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EFFECTIVENESS OF VIRTUAL REALITY TRAINING FOR BALANCE AND GAIT REHABILITATION IN PEOPLE WITH MULTIPLE SCLEROSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract:	Objective. To evaluate the evidence for the use of virtual reality to treat balance and gait impairments in multiple sclerosis rehabilitation. Design. Systematic review and meta-analysis of randomised controlled trials and quasi-randomised clinical trials. Methods. An electronic search was conducted using the following databases: MEDLINE (PubMed), Physiotherapy Evidence Database (PEDro), Cochrane Database of Systematic Reviews (CDSR) and CINHAL. A quality assessment was performed using the PEDro scale. The data were pooled and a meta-analysis was completed. This systematic review was conducted in accordance with the PRISMA guideline statement. It was registered in PROSPERO database (CRD42016049360). Results. Eleven studies were included. The data were pooled, allowing meta-analysis of seven outcomes of interest. A total of 466 participants clinically diagnosed with multiple sclerosis were analysed. Results showed that virtual reality balance training is more effective than no intervention for postural control improvement (SMD= -0.64; 95% CI= -1.05,-0.24; P=0.002). However, significant overall effect was not showed when compared with conventional training (SMD= -0.04; 95% CI=-0.70,0.62; P=0.90). Inconclusive results were also observed for gait rehabilitation. Conclusions. Virtual reality training could be considered at least as effective as conventional training and more effective than no intervention to treat balance and gait impairments in multiple sclerosis rehabilitation.

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INTRODUCTION

Balance impairment is frequently observed in people with multiple sclerosis and is considered to be one of the most disabling symptoms because it reduces mobility and independence and affects overall quality of life(1). Impaired balance and gait has been also associated with increased risk of falling in multiple sclerosis patients(2). Specific rehabilitation programmes for balance and gait improvement have showed small but significant effects in this population(3).

In recent years, the effectiveness of virtual reality as a therapeutic tool has become an interesting topic of research in neurorehabilitation(4). From a motor learning approach, virtual reality offers the possibility of high intensity, task-oriented, multisensorial feedback training. Several systematic reviews and meta-analysis have been conducted concerning its use for balance and gait training in stroke patients (5–9),sufferers of Parkinson's disease(10), or in older populations(10–13). Exergaming or interactive gaming-systems are terms usually used to describe non-immersive commercially available virtual reality systems(13).

The clinical effectiveness of virtual reality for balance and gait training in multiple sclerosis remains unclear. Concerning this topic, only two bibliographic reviews focusing on general motor rehabilitation benefits have been published(14,15). These previous reviews reported only a narrative description of the results; different types of designs were included, quality assessment of the publications was not provided and pooled effects were not calculated. Therefore, it is necessary to systematically evaluate the evidence for the use of virtual reality to treat balance and gait impairments in multiple sclerosis rehabilitation.

For these reasons, the objectives of this research were: (1) to systematically review and summarise the evidence about virtual reality interventions for balance and gait training in multiple sclerosis patients; (2) to determine the magnitude of the effects of these interventions in a meta-analysis.

METHODS

Data Sources and Search Strategy

This systematic review was performed following the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)(16) and was registered in the PROSPERO database (CRD42016049360).

An electronic search was conducted using the following databases: MEDLINE (PubMed), Physiotherapy Evidence Database (PEDro), Cochrane Database of Systematic Reviews and CINHAL. All databases were searched from their inception until February, 2018. Search terms included key words related to virtual reality interventions (e.g, "game", "gaming", "exergaming"), balance (e.g, "postural control", "posture"), gait (e.g, "walking", "ambulation") and "multiple sclerosis". These terms were used as key words in the title and abstract in all databases. Simple or advanced search when possible was conducted (refer to the Appendix for an example of the search strategy).

Research Question and Study Selection

Our research question was established following recommendations from the PICO model (Population, Intervention, Comparison and Outcome measures). Patients included were male and female subjects, clinically diagnosed with multiple sclerosis in accordance with the revised McDonald criteria(17), with an Expanded Disability Status Scale(18) ≤6 (equivalent to being at least able to walk 100 meters with or without resting with the use of one stick or crutch). The intervention was balance and gait training using any virtual reality system, compared with no intervention or conventional balance and gait rehabilitation. The primary outcome measures were postural control, functional balance and walking speed. Secondary outcomes were mobility, negotiation of standing obstacles and self-reported measures.

Clinical trials and randomised controlled trials that used virtual reality (immersive and non-immersive), including interactive gaming or commercially available systems, for balance and gait rehabilitation were included. Only the systems that provided an interaction and/or engagement of the participants with the computer hardware or software were included. Full texts in English were included. Other methodological designs were excluded.

