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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

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Abstract.
Background: Studies on robot-assisted gait training rehabilitation in multiple sclerosis have reported positive effects on mobility and quality of life. However, their effects on cognitive functions are difficult to determine because not all trials have included cognition assessments. Virtual reality-based training provides enhanced opportunity for stimulating cognitive abilities by repetitive practice, feedback information, and motivation for endurance practice.
Objective: To compare the effects of innovative robot-assisted gait training combined with virtual reality versus standard robot-assisted gait training on information processing speed, sustained attention, working memory, and walking endurance in patients with multiple sclerosis.
Methods: Seventeen outpatients were randomly assigned to receive robot-assisted gait training either with or without virtual reality. The robot assisted gait training + virtual reality group underwent end-effector system training engendered by virtual reality. The standard training group underwent end-effector system training. A blinded rater evaluated patients before and after treatment and at one month follow-up. The outcome measures were the Paced Auditory Serial Addition Test, Phonemic Fluency Test, Novel Task, Digit Symbol, Multiple Sclerosis Quality of Life-54, 2-Minutes Walk Test, 10-Meter Walking Test, Berg Balance Scale, gait analysis, and stabilometric assessment.
Results: Between-group comparisons showed a significant change on the 2-Minutes Walk Test ($p = 0.023$) after treatment in the robot-assisted gait training + virtual reality group. Significant improvement were obtained also in executive functions ($p = 0.012$). Both gains were maintained at the 1-month follow-up evaluation ($p = 0.012$, $p = 0.012$) in the robot-assisted gait training + virtual reality group. Both group improved quality of life after treatment (Multiple Sclerosis Quality of Life-54: Mental Health $p = 0.018$, Physical Health $p = 0.017$).
Conclusions: Both training lead to positive influenced on executive functions. However larger positive effects on gait ability were noted after robot-assisted gait training engendered by virtual reality with multiple sclerosis. Robot-assisted gait training provides a therapeutic alternative and motivational of traditional motor rehabilitation.

Keywords: Executive functions, quality of life, rehabilitation, robotics, walking

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1. Introduction

Multiple sclerosis (MS) is a major cause of chronic neurologic disability in adults (aged 18–50 years) (Khan & Amatya, 2017). The severe burden on individuals and their families beside the loss in productivity and the socioeconomic impact on society can be substantial (Krause et al., 2013; Shah, 2015).

Symptoms differ individually depending on the location and characteristics of the morphological changes in both white and gray matter in the brain. The most common are cognitive dysfunction (especially executive functions) and motor impairment (gait and balance) (Khan & Amatya, 2017). Cognitive deficits manifest in 40 to 70% of patients at any stage of the disease (Loitfelder et al., 2014). They frequently accompany motor impairment (Yogev-Seligmann et al., 2008); processing speed, sustained attention, and working memory are the domains most often impaired (Jongen et al., 2012). Approximately 85% of individuals with MS report walking dysfunctions to be a major impairment in their daily lives (Larocca, 2011), and 50 to 80% have balance problems (Gunn et al., 2013; Cameron et al., 2014). Gait in MS patients is characterized by shorter stride length, slower walking speed, and prolonged double limb support time (Sosnoff et al., 2012). While pharmacotherapy has been proposed for MS-related gait and balance impairments (Goodman et al., 2009; Goodman et al., 2010; Cameron et al., 2014; Bisht et al., 2017), its limited effects on disability have highlighted the need for non-pharmacological interventions in MS (Maggio et al., 2019). Although cognitive and motor tasks are not typically performed independent of each other during daily life activities, they are separately treated in rehabilitation programs. However in the our knowledge motor treatments have impacts on cognitive functions (Fonte et al., 2019). Consequently, the complexity of MS calls for a comprehensive approach that encompasses both cognitive and motor rehabilitation.

