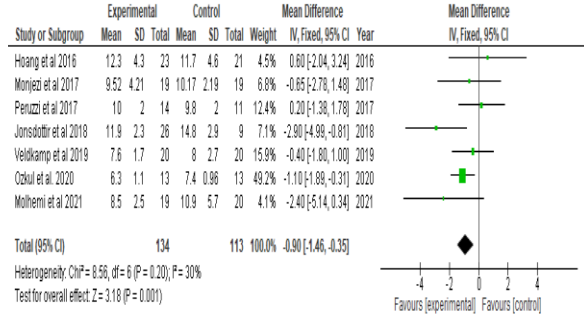

Fig. (7): Forest plot of Comparison between dual-task group (DTG) and control, outcome: Mobility via TUG.

Effect of cognitive training on patient-reported outcomes:

Multiple Sclerosis Walking Scale-12 (MSWS-12)

Three studies examined the effects of dual-task cognitive training on the ability of multiple sclerosis patients to walk via the Multiple Sclerosis Walking Scale-12 (MSWS-12) [20,21,30]. Pooled statistical analysis revealed no significant difference between the groups (SMD = -0.09 [-0.28, 0.10], P = 0.37) (**Figure 8**).

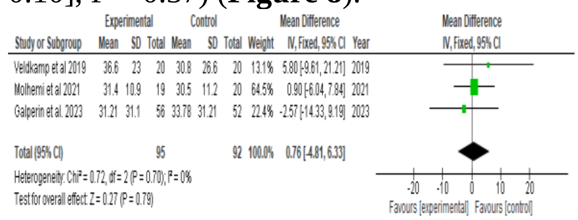

Fig. (8): Forest plot of Comparing between dual-task group (DTG) and control, outcome: MSWS-12.

DISCUSSION

This systematic review aimed to provide evidence of the effectiveness of cognitive rehabilitation on gait and balance in multiple sclerosis patients. Sixteen studies were included in this systematic review, and only 13 studies were included in the quantitative meta-analysis [7,14,24,25,27,15–18,20–23], with gait and balance as primary outcomes and mobility and patient-reported outcomes as secondary outcomes. Although various cognitive and motor interventions were analyzed, the results revealed a mixed impact of CR on these physical functions. Specifically, dual-task cognitive rehabilitation has shown some promise in improving mobility in certain studies. Moreover, the effects on gait and balance remained inconsistent across different trials.

This is the first systematic review to examine the effectiveness of CR in MS, and a previous systematic review examined the effects of dual-task therapy on MS patients and other neurological disorders, such as stroke, PD, and AD [31–33].

The mean Pedro scale of the quality assessment of the included RCTs was 6.8, which represents good quality. The included studies did not file some points, as only one study applied the blinding of the subjects [17], one study blinded the therapists [25], and five studies mentioned an intention-to-treat analysis [14,21,24,25,30].

Cognitive rehabilitation interventions demonstrated limited efficacy in improving balance outcomes. Pooled analyses revealed no significant differences between cognitive training approaches and control interventions, irrespective of whether single-task or dual-task paradigms were employed. This lack of effect may be attributed to the heterogeneity in the types of cognitive tasks used, the severity of MS-related disability, and the variability in intervention duration and intensity. These findings align with those of previous studies suggesting that balance impairments in MS may be more strongly influenced by structural damage to motor-related neural pathways than by cognitive deficits [19,24]. This may also be attributed to the diverse cognitive tasks employed, which may not specifically target the cognitive domains crucial for balance maintenance. For example, if balance relies heavily on attention or executive function, cognitive training programs may need to be tailored to strengthen these specific areas [34].

Contrary to our hypothesis, cognitive rehabilitation did not significantly reduce postural sway in MS patients, as shown in the studies assessing this outcome. This may be because postural sway is heavily influenced by proprioceptive and neuromuscular control [35], which might not be sufficiently targeted by cognitive rehabilitation alone. These results suggest that future interventions might benefit from integrating proprioceptive and motor training to achieve meaningful improvements in postural stability.

Gait performance, assessed via measures such as gait speed and endurance, also showed limited improvement following cognitive rehabilitation.

The lack of substantial changes in 10-MWT and 6-MWT scores highlights the challenges of addressing motor impairments through cognitive interventions alone. These findings are consistent with the hypothesis that gait dysfunction in MS patients results from a combination of sensory, motor, and cerebellar deficits, which may not be adequately addressed through cognitive-focused rehabilitation [7,20]. These results suggest that interventions might benefit from the integration of all the factors that affect gait to achieve meaningful improvements in gait speed and endurance.