Data Extraction and Quality Assessment

First, articles were selected by screening of the title, and abstract if available, by two independent reviewers (MJCH and MDCV) and duplicates were removed. After that, the full texts of selected studies and those for which abstracts were not accessible were analysed. The reviewers then checked whether the studies met the inclusion and exclusion criteria. When articles suitable for inclusion in this research were identified, data extraction and quality assessment (risk of bias) was carried out independently by the reviewers named above. Data extraction consisted of summarising the information for qualitative and quantitative synthesis. The study characteristics (type of intervention, comparison group, outcome measures) were determined and the results (mean and SD) for primary and secondary outcome measures were also recorded using Excel files. Quality assessment was assessed using the PEDro scale, which is a valid and reliable tool for rating the quality of clinical trials and randomized clinical trials(19–21). Any disagreements on data extraction or quality assessment were resolved by consensus.

Data Synthesis and Meta-analysis

The results for the primary and secondary outcome measures were described narratively and where possible study results were pooled and meta-analysis was conducted. Mean differences (MD) or standard mean differences (SMD) were calculated with 95% confidence intervals (95% CI). A random-effects model was applied to present the pooled effect. We decided to pool studies based on the control group (no intervention or standard balance training) and the same underlying outcome. Analysis of the effect size values was based on the work of Cohen (22), who determined 0.2, 0.5 and 0.8 as small, moderate and large effect sizes, respectively. Heterogeneity was assessed using the I^2 statistic. Review Manager (RevMan) version 5.0 software was used to summarise the effects and construct forest plots.

RESULTS

Study selection and methodological quality assessment

The initial database searches returned 399 potential studies. Upon screening, nine randomized controlled trials (23–31) and two clinical trials (32,33) were included in the systematic review (Figure 1). Application of the PEDro scale criteria showed a mean score of 6 (range from 5 to 8). The full assessment can be found in Table 1.

[Insert Figure 1]

[Insert Table 1]

Study design and population characteristics

A total of 466 participants (65.8% female) clinically diagnosed with multiple sclerosis were recruited. Most of the interventions consisted in a one to one tailored training regime supervised by a physiotherapist (23,25–30,33). Two home-based interventions (24,31) and one intervention based on telerehabilitation were also included(32). Long-term effects were only assessed in one study(31). Additional information about the interventions is available in Table 2.

[Insert Table 2]

Results of primary outcomes

Postural control

Compared with no intervention, significant postural control improvements in the virtual reality group were observed in all measures in bipedal eyes opened tests(23,24,28). The pooled SMD showed that virtual reality balance training is more effective than no intervention (SMD= -0.64; 95% CI= -1.05,-0.24; P=0.002), without observed heterogeneity (I^2 =0%) and a moderate effect size (Figure 2.A). However, when virtual reality balance training was compared with conventional training, significant differences were only observed in two studies(25,32). No

differences between groups were reported in three studies(23,27,33). The effect of virtual reality training on postural control was further examined by pooling the data. The SMD did not show a significant overall effect for bipedal eyes opened tests (SMD= -0.04; 95% CI=-0.70,0.62; P=0.90) (Figure 2.B), bipedal eyes closed tests (SMD= -0.30; 95% CI=-0.79,0.18; P=0.22) (Figure 2.C) or unipedal eyes opened tests (SMD= -0.14; 95% CI=-0.31,0.59; P=0.54) (Figure 2.D). Heterogeneity was high in bipedal eyes opened conditions (I^2 = 80%). A sensitivity analysis showed that this heterogeneity was mainly due to the magnitude of the effect found in the study by Brichetto et al.(25). When this study was excluded, the I^2 of the pooled effect became 0% with an SMD of 0.318 (95% IC=0.001,0.316; P=0.049).

[Insert Figure 2]

Functional balance

Functional balance was only compared with no intervention in two studies(26,28) and no significant differences were observed between the virtual reality and control groups. Meta-analysis was not possible as different balance measures were used. When virtual reality training was compared with standard balance training, significant differences in balance improvements in favour of the virtual reality group were found in two studies(25,27), while no differences between groups were reported by Lozano et al.(29) and Ortiz-Gutiérrez et al.(32). In the study by Peruzzi et al.(30), no significant differences between groups were observed, but only for the experimental group, balance improvement after intervention was significant. Pooled analysis of the five studies using the Berg balance scale did not show a significant overall effect (MD=0.983; 95% CI=-2.246,4.212;P=0.55) (Figure 3). Heterogeneity was high, with I^2= 79%. A sensitivity analysis revealed that this heterogeneity was mainly due to the magnitude of the effect in the studies by Brichetto et al.(25) and Ortiz-Gutierrez et al.(32). When these studies were excluded, the I^2 of the pooled effect became 13%, with a MD of 0.635 (95% IC=-1.44,2.709; P=0.549). Pooled analysis of two studies using the Tinetti test showed significant differences in favour of standard therapy (MD= -1.98; 95% CI=-3.17,-0.79;P=0.001; I^2=0%)(Figure 4).