Studies on robot-assisted gait training (RAGT) rehabilitation in MS have reported positive effects on gait, balance, and quality of life (Schwartz et al., 2012; Straudi et al., 2013; Straudi et al., 2016; Gandolfi et al., 2014). But because not all trials have included cognition as an outcome variable, it is difficult to determine the effect of RAGT on cognitive impairment (Peruzzi et al., 2017; Russo et al., 2018; Casuso-Holgado et al., 2018). An optimal approach to maximize efficacy and improve motor and cognitive domains may be with multifactorial intervention (Varalta et al., 2018). Virtual reality (VR) during motor rehabilitation, for example, has been demonstrated a potentially useful tool in motor assessment and rehabilitation (Leocani et al., 2007; Taylor & Griffin, 2015; Massetti et al., 2016; Russo et al., 2018). VR-based training provides enhanced opportunity for repetitive practice, feedback information, and motivation for endurance practice, thus promoting visual, auditory and tactile input, and motor learning (Laver et al., 2017; De Keersmaecker et al., 2019). In their recent narrative review, Maggio and colleagues showed that VR is a motivational and effective tool that can enrich traditional motor and cognitive rehabilitation for MS patients, with positive effects on cognitive and/or motor deficits (Maggio et al., 2019). A recent meta-analysis by Casuso-Holgado and collaborators concluded that VR training may be considered at least as effective as conventional training and more effective than no intervention in improving balance and gait abilities in patients with MS (Casuso-Holgado et al., 2018).

The primary aim of this study was to compare the effects of RAGT combined with VR to those of standard RAGT on information processing speed, sustained attention, working memory, and walking endurance in MS patients. The secondary aim was to assess the training effects on verbal initiation, visual-motor coordination, gait speed, balance performance, and quality of life. Our hypothesis was that the increase in performance in information processing speed, sustained attention, working memory, and walking endurance would be greater after RAGT combined with VR than after standard RAGT alone.

2. Methods

2.1. Trial design

For this pilot, single-blind, randomized controlled trial the examiner was blinded to group assignment (allocation ratio 1:1). The study is reported in accordance with the CONSORT guidelines for pilot randomized controlled trials (Eldridge et al., 2016). It was carried out in accordance with the tenets of the Helsinki Declaration and approved by the local ethics committee. The patients enrolled in this study were a subgroup of those involved in a clinical trial registered at http://clinicaltrials.gov (NCT02896179).

2.2. Subjects

Consecutive outpatients with primary progressive, secondary progressive, and relapsing-remitting MS attending our Neurorehabilitation Unit were recruited between November 2016 and November 2017. A blinded physician experienced in neurorehabilitation screened the patients for eligibility. Inclusion criteria were: diagnosis of primary progressive, secondary progressive, relapsing-remitting MS; Expanded Disability Status Scale (EDSS) score between 3 and 6 (Kurtzke et al., 1983); Mini Mental State Examination score > 24 (Folstein et al., 1975); age > 18 years and <65 years. Exclusion criteria were: MS relapse during the 3 months prior to recruitment; any rehabilitation training in the 6 months prior to recruitment; subjects with psychiatric disorders and/or drugs/alcohol abuse; changes in disease-modifying and symptomatic therapy for MS during the study period; contraindications to RAGT such as inability to sit without trunk support, inability to stand for at least 10 seconds with support; other neurological or orthopedic conditions involving the lower limbs (musculoskeletal diseases, severe osteoarthritis, peripheral neuropathy, joint replacement); cardiovascular co-morbidity (recent myocardial infarction, heart failure, uncontrolled hypertension, orthostatic hypotension); and concurrent participation in other clinical studies. Patients were informed about the experimental nature of the study and gave their written, informed consent.

2.3. Interventions

Prior to the start of the study, we designed the combined RAGT + VR and the standard RAGT protocol. Two physiotherapists experienced in neurorehabilitation, one per treatment group, unaware of patient allocation, conducted the training sessions. Irrespective of group assignment, all patients received individualized treatment for 40 minutes/day, 2 days/week (Tuesday and Thursday) for 6 consecutive weeks, for a total of 12 sessions.

The patients were asked to refrain from any form of physical therapy during the study period other than that scheduled under the present study protocol.

RAGT was performed on a G-EO System (Reha Technology, Olten, Switzerland), which is an end-effector device with body weight support and footplates attached to a double crank and a rocker gear system with three degrees of freedom each that allows control of step length and height (Hesse et al., 2012). The step length of each patient was evaluated with the GAITRite system (CIR Systems, Havertown, PA, USA) and individually defined (Givon et al., 2009).

Each session lasted up to 40 minutes: 5 minutes for positioning the patient on the device, 30 minutes for RAGT, and 5 minutes for removing the patient from the device. To reduce fatigue, the body weight support protocol was gradually set to 2 weeks at 30% of body weight, 2 weeks at 20%, and 2 weeks at 10%.

The RAGT + VR group underwent training on the same device (GE-O System) engendered by non-immersive VR (i.e., the environment displayed on the 2D video screen was not a computer-generated gaming application) (see Fig. 1). Instead, the visual scenario was a simulation of a real walking trail in a natural park and showed a high-definition video on a 42” LED monitor (mod. UE42F5300, Samsung), which was synchronized with the movements of the footplates of the G-EO1 System.