A significant improvement in mobility, as measured by the timed up and go (TUG) test, was observed in the dual-task training group. but not in gait speed or endurance. This selective improvement indicates that cognitive training might enhance certain motor–cognitive integrations without broadly affecting walking parameters. This finding underscores the potential of dual-task interventions to increase functional mobility by simultaneously engaging the cognitive and motor systems [(14, 16, 18–20, 22, 25)]. The TUG test, which assesses both mobility and balance, may be more sensitive to the integrative effects of dual-task training than isolated balance or gait measures are. This aligns with previous studies demonstrating the benefits of dual-task training in improving functional outcomes in neurological populations [5, 14].

The lack of significant changes in patient-reported outcomes, such as the Multiple Sclerosis Walking Scale-12 (MSWS-12), suggests that while some functional gains are achievable, these gains may not necessarily translate into perceived improvements in daily life, the multifactorial nature of quality of life and the potential influence of nonmotor symptoms, such as fatigue and depression, on patients' perceptions of functional capacity may affect [22,28].

The role of the cognitive–motor interaction is a crucial element in understanding the potential mechanisms behind the effect of CR on motor functions. Multiple sclerosis patients often struggle with dual-tasking due to impaired executive functions, which are responsible for managing divided attention between motor and cognitive tasks[24]. This review supports the hypothesis that dual-task training can partially mitigate the detrimental effects of cognitive–motor interference, but only under certain conditions. For example, improvements were more noticeable in studies employing specific task combinations that closely simulate real-world cognitive and motor challenges, such as walking while performing decision-making tasks [17,18,29]. While several studies demonstrated significant improvements in cognitive tasks performed alongside motor tasks, these enhancements did not always translate into better functional mobility outcomes [21,27].

This finding suggests that while cognitive rehabilitation might improve task switching and attention, its direct effects on motor functions such as balance and gait may require supplementary motor-focused interventions. In the future, further investigations into the specific types of cognitive tasks that may enhance balance in MS patients are needed. Additionally, exploring the impact of cognitive training across different stages of MS could provide insights into its effectiveness in managing disease progression. Practical considerations, such as the feasibility and cost-effectiveness of implementing cognitive training in clinical settings, should also be addressed in future studies.

Limitations of the Current Evidence:

Several limitations in the current body of evidence should be acknowledged. First, the methodological quality of the included studies varied widely, with some studies classified as "fair" or "good" on the basis of the PEDro scale. The heterogeneity in CR protocols (single cognitive task, dual task: cognitive–motor or motor–motor task), outcome measures, severity, type of MS among the cohorts of the included studies, and follow-up durations also posed challenges in synthesizing the data. Many studies lack long-term follow-up, making it difficult to assess the sustainability of CR-induced improvements.

Additionally, the sample sizes in many studies were small, which limits the generalizability of the findings. This highlights the need for larger, multicenter trials with standardized outcome measures and comprehensive reporting of both benefits and risks.

Implications for Clinical Practice:

Despite the mixed evidence, this review suggests that cognitive rehabilitation, especially when integrated with motor tasks, holds potential as a complementary intervention for improving functional outcomes in MS patients. Physical therapists working with MS populations may consider incorporating dual-task CR programs to target the multifactorial nature of balance and gait dysfunctions in MS, which emphasize cognitive–motor coordination to enhance both motor and cognitive functions.

However, its effects on motor outcomes such as balance and gait remain limited. Moreover, the variability in intervention protocols across studies highlights the need for standardized guidelines to optimize cognitive rehabilitation for this population.

Tailoring CR interventions to target the most impaired cognitive domains, such as attention or executive function, may further increase the efficacy of rehabilitation programs aimed at improving gait and balance.

CONCLUSION

Cognitive rehabilitation, particularly dual-task interventions, shows promise for enhancing mobility in patients with multiple sclerosis. However, the evidence regarding its effects on gait, balance, and postural sway remains inconclusive. The variability in cognitive rehabilitation protocols, outcome measures, and follow-up durations across studies presents challenges in the formation of definitive clinical guidelines.

Future research should focus on standardizing intervention protocols and incorporating motor and proprioceptive training alongside cognitive rehabilitation to achieve more meaningful improvements in motor outcomes. Larger multicenter RCTs with long-term follow-up are needed to validate these findings and establish clearer clinical guidelines for the use of cognitive rehabilitation in MS patients.