[Insert Figure 3] [Insert Figure 4]

Walking speed

Compared with no intervention, significant differences between groups were only observed in one of the three included studies(24). Pooled effect analysis did not show significant differences in favour of the virtual reality group (SMD=-0.04, 95% CI=-0.37, 0.28; P=0.79); and heterogeneity was not observed (I^2=0%)(Figure 5.A).

No significant differences between groups were reported when virtual reality was compared with standard gait therapy(23,29,30,33); however, Peruzzi et al.(30) observed significant walking speed improvements only in their virtual reality training group. The pooled effect was not significant, with a SMD of -0.09 (95% CI=-0.46, 0.28; P=0.64; I^2 =0%) (Figure 5.B).

[Insert Figure 5]

Results of secondary outcomes

Mobility

Compared with no intervention, significant differences in favour of the virtual reality group were reported in one study(28). No significant pooled MD was observed (MD= -0.541; 95% CI=-3.225, 2.142; P=0.693; I^2=40%) (Figure 6.A).

Compared with standard therapy, significant differences were observed in favour of the control group in one intervention(29); as was the case for functional balance and walking speed, Peruzzi et al.(30) reported significant mobility improvement only in the experimental group, although without differences between groups. The pooled MD was not significant (MD=1.190; 95% CI=-0.109,2.490; P=0.073; I^2=0%) (Figure 6.B).

[Insert Figure 6]

Negotiation of obstacles

Compared with no intervention, significant differences between groups were observed in favour of virtual reality by Prosperini et al. (24). The MD did not show a significant overall effect (MD= -0.72; 95%CI= -2.78,1.34; P=0.49; I^2=0%) (Figure 7.A). When compared with standard balance and gait training, the virtual reality group did not show significant improvements in obstacle negotiation. In the study by Peruzzi et al.(30), significant intra-group differences were again only reported in the experimental group. The pooled effect analysis did not show a significant overall effect (MD=0.84; 95% CI=-1.03, 2.71; P=0.38; I^2=0%) (Figure 7.B).

[Insert Figure 7]

Self-reported measures

At least one self-reported measure was assessed in six of the eleven studies (23–27). In comparison with no intervention, significant differences were observed for self-reported walking ability (p<0.001)(23), and for the perceived physical and psychological impact of multiple sclerosis disease (p=0.023)(24). In comparison with standard training, significant differences were observed for flow experience (p≤0.05)(23), fatigue (p<0.05)(25) and fear of falling (p=0.021)(27).

DISCUSSION

This meta-analysis supports that virtual reality training could be considered at least as effective as conventional training and more effective than no intervention in improving balance and gait abilities in patients with multiple sclerosis. However, these results should be interpreted with caution due to differences in the intensity of the therapy and differences in effect sizes among the included studies. Virtual reality has been also suggested as a more motivational and cost-effective alternative, although research supporting these benefits is needed.

Our findings are in agreement with previous research in a Parkinson's disease population. Dockx et al. (34) concluded that virtual reality and physiotherapy interventions have similar

effects on gait and balance improvement in people with Parkinson's. The available evidence comparing virtual reality exercise with a passive control was more limited, as in our study, and the quality of evidence of included studies was, similarly, moderate to low. Harris et al.(10) indicated that exergaming had similar effects on balance as balance-specific training in people with idiopathic Parkinson's disease. However, the number of studies included in their meta-analysis was small as they focused mainly on interventions in healthy older adults. Inconclusive results were also observed for improving mobility in older adults (12) and in adults with impaired balance due to various aetiologies(13). All of this previous research can neither support nor refute the use of virtual reality interventions instead of conventional physiotherapy.

Most of the available evidence supporting virtual reality interventions is about post-stroke rehabilitation. Compared with controls, people who received interactive interventions after a stroke showed marked improvements on the Berg balance scale and in timed up and go tests (9). Compared with conventional rehabilitation, significant improvements were also found in favour of the virtual reality group in functional balance and gait velocity(5,7). In a recent systematic review on this topic(6), virtual reality was found to be more effective in training gait and balance than conventional training in stroke patients when it was added to conventional therapy and when the time dose training was matched. The lack of virtual reality and control protocols will be further discussed as a study limitation. Nonetheless, it seems clear that virtual reality interventions are just as effective as conventional therapy for improving balance and gait in stroke patients.