Before starting the training, the patients were instructed to focus in the scenario which was shown to them during the training session. In order to increase the patients’ perception to be involved in a real life situation, they had to pay attention to the screen in which various stimuli (e.g., persons, trees, benches) appeared during the walk. Furthermore the video screen and patients were enclosed in a black curtain to shut out disturbing visual input.

2.4. Outcome measures

The outcome measures were: The Paced Auditory Serial Addition Task (PASAT), The 2-Minutes Walk Test (2MWT), The Phonemic Fluency Test (PFT), The Novel Task, The Digit Symbol (DSymb), The Multiple Sclerosis Quality Of Life-54 (MSQOL-54), The 10-Meter Walking Test (10MWT), The Berg Balance Scale (BBS), Gait analysis and Stabilometric assessment.

All the enrolled subjects in the study were evaluated before, immediately after treatment, and then at one-month follow-up by the same blinded examiners (physician and neuropsychologist). The test order was consistent across evaluation sessions as reported below. To avoid fluctuation in performance due to potential confounders, patients were evaluated in a spacious and silent environment at the same time of day (around at 10 a.m.) for each session.

2.4.1. Primary outcomes

PASAT is a serial addition test to assess information processing speed, sustained attention, and

Fig. 1. G-EO System with VR device (Reha Technology, Olten, Switzerland).

working memory (Ciaramelli et al., 2006). Individuals are asked to listen to an audio recording of a series of single-digit numbers (1–9) and say aloud the sum of the last number presented plus the number preceding it (score range 0–60, higher scores indicate better performance).

2MWT measures self-paced walking ability and functional capacity. It was administered according to the protocol described by Guyatt and colleagues (Guyatt et al., 1984). Patients were asked to walk back and forth along a 30-m indoor corridor as fast as they could in 2 minutes. They were allowed to rest at any point during the test but received no verbal encouragement from the test leaders. No talking was permitted during the tests. The distance walked (in meters) was recorded (higher scores indicated better performance) (Gijbels et al., 2011).

2.4.2. Secondary outcomes

PFT is a measure of verbal initiation. Subjects have 1 minute to produce as many words as possible that begin with a given letter (higher scores indicate better performance) (Mondini et al., 2011).

The Novel Task is a substest of the Rivermead Behavioral Memory Test that explores long-term memory. The subtest evaluates visuo-spatial learning; it is composed of two parts: the Novel Task - Immediate Recall (NT-IR) and the Novel Task - Delayed Recall (NT-DR); for the first the patient uses different colored pieces to replicate a shape demonstrated by the examiner, while for the second the patient uses different colored pieces to replicate the same shape later in the same testing session but without demonstration by the examiner (score NT-IR range 0–51, NT-DR range 0–17, higher scores indicate better performance) (Higginson et al., 2000).

The Digit Symbol (DSymb) is a subtest of the Wechsler Adult intelligence Scale. It measures psychomotor speed, visual-motor coordination, attention, and concentration. Within a specified time limit, the patient presses a key to copy symbols that are paired with numbers (higher scores indicate better performance) (Wechsler, 1955).

MSQOL-54 is a multidimensional health-related quality of life measure that combines both generic and MS-specific items into a single instrument (Solari et al., 1999). This 54- item instrument generates

12 subscales, along with 2 summary scores and 2 additional single-item measures. The subscales are: physical function, role limitations-physical, role limitations-emotional, pain, emotional well- being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life, and sexual function. The summary scores are the Mental Health (MHC) and Physical Health (PHC) composite summaries (higher scores indicate better performance).

10MWT tests self-selected gait speed. For this validated test, subjects walk on a flat, hard floor at their fastest speed for 10 meters (higher scores indicate better performance) (Paltamaa et al., 2005).

BBS is a performance-based assessment tool that evaluates standing balance during functional activities. The scale rates performance from 0 (cannot perform) to 4 (normal performance) on 14 items (corresponding to 14 tasks such as sitting, changing position, transferring, standing, turning, stepping, and reaching) (score range 0–56, higher scores indicate better performance) (Cattaneo et al., 2006).