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Appendix I: Detailed search strategy:

	Pubmed	Cochrane	Web of science	Scopus	Pedro
Search strategy	(("multiple sclerosis"[MeSH Terms] OR "multiple sclerosis"[Title/Abstract]) AND ("cognition"[MeSH Terms] OR "cognition"[Title/Abstract] OR "cognitive"[Title/Abstract] OR "dual"[Title/Abstract] OR "divided"[Title/Abstract] OR "attention"[Title/Abstract]) AND ("balance"[Title/Abstract] OR "gait"[Title/Abstract])) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]) Results 73	Trials matching MeSH descriptor: [Multiple Sclerosis] explode all trees AND (cognition):ti,ab,kw OR (cognitive):ti,ab,kw OR (dual):ti,ab,kw OR (divided):ti,ab,kw OR (attention):ti,ab,kw AND (balance):ti,ab,kw OR (gait):ti,ab,kw (Word variations have been searched) Results 189	TS=(" Multiple Sclerosis " AND TS=(“ cognition” OR “cognitive” OR “dual” OR "divided" OR "attention AND TS=(“ gait” OR "balance") Results 704	TITLE-ABS-KEY ("multiple sclerosis") AND (TITLE-ABS-KEY ("cognition" OR "cognitive" OR "dual" OR "divided" OR "attention")) AND (TITLE-ABS-KEY ("gait" OR "balance")) AND (LIMIT-TO (SRCTYPE , "j")) AND (LIMIT-TO (LANGUAGE, "English")) Results 596	“multiple sclerosis” AND “cognition” OR "cognitive" in title and abstract Results 19

Appendix 2: Excluded studies:

Title	Author	Reason for exclusion
Exergaming with additional postural demands improves balance and gait in patients with multiple sclerosis as much as conventional balance training and leads to high adherence to home-based balance training	Kramer et al. 2014 (1)	Not RCT
Randomized controlled trial of physical activity, cognition, and walking in multiple sclerosis	sandroff et al. 2014 (2)	Not the intervention (behavior therapy)
Effects on Balance and Walking with the CoDuSe Balance Exercise Program in People with Multiple Sclerosis: A Multicenter Randomized Controlled Trial	Forsberg et al. 2016 (3)	Not the intervention (CoDuSe)
Robotic gait training in multiple sclerosis rehabilitation: Can virtual reality make the difference? Findings from a randomized controlled trial	Calabrò et al. 2017 (4)	Not the intervention (VR+ robot)
Randomised controlled pilot trial of an exercise plus behaviour change intervention in people with multiple sclerosis: the Step it Up Study	Hayes et al. 2017 (5)	Not the intervention (behavior therapy)
Multimodal exercise training in multiple sclerosis: A randomized controlled trial in persons with substantial mobility disability	Sandroff et al. 2017 (6)	Not the same intervention (multimodal Ex's)
Do patients with multiple sclerosis benefit from semi-immersive virtual reality? A randomized clinical trial on cognitive and motor outcomes	Maggio, et al. 2019 (7)	Compare different types of cognitive training
Effect of a Combined Program of Strength and Dual Cognitive-Motor Tasks in Multiple Sclerosis Subjects	Gutiérrez-Cruz et al. 2020 (8)	Not the intervention (combined)

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Effects of robot-assisted gait training combined with virtual reality on motor and cognitive functions in patients with multiple sclerosis: A pilot, single-blind, randomized controlled trial	Munari et al. 2020 (9)	Not the intervention (VR+ robot)
Effect of video-based exergaming on arm and cognitive function in persons with multiple sclerosis: A randomized controlled trial	Ozdogar et al. 2020 (10)	Not the intervention (exregaming)
The immediate effect of stroboscopic visual training on information-processing time in people with multiple sclerosis: an exploratory study	Shalmoni et al. 2020 (11)	Immediate effect (one session)
Effect of CoDuSe and step square exercises on risk of fall in multiple sclerosis: a randomized controlled trial	Mahmoud et al. 2022 (12)	Not the intervention (CoDuSe)
Effects and safety of exergaming in persons with multiple sclerosis during corticosteroid treatment: a pilot study	Ozdogar et al. 2022 (13)	Not the intervention (exregaming)
Limb apraxia in individuals with multiple sclerosis: Is there a role of semi-immersive virtual reality in treating the Cinderella of neuropsychology?	Maggio et al. 2023 (14)	Not same outcome
Effects of exergaming on cognition, lower limb functional coordination, and stepping time in people with multiple sclerosis: a randomized controlled trial	Molhemi et al. 2023 (15)	Not the intervention (exregaming)

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