This study has some limitations. First, there is significant variation in what is meant by the term virtual reality. Although virtual reality was defined by Weiss et al.(35) as the use of interactive simulations created with computer hardware and software to present users with opportunities to engage in environments that appear and feel similar to real world, there are many different terms used to describe the commercially available systems employed within the healthcare sector(13). Interactive-gaming systems, exergaming, gaming technology or video gaming are terms commonly used when describing the non-immersive virtual reality systems(10,13,15). For this reason, we tried to solve the difficulty in identifying interventions that might be called virtual reality using a broad strategy search regarding the virtual reality interventions. This procedure suggests that we did not miss studies.

Second, heterogeneity in virtual reality interventions was observed. Different commercial systems were used, different modalities of training were carried out and different training

protocols were implemented. The total number of sessions ranged from eight to 48, with a training frequency from one to four sessions per week and a training time from 20 to 60 minutes per session. Although the inclusion criteria were well established, it is difficult to generalise the results. This is a frequent limitation reported in other systematic reviews regarding virtual reality interventions(6,13–15).

Third, although standard balance and gait training in the control groups are generally time-dose matched, only two training protocols are described(27,32). Furthermore, an appropriate control group should match the virtual reality intervention not only in dose, but also in intensity, structure and task demand. Only in two studies(23,30) was a comparable standard balance and gait training program designed.

Fourth, some heterogeneity in the purpose of using outcome measures purposes within the included studies was observed. For instance, the four-step square test is proposed as a measure of dynamic standing balance(31,34), but also as a fall risk measure(26) or as an obstacle negotiation test(30). In order to generalise pooled effects, an attempt was made to homogenise outcome meanings as shown in Table 1, although this is obviously a simplification of several test interpretations.

Finally, long-term effects or a functional translation of the balance and gait improvements was only reported in one of the studies(31), and it would be interesting to investigate this area.

This meta-analysis has also some clinical implications for rehabilitation practice. Virtual reality appears as a possible alternative for balance and gait training in multiple sclerosis; clearer goals, greater task concentration and clearer immediate feedback have been also reported when using virtual reality training, and proposed as psychological advantages which could enhance patient motivation(23). However, to improve the strength of the evidence on the effects of virtual reality training, future studies need to be large randomized controlled trials, reporting clear protocols for virtual reality and control groups and incorporating within the design comparable task demands and training times between the groups.

Clinical messages

- → Pooled effect from current literature neither support nor refute the use of virtual reality for improving balance and gait abilities in people with multiple sclerosis.
- → Virtual training could be considered at least as effective as conventional training.
- → However, heterogeneity in protocols, effect sizes and outcome measures makes generalisation of the results difficult.

Author contributions

MJCH and RMV established the research question and conducted the data extraction and quality assessment of the studies. AFC performed the statistical analysis and the forest plots. All the authors draft the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that there is no conflict of interest.

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35. Weiss PL, Rand D, Katz N, Kizony R. Video capture virtual reality as a flexible and effective rehabilitation tool. J Neuroeng Rehabil. 2004;1:12.

Search strategy for PubMed:

((((((((((("virtual reality"[Title/Abstract]) OR game[Title/Abstract]) OR gaming[Title/Abstract]) OR exergaming[Title/Abstract]) OR interactive[Title/Abstract]) AND balance[Title/Abstract]) OR "postural control"[Title/Abstract]) OR posture[Title/Abstract]) OR gait[Title/Abstract]) OR walking[Title/Abstract]) OR ambulation[Title/Abstract]) AND "multiple sclerosis"[Title/Abstract] Filters: Clinical Trial; Randomized Controlled Trial.

Table 1. PEDro Scale items assessment.

Section/Theme	Robinson et al.[23]	Prosperini et al. [24]	Brichetto et al. [25]	Nilsagard et al. [26]	Kalron et al. [27]	Eftekharsadat et al. [28]	Lozano-Quilis et al. [29]	Ortiz-Gutierrez et al. [32]	Kramer et al. [33]	Peruzzi et al.[30]	Thomas et al.[31]
Eligibility criteria	√	√	√	√	√	√	√	√	√	√	√
Random allocation	√	√	√	√	√	√	√	X	X	√	√
Concealled allocation	X	√	X	√	√	X	X	X	X	√	√
Baseline comparability	√	√	√	√	√	√	√	√	√	√	√
Blind subjects	X	X	X	X	X	X	X	X	X	√	X
Blind therapists	X	X	X	X	X	X	X	X	X	X	X
Blind assessors	X	√	√	√	√	√	X	√	√	√	X
Adequate follow-up	X	√	X	√	√	√	√	√	√	√	√
Intention to treat analysis	√	X	X	X	X	X	X	X	X	X	√
Between-group comparisons	√	√	√	√	√	√	√	√	√	√	√
Point estimates and variability	√	√	√	√	√	√	√	√	√	√	√
Total score	5/10	7/10	5/10	7/10	7/10	6/10	5/10	5/10	5/10	8/10	7/10

Note: Eligibility criteria item does not contribute to total score.