Gait analysis was performed by means of an electronic system (GaitRite System Gold, version 3.2b–CIR Systems, Havertown, PA, USA) for gathering temporal-spatial data on deambulation. It is made up of an 8-meter long sensorized walkway connected to a PC. The system records the signal, reproducing the pressure maps of each step on a video, thus identifying the progression of the center of gravity and recording the temporal-spatial features of the subject's gait. The main gait parameters were: gait speed, step length, heel-to-heel base support (HH), single support time (SS), double support time (DS), stance and swing phase. The patients walked 4 times at a self-selected speed along a mat with integrated sensors. They were be allowed to use orthoses but no other walking aids (Menz et al., 2004).

Stabilometric assessment was carried out on a monoaxial platform, an electronic system (Technobody, Milan, Italy) that evaluates the instant position of the center of pressure (CoP). The parameters were length (mm) and sway area of CoP trajectory (mm2). Foot position on the platform was standardized for all patients by means of a V-shaped frame. While standing, the patients placed the medial border of their feet alongside the frame. The malleoli were aligned with the vertical bars. The distance between two malleoli was 3 cm and the medial borders of the feet were extra-rotated 12° with respect to the anterior-posterior axis. Patients were evaluated while standing without upper-limb support. An operator stood behind them to prevent them from falling. Each patient was tested in two consecutive conditions (eyes-open and eyes-closed), each lasting 30 s according to the protocol described by Catteneo and colleagues (Cattaneo et al., 2007).

2.5. Randomization and masking

After screening, the principal investigator (PI) randomly assigned eligible patients to the RAGT + VR or the RAGT group according to a simple software-generated randomization scheme. The PI was unaware of which group the subject would be allocated to (allocation was by sealed opaque envelopes). The randomization list was locked in a desk drawer accessible only to the PI (Bryant & Machin, 1997).

2.6. Statistical analysis

Descriptive statistics included mean, median, standard deviation, percentage, and effect size measures between the two independent groups (Cohen's d calculation). Non-parametric tests were applied for inferential statistics because of the non-normal data distribution (Shapiro). The Mann-Whitney U test measured between-group homogeneity at baseline for the following parameters: age (years), education (years), time since diagnosis (years), scores on EDSS, MMSE, PASAT, 2MWT, and MSQOL-54. The Wilcoxon signed rank test was used to compare within-group changes between baseline and post-treatment measures, and baseline and 1-month follow- up. The Mann-Whitney U test was used for between-group comparisons. For this purpose, the difference (Δ) was computed between post/pre-treatment and 1-month follow-up/pre-treatment scores for all outcome measures. Significance was set at $p < 0.05$. Bonferroni correction was applied for multiple comparisons ($p < 0.025$). Data were analyzed using IBM SPSS software (20.0) for Macintosh (IBM-SPSS, Armonk, NY, USA).

3. Results

3.1. Demographic data

Seventeen patients with MS (7 men and 10 women) were randomized to the RAGT + VR group ($n = 8$)

or the RAGT group ($n = 9$). Fourteen patients had a secondary progressive clinical course (7 in the RAGT + VR and 7 in the RAGT group) and 3 had a relapsing-remitting clinical course (1 in the RAGT + VR and 2 in the RAGT group). No adverse events were reported during the study period. Two patients in the RAGT group withdrew because of difficulty arranging transportation to the study site. MS type, age, education, time since diagnosis, scores on EDSS, MMSE, PASAT, 2MWT, and MS-QOL-54 were not statistically different between the two groups at baseline. Table 1 presents the demographic and clinical characteristics of the study sample. The study flow diagram is illustrated in Fig. 2.

3.2. Primary outcomes

Between-group comparison showed a significant change on the 2MWT ($p = 0.023$; Z:–2.269) after treatment (Table 2). No significant post-training effects were observed for the RAGT group (Table 3). Within-group comparison showed a significant improvement in the PASAT score for the RAGT + VR group after treatment ($p = 0.012$; Z:–2.521) and at follow-up ($p = 0.012$; Z:–2.521) and significant changes on the 2MWT ($p = 0.012$; Z:– 2.524) (see Tables 4 and 5).

3.3. Secondary outcomes

Significant post-treatment improvement for the RAGT group were found in the MSQOL-54 MHC ($p = 0.018$; Z:– 2.375), MSQOL-54 PHC ($p = 0.017$; Z:–2.384), 10MWT ($p = 0.018$; Z:–2.371), and BBS ($p = 0.016$; Z:–2.414) (Tables 2 and 3).