√= yes/ X= No

Table 2. Main characteristics of included studies.

Study	Design, PEDro Score	Participants Characteristics, Sample size	Intervention (VR group)	Control Group (or intervention 2)	Outcome measures	Main Results
Robinson et al.[23]	RCT 5/10	Mean age= 52, SD=5.8 38 women Mean EDSS score: no reported N=56 2 drop out	Individual supervised exercise sessions with Nintendo Wii Fit™ games in standing position 2 sessions/week, 40-60 min Duration: 4 weeks, 8 sessions	Group 2: balance training exercises replicating the actions and demands of the Wii Fit games Same frequency and duration CG: no intervention	Postural control (force plate): CoP displacements bipedal (BP) and monopedal (MP) eyes opened Gait parameters (GAITRite™) Technology acceptance (UTAUT) Flow experience (FSS) Self-reported walking ability (MSWS-12) Perceived activity and participation restrictions (WHODAS 2.0)	VR-CG (favors VR group): AP CoP range (p=0.04) ML CoP range (p=0.04) COP velocity (p=0.01) WHODAS (P<0.001) MSWS-12 (P=NS) Group 2-CG (favors group 2): AP CoP range (p=0.04) ML CoP range (p=0.01) COP velocity (p=NS) WHODAS (P<0.001) MSWS-12 (P=0.03) Only for flow experience, significant differences were found between the two intervention groups (p≤0.05) in favor VR

Prosperini et al. [24]	RCT Crossover 6/10	Mean age=36.2, SD=8.6 25 women Mean EDSS score=3.5 (range 1.5-5.0) Mean disease duration=10.7,SD=5.8 N=36 2 drop out	Home-Based Balance training with Nintendo Wii™ Balance Board in sitting and standing position 4 sessions/week, 30 min First session and one session every 4 weeks supervised by PT Duration: 12 weeks, 48 sessions	CG: no intervention 12 weeks	Postural control (force plate): CoP displacements bipedal, eyes opened Walking speed (T25-WT) Obstacles negotiation (FSST) Physical and psychological perceived impact of MS (MSIS-29)	Significant between-group differences over time favors intervention: CoP displacements (p=0.016) FSST (p=0.034) 25-FWT (p=0.048) MSIS-29 (p=0.023) Virtual training was effective in all endpoints, regardless of the order of treatment. A residual effect was observed
Brichetto et al. [25]	RCT 7/10	Mean age=41.9, SD=11 22 women Mean EDSS score=4, SD= 1.6 Mean disease duration=11.7,SD=6.8 N=36	Supervised exercise sessions with Nintendo Wii Fit™ games in sitting and standing position 3 sessions/week, 60 min Duration: 4 weeks, 12 sessions	CG: standard balance training Static and dynamic exercises in single and double leg stance, with or without equilibrium board and half-kneeling, tailored to each participant Same frequency and duration	Postural control (force plate): CoP displacements bipedal, eyes opened and closed Functional balance (BBS) Fatigue (MFIS)	Significant between-group differences favors experimental group: CoP displacements eyes opened and closed (p<0.05) BBS (p<0.05) MFIS (p<0.05)

Nilsagard et al. [26]	RCT 7/10	Mean age=49.7, SD=11.3 64 women Mean EDSS score: no reported Mean disease duration=12.3,SD=8.6 N=84 4 drop out	Individual PT-supervised sessions with Nintendo Wii Fit™ games in standing position 2 sessions/week, 30 min Duration: 6 weeks, 12 sessions	CG: no intervention	Functional balance (TCS, DGI) Walking speed (T25-WT) Mobility (TUG) Obstacles negotiation (FSST) Self-reported walking ability (MSWS-12) Self-confident related falling (ABC)	There were no statistically significant differences between groups after the intervention period in any outcome
Kalron et al. [27]	RCT 7/10	Mean age=45.2, SD=11.6 19 women Mean EDSS score=4.1, SD= 1.3 Mean disease duration=11, SD=8.9 N=32 2 drop out	Individual PT-supervised sessions with CAREN™ VR system in standing position 2 sessions/week, 30 min Duration: 6 weeks, 12 sessions	CG: convenctional balance training 10 min stretching 20 min training (static postural control, weight shifting and perturbation exercises)	Postural control (force plate): CoP displacements, bipedal eyes opened and closed Functional balance (FRT, BBS) Obstacles negotiation (FSST) Fear of falling (FES-I)	Significant differences in favor of VR group were observed for FRT (p=0.009) and FES-I (p=0.021) Both groups improved significantly postural control (p=0.024), FRT (p=0.001), FSST (p=0.031) and FES-I (p=0.023)

Eftekharsadat et al. [28]	RCT 6/10	Mean age=35.2, SD=8.2 22 women Mean EDSS score: no reported Mean disease duration=7.1, SD=4.2 N=30	Individual PT-supervised sessions with BIODEX™ Balacne System in standing position 2 sessions/week, 20 min Duration: 12weeks, 24 sessions	CG: no intervention	Postural control (force plate): OSI Functional balance (BBS) Mobility (TUG) Fall Risk (FRi)	Significant differences in favor VR group were observed for TUG (p=0.01), FRi (p=0.002) and OSi (p<0.04)
Lozano-Quilis et al. [29]	RCT 5/10	Mean age=44.4, SD=10 4 women Mean EDSS score: no reported Mean disease duration=9.3, SD=7.9 N=11	Individual PT-supervised sessions with RemoviEM™ VR system in standing position 1 session/week, 60 min (45 min standard rehabilitation + 15 min VR training) Duration: 10 weeks, 10 sessions	CG: standard balance and gait rehabilitation exercises Same frequency and duration	Functional balance (SLB, BBS, TBT) Walking speed (10 Mwt) Mobility (TUG)	Significant differences in favor control group for TUG test (p=0.027)
Ortiz-Gutierrez et al. [32]	CT 5/10	Mean age=41.23, SD=7.7 27 women Mean EDSS score=3.95, SD= 0.6 Mean disease duration=10.27, SD=6.1	Individual monitored telerehabilitation via videoconference usin X-Box 360™ 4 sessions/week, 20 min Duration: 10 weeks, 40 sessions	CG: : convenctional balance training 2 sessions/week, 40 min 10 weeks 10 min low loads strength exercises	Postural control (force plate): CES, MTC Functional balance (BBS, TBT)	Significant differences in favor VR group were observed for CES (p<0.001), MTC (p=0.003)

		N=50 3 drop out		20 min propioception on unstable surfaces and gait facilitation exercises 10 min muscle-tendon stretching		
Kramer et al. [33]	CT 5/10	Mean age=47, SD=9 44 women Mean EDSS score=3, SD= 1 N=70 9 drop out	Individual PT-supervised sessions with Nintendo Wii Fit™ games in standing position 3 sessions/week, 30 min Duration: 3 weeks, 9 sessions	Group 2: 5 single task exercises over the posturomed CG: standard balance training Romberg stance, tandem stance, one leg stance on an aerobic mall, standing on the toe or the heel, walking forward and backward on a line	Postural control (force plate): CoP displacements bipedal and monopedal, single and dual task Walking speed (10Mwt)	There were no statistically significant differences between groups after the intervention period in any outcome Only VR group showed significant improvements in postural control, single and dual task
Peruzzi et al. [30]	RCT 8/10	Mean age=42.8, SD=11.1 15 women Mean EDSS score=3.8, SD=0.9 Mean disease duration=12.1, SD=5.4 N=31	Supervised treadmill walking while watching a VR tree-lined trail with obstacles 3 sessions/week, 45 min First week treadmill speed 80% of the subject overground walking spedd; every	CG: supervised treadmill walking Same frequency, duration and speed parameters	Gait data (six camera stereophotogram metric system) Functional balance: BBS Walking speed (10Mwt)	Significant improvements over time in the 6Mwt in both groups with no differences between groups Significant improvement on 10Mwt ($p<0.001$), TUG ($p=0.042$), BBS ($p=0.003$) and FSST ($p=0.028$) only observed in the VR group,

		9 drop out	week speed was increased 10% Duration: 6 weeks, 18 sessions		Mobility: TUG Obstacles negotiation: FSST Walking endurance (6Mwt)	but without significant diferences between gruops
Thomas et al.[31]	RCT 7/10	Mean age=49.3, SD=8.7 27 women Mean EDSS score= 4.23, SD=1.16 Disease duration= 10% <1 year, 37% 1-5 years, 23% 6-10 years, 10%>11-15 years, 20% >16 years N=30 2 drop out	Usual care plus physiotherapist-supported home-based Wii intervention (Mii-vitaliSe) Intervention parameters are not established. Patients are encouraged to train everyday Duration: 12 months	CG: usual care during 6 months After this time, CG received intervention Duration: 12 months	Physical activity: GLTEQ, accelerometer Well-being, quality of life: HADS, EQ-5D-5L, MSIS-29, FSI, SF-36 v.2 Self-efficacy: SCI-ESES, MSSE Postural control: Steady Stance Test, Equilibrium Quotient index Functional balance: Step test Mobility: TUG Walking speed: portable sensors Walking endurance:	Only descriptive data were reported All the balance and gait measures produced standardised effect sizes in the direction of benefit for the intervention. However, the confidence intervals were wide and spanned zero.