Within-group comparison showed significant improvement on the PFT ($p = 0.012$; Z:–2.521) and the NT-IR after treatment ($p = 0.012$; Z:–2.521) and at follow-up ($p = 0.012$; Z:–2.521; $p = 0.012$; Z:–2.521) for the RAGT + VR group. Significant improvements were found in the MSQOL-54 PHC composite ($p = 0.017$; Z:–2.384) and the MSQOL-54 MHC composite ($p = 0.018$; Z:–2.371) after treatment. Significant changes were found on the 10MWT ($p = 0.012$; Z:–2.251) and the BBS ($p = 0.011$; Z:–2.539) after treatment. See Tables 4 and 5.

4. Discussion

The main aim of the present pilot study was to compare changes in information processing speed, sustained attention, working memory, and walking endurance after administration of an innovative combined RAGT + VR protocol versus RAGT alone in MS patients. The secondary aim was to assess the training effects on verbal initiation, visual-motor coordination, gait speed, balance performance, and quality of life.

No significant differences in cognitive test scores were found between the two groups. Nevertheless we showed a significant improvement in the processing speed, sustained attention, working memory and walking endurance in the RAGT-VR group after the treatment Taking into account the numbers available in the present study, it should be emphasized

Table 1

Demographic and clinical features of patients

	RAGT-VR group (8)	RAGT group (9)	p-value (Z)
Numbers	3♂/5♀	4♂/5♀	
MS type (SPMS/RRMS)	7/1	7/2	
Age (years)	57 ± 5,83	51,7 ± 10,24	0.310 (–1,015)
Education (years)	13,5 ± 2,98	10,5 ± 3,21	0.093 (–1,679)
Time since diagnose (years)	17,7, ± 9,62	13,9 ± 9,23	0.470 (–0,723)
EDSS (1–10)	5,4 ± 0,9	5 ± 1,01	0.417 (–0,812)
MMSE (0–30)	28 ± 1,53	27,8 ± 1,31	0.882 (–0,148)
PASAT (0–60)	42,7 ± 13,3	33,8 ± 11,16	0.112 (–1,590)
2MWT (m)	67,6 ± 22,61	74,6 ± 32,7	0.643 (–0.463)
MSQOL-54			
PHC (0–100)	53,6 ± 19,05	45 ± 12,17	0.176 (–1,352)
MHC (0–100)	65,5 ± 23,13	66,7 ± 8,02	0.441 (–0,771)

Data are given as mean ± stardard deviation; p-value (Z) = p-value identified from the Mann-Whitney test. Abbreviations: RAGT-VR: Robot-assisted Gait Training combined with Virtual Reality; RAGT: Robot-assisted Gait Training; MS: Multiple Sclerosis; SPMS: Secondary Progressive Multiple Sclerosis; RRMS: Relapsing/Remitting Multiple Sclerosis; EDSS: Expanded Disability Status Scale; MMSE: Mini Mental State Examination; PASAT: Paced Auditory Serial Addition Task; 2MWT: Two Minutes Walking Test; MSQOL-54: Multiple Sclerosis Quality of Life-54; PHC: Physical Health Composite; MHC: Mental Health Composite. *Statistically significant at $p \leq 0.05$.