					2MWT Hand dexterity/coordination: 9HPT	

ABC: Activities-Specific Balance Confidence Scale, **AP:** anteroposterior, **BBS**: Berg Balance Scale, **BP:** bipedal, **CES**: Composite Equilibrium Score, **CG:** control group, **CoP:** centre of pressure, **CT:** clinical trial, **DGI:** Dynamic Gait Index, **EDSS:** Expanded Disability Status Scale, **EQ-5D-5L:** EuroQol-5 Dimensions-5Levels, **FES-I:** Falls Efficacy Scale International, **FRi:** Fall Risk index, **FRT:** Functional Reach Test, **FSI:** Fatigue Symptom Inventory, **FSS:** Flow State Scale, **FSST:** Four Step Square Test, **GLTEQ:** Godin Leisure-Time Exercise Questionnaire, **HADS:** Hospital Anxiety and Depression Scale, **MCT:** Motor Control Test, **MFIS:** Modified Fatigue Impact Scale, **ML:** mediolateral, **MP:** monopedal, **MSIS-29:** Multiple Sclerosis Impact Scale, **MSSE:** Multiple Sclerosis Self-Efficacy Scale, **MSWS-12:** 12-item World Health Organization Disability Assessment Schedule 2.0 questionnaire**, OSI:** overall stability index, **PT:** physiotherapist, **RCT:** randomized controlled trial, **SCI-ECES:** Spinal Cord Injury Exercise Self-Efficacy Scale, **SD:** standard deviation, **SF-36 v.2:** Medical Outcomes Short-Form Survey version 2, **SLB:** Single Leg Balance test, **T25-FW:** Time 25 Foot Walk, **TCS:** Timed Chair Stand Test, **TBT:** Tinetti Balance Test, **TUG:** Timed Up and Go test, **UTAUT:** Unified Theory of Acceptance and Use of Technology, **VR:** virtual reality, **WHODAS 2.0:** World Health Organization Disability Assessment Schedule 2.0, **2MWT:** Two-Minute Walk Test, **6Mwt:** Six-minute Walk Test, **10Mwt:** 10-meter Walking Test, **9HPT:** Nine-Hole Peg Test.

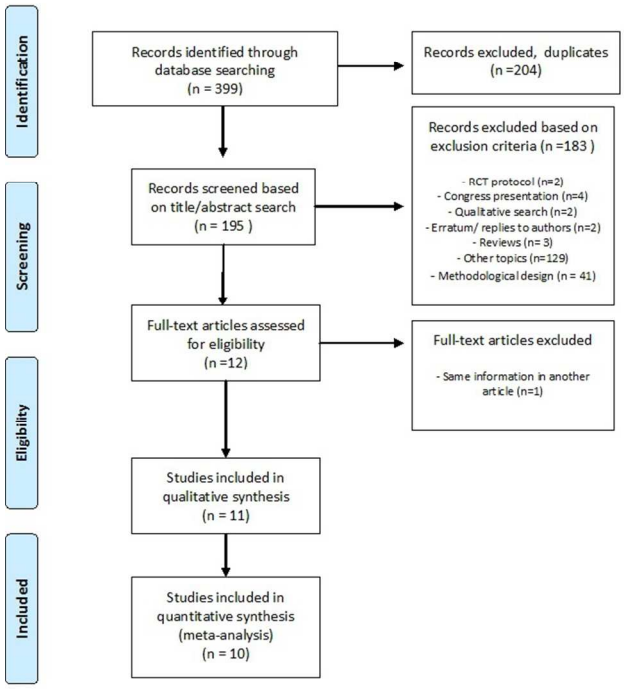

Figure 1. Flow diagram of trial selection based on PRISMA guidelines.

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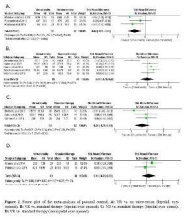

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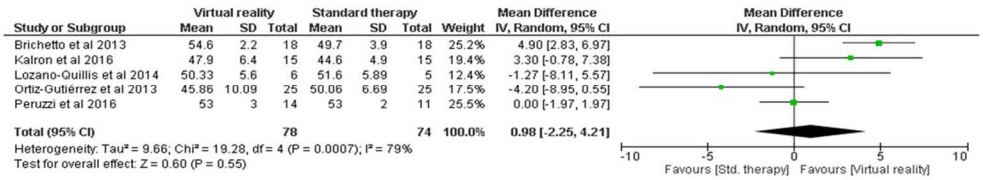

Figure 3. Forest plot of the meta-analysis of Berg Balance Scale VR vs. standard therapy.