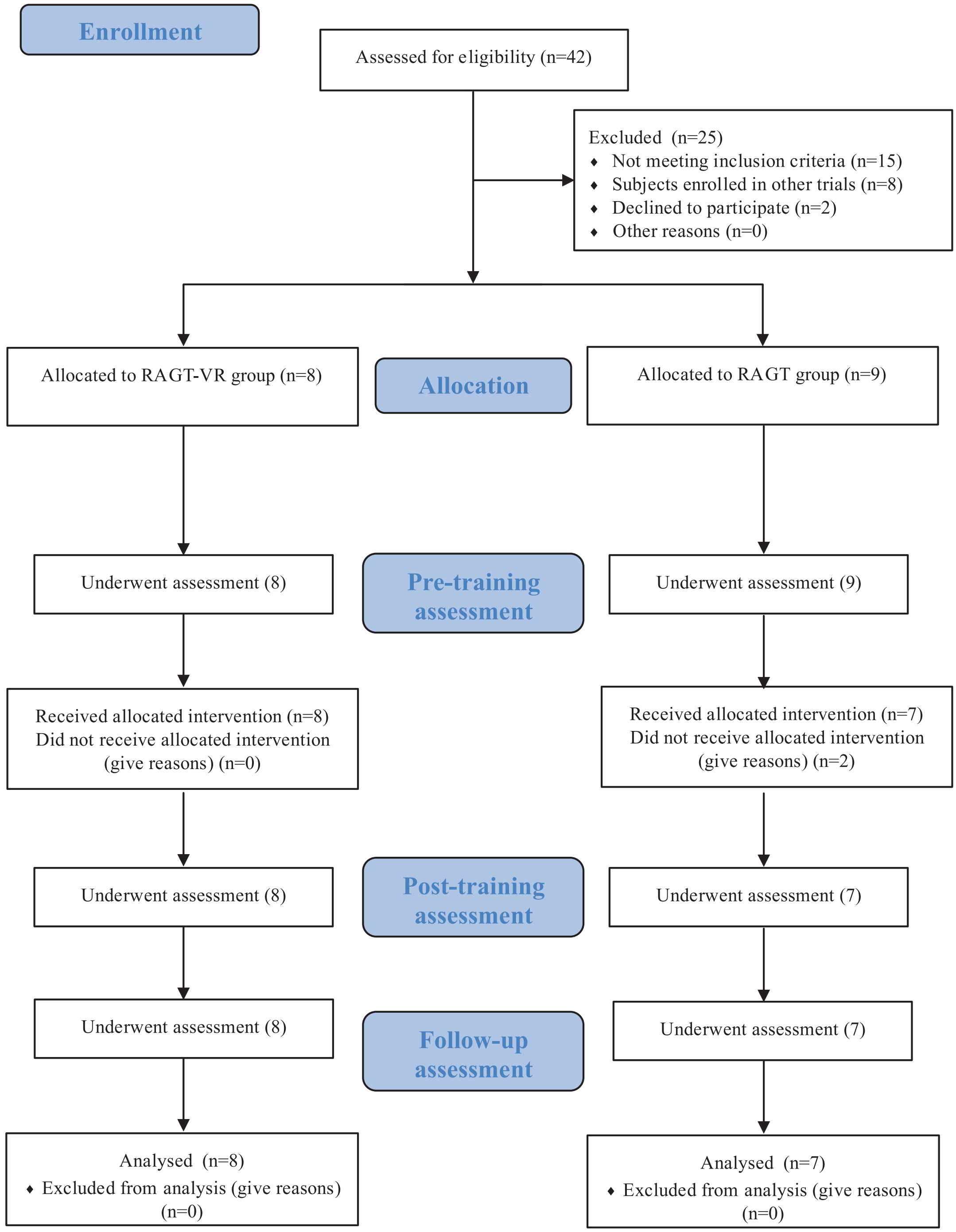

Fig. 2. CONSORT Flow diagram of the study.

that the strength of our conclusions is limited. However, to the best of our knowledge, this is the first study to investigate the effects of combined RAGT + VR on cognitive impairment in MS patients. A similar study conducted by Calabrò and colleagues assessed the efficacy of RAGT in MS patients by means of an exoskeleton device equipped with a VR system and found improved psychological outcome in the patients using the VR system, as shown by improvement in coping strategies. Cognitive deficits

Table 2
Between-group comparisons as to cognitive and quality of life outcomes

	Before/after p value (Z)	Before-FU p value (Z)
PASAT (0–60)	0.324 (–0.986)	0.772 (–0.290)
PFT (n. words)	0.523 (–0.638)	0.201 (–1.279)
RBMT		
NT-IR	0.485 (–0.697)	0.487 (–0.696)
NT-DR	0.244 (–1.165)	0.562 (–0.580)
DSymb (score)	0.070 (–1.815)	0.254 (–1.141)
MSQOL-54		
PHC (0–100)	0.556 (–0.589)	0.771 (–0.291)
MHC (0–100)	0.080 (–1.753)	0.862 (–0.174)

Abbreviations: SD = Standard Deviation; FU = follow-up; *p* value. (Z) = *p*-value and corresponding Z-value identified from the Wilcoxon test; RAGT-VR: Robot-assisted Gait Training combined with Virtual Reality; RAGT: Robot-assisted Gait Training; PASAT: Paced Auditory Serial Addition Task; PFT: Phonemic Fluency Test; RBMT: Rivermead Behavioral Memory Test; DSymb: Digit Symbol; NT-IR: Novel Task - Immediate Recall; NT-DR: Novel Task - Delayed Recall; MSQOL-54: Multiple Sclerosis Quality of Life-54; PHC: Physical Health Composite; MHC: Mental Health Composite. *Statistically significant at $P \leq 0.025$.

Table 3
Between-group comparisons as to gait and balance outcomes

	Before/after P value (Z)	Before-FU p value (Z)
2MWT (m)	0.023 (–2.269)*	0.772 (–0.290)
10MWT (sec)	0.037 (–2.083)	0.643 (–0.463)
BBS (0–56)	0.281 (–1.079)	0.439 (–0.773)
Spatio-temporal gait parameters		
Cadence (step/min)	0.418 (–0.810)	0.568 (–0.571)
Stride (cm)	0.487 (–0.694)	0.668 (–0.429)
Single Support (sec)	0.082 (–1.737)	0.063 (–1.857)
Double Support (sec)	0.817 (–0.231)	0.886 (–0.143)
Stabilometric assessment		
Length of CoP (mm)		
Eyes opened	0.082 (–1.739)	0.817 (–0.231)
Eyes closed	0.908 (–0.116)	0.475 (–0.714)
Sway Area ($mm^{2)}$		
Eyes opened	0.562 (–0.579)	0.317 (–1.000)
Eyes closed	0.908 (–0.116)	0.848 (–0.192)

Abbreviations: SD = Standard Deviation; FU = follow-up; *p* value. (Z) = *p*-value and corresponding Z-value identified from the Wilcoxon test; RAGT-VR: Robot-assisted Gait Training combined with Virtual Reality; RAGT: Robot-assisted Gait Training; 2MWT: Two Minutes Walking Test; 10MWT: Ten Meters Walking Test; BBS: Berg Balance Scale; CoP: Center of Pressure. *Statistically significant at $P \leq 0.025$.

were not directly assessed, however (Calabrò et al., 2017).

The novelty of our findings is that a significantly larger improvement in gait endurance as assessed by 2MWT was noted in the RAGT + VR group than in the RAGT group. This difference can be explained as the result of a repetitive task in a "real life" condition performed by an end-effector device engaged with VR. Indeed, a repetitive gait task with several steps is performed in a single RAGT session and the addition of VR offers an enriched environment where patients can experience walking as if in a real everyday life situation, which otherwise could be cognitively overwhelming for a person with MS. In such patients, the most frequently impaired cognitive domains are complex attention, information processing speed, (episodic) memory, and executive functions (Sepulcre et al., 2006; Sumowski et al., 2009; Benedict et al., 2011). Gaming VR interventions to stimulate cognitive function and optimize sensory information processing and integration systems have been reported to enable anticipatory postural control and response mechanisms (Ortiz-Gutiérrez et al., 2013). Furthermore, VR might target brain networks, speeding up the recovery process (Brütsch et al., 2011). You and colleagues investigated by functional magnetic resonance imaging whether VR induced cortical reorganization in the lower extremity of patients with chronic stroke and suggested that VR may have attributed to positive changes in neural reorganization (You et al., 2005).

In our study, the RAGT + VR group patients obtained significant improvement in executive functions, including sustained attention, working memory, lexical access speed, and visual-spatial learning, and these gains were maintained at the 1-month follow-up evaluation. We can speculate that these positive cognitive effects may transfer to functional abilities (Peruzzi et al., 2017), such as improvement in gait abilities (Fulk, 2005; Baram & Miller, 2010), and we speculate further that these gains are related to an improvement in information processing speed. Furthermore, RAGT + VR was able to maintain enhanced active participation during prolonged training conditions better than RAGT alone. These findings highlight the potential use of VR-based training for improving gait in MS patients. VR has been proposed as a potentially useful tool in rehabilitation (Leocani et al., 2007), as VR-based training provides an enriched opportunity for repetitive practice, feedback information, and motivation for endurance practice, thus promoting cognitive stimulus (visual, auditory and somato-sensory input) and motor learning (Lehrer er al., 2011; Massetti et al., 2016; Laver et al., 2017).

Our findings on cognitive functions are shared by previous studies that investigated the effects of locomotor training and VR in MS patients (Fulk, 2005;

Table 4

Within-group comparison of treatment effects in cognitive and quality of life outcome measures