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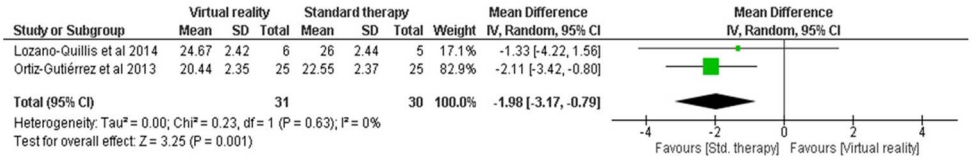

Figure 4. Forest plot of the meta-analysis of Tinetti Test VR vs. standard therapy.

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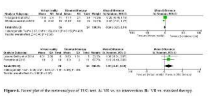

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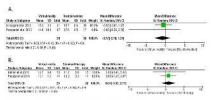

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Appendix 1. Detailed search strategy.

N°	Terms used
#1	"Virtual reality"
#2	"Game"
#3	"Gaming"
#4	"Exergaming"
#5	"Interactive"
#6	"Balance"
#7	"Postural control"
#8	"Posture"
#9	"Gait"
#10	"Walking"
#11	"Ambulation"
#12	"Multiple Sclerosis"

PUBMED (257 potencial articles):

((((((((((("virtual reality"[Title/Abstract]) OR game[Title/Abstract]) OR gaming[Title/Abstract]) OR exergaming[Title/Abstract]) OR interactive[Title/Abstract]) AND balance[Title/Abstract]) OR "postural control"[Title/Abstract]) OR posture[Title/Abstract]) OR gait[Title/Abstract]) OR walking[Title/Abstract]) OR ambulation[Title/Abstract]) AND "multiple sclerosis"[Title/Abstract] Filters: Clinical Trial; Randomized Controlled Trial

PEDro (14 potencial articles):

- #1 AND #6 AND #12 (6 potencial articles)
- #4 AND #6 AND #12 (1 potencial article)
- #5 AND #6 AND #12 (2 potencial articles)
- #1 AND #9 AND #12 (2 potencial articles)
- #4 AND #9 AND #12 (1 potencial article)
- #5 AND #9 AND #12 (1 potencial article)
- #3 AND #6 AND #12 (1 potencial article)

Cochrane Database of Systematic Reviews (56 potencial articles):

- #1 AND #6 AND #12 (13 potencial articles)
- #2 OR #3 AND #6 AND #12 (10 potencial articles)
- #4 AND #6 AND #12 (2 potencial articles)
- #5 AND #6 AND #12 (5 potencial articles)
- #1 AND #7 AND #12 (7 potencial articles)
- #1 AND #9 AND #12 (3 potencial articles)
- #2 AND #7 AND #12 (1 potencial article)
- #2 OR #3 OR #4 AND #8 AND #12 (1 potencial article)
- #1 AND #9 OR 10 AND #12 (3 potencial articles)
- #2 OR #3 AND #9 AND #12 (3 potencial articles)
- #4 AND #9 AND #12 (2 potencial article)
- #5 AND #9 AND #12 (1 potencial article)
- #2 OR #3 AND #10 AND #12 (2 potencial articles)
- #4 AND #10 AND #12 (1 potencial article)
- #5 AND #10 AND #12 (3 potencial articles)

CINAHL (72 potencial articles):

- t:("virtual reality") t:(balance) t:("multiple sclerosis") c:1 (10 potencial articles)
- t:("virtual reality") t:("postural control") t:("multiple sclerosis") c:1 (6 potencial articles)
- t:("virtual reality") t:(gait) t:("multiple sclerosis") c:1 (14 potencial articles)

- t:(game) t:(balance) t:("multiple sclerosis") c:1 (16 potencial articles)
- t:(game) t:("postural control") t:("multiple sclerosis") c:1 (5 potencial articles)
- t:(gaming) t:(balance) t:("multiple sclerosis") c:1 (1 potencial article)
- t:(exergaming) t:(balance) t:("multiple sclerosis") c:1 (8 potencial articles)
- t:(exergaming) t:(gait) t:("multiple sclerosis") c:1 (8 potencial articles)
- t:(interactive) t:(walking) t:("multiple sclerosis") c:1 (4 potencial articles)

Note: only search strategies with results are showed.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract page
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2-3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2-3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2-3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 4 and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 4 and Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 5 and table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

PRISMA 2009 Checklist

doi:10.1371/journal.pmed1000097

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