	Group	Before	After	FU	Before/after		Before-FU	
		Mean ± SD	Mean ± SD	Mean ± SD	*p* value (Z)	Effect size	*p* value (Z)	Effect size
PASAT (0–60)	RAGT-VR group	42,75 ± 13,31	48 ± 11,28	47,88 ± 11,96	0.012 (–2521)*	0.81	0.012 (–2521)*	0.57
	RAGT group	34,43 ± 11,82	36,86 ± 15,44	40,14 ± 14,96	0.445 (–0.763)		0.176 (–1.355)	
PFT (n. words)	RAGT-VR group	31,25 ± 12,76	41,38 ± 15,28	42 ± 11,83	0.012 (–2.521)*	–0.17	0.012 (–2.521)*	0.02
	RAGT group	36 ± 10,50	44,14 ± 16,38	41,71 ± 11,83	0.236 (–1.185)		0.175 (–1,357)	
NT-IR (0–51)	RAGT-VR group	28,5 ± 10,50	38 ± 10,29	37,88 ± 9,03	0.012 (–2.521)*	0.37	0.012 (–2.521)*	0.49
	RAGT group	26,43 ± 9,27	33,57 ± 13,28	32 ± 14,17	0.063 (–1.859)		0.075 (–1.782)	
NT-DR (0–17)	RAGT-VR group	10,50 ± 5,81	13,88 ± 3,72	14 ± 2,71	0.071 (–1.807)	0.11	0.671 (–0.425)	
	RAGT group	10 ± 4,40	13,43 ± 4,54	15,60 ± 1,95	0.173 (–1.362)		0.223 (–1.192)	–0.68
DSymb (score)	RAGT-VR group	34,13 ± 16,46	33,88 ± 15,36	37 ± 15,72	0.914 (–0.108)	–0.42	0.131 (–1.511)	0.07
	RAGT group	34,29 ± 9,86	39,86 ± 12,92	36 ± 13,34	0.063 (–1.863)		0.705 (–0.378)	
MSQOL-54								
PHC (0–100)	RAGT-VR group	53,26 ± 18,97	60,01 ± 20,8	58,45 ± 20,88	0.017 (–2.384)*	0.59	0.042 (–2.032)	0.43
	RAGT group	44,76 ± 14,12	49,81 ± 12,95	50,74 ± 14,18	0.018 (–2.375)*		0.028 (–2.201)	
MHC (0–100)	RAGT-VR group	65,54 ± 23,14	72,77 ± 19,88	69,55 ± 22,09	0.018 (–2.371)*	0.14	0.049 (–1.973)	–0.1
	RAGT group	66,9 ± 8,87	70,63 ± 7,66	71,01 ± 8,87	0.017 (–2.384)*		0.046 (–1.997)	

Abbreviations: SD = Standard Deviation; FU = follow-up; *p* value (Z) = *p*-value and corresponding Z-value identified from the Wilcoxon test; RAGT-VR: Robot-assisted Gait Training combined with Virtual Reality; RAGT: Robot-assisted Gait Training; PASAT: Paced Auditory Serial Addition Task; PFT: Phonemic Fluency Test; DSymb: Digit Symbol; NT-IR: Novel Task - Immediate Recall; NT-DR: Novel Task - Delayed Recall; MSQOL-54: Multiple Sclerosis Quality of Life-54; PHC: Physical Health Composite; MHC: Mental Health Composite. *Statistically significant at $P \leq 0.025$.

Table 5

Within-group comparison of treatment effects in gait and balance outcome measures

	Group	Before	After	FU	Before/after		Before-FU	
		Mean ± SD	Mean ± SD	Mean ± SD	*p* value (Z)	Effect size	*p* value (Z)	Effect size
2MWT (m)	RAGT-VR group	67,63 ± 22,61	82,87 ± 19,65	72,13 ± 20,59	0.012 (–2.524)*	0.16	0.398 (–0.845)	–0.16
	RAGT group	74,57 ± 32,74	78,43 ± 34,65	77 ± 36,36	0.018 (–2.375)*		0.446 (–0.672)	
10MWT (sec)	RAGT-VR group	15,26 ± 4,69	11,78 ± 3,41	14,13 ± 4,23	0.012 (–2.521)*	–0.43	0.293 (–1.501)	–0.13
	RAGT group	15,35 ± 8,15	14,38 ± 7,88	14,98 ± 7,96	0.018 (–2.371)*		0.128 (–1.521)	
BBS (0–56)	RAGT-VR group	40,88 ± 5,96	43,50 ± 5,50	43,86 ± 4,60	0.011 (–2.539)*	–0.53	0.088 (–1.706)	–0.38
	RAGT group	44,29 ± 4,82	46,29 ± 5,06	45,86 ± 5,81	0.016 (–2.414)*		0.223 (–1.219)	
Spatio-temporal gait parameters								
Cadence (step/min)	RAGT-VR group	77,74 ± 19,55	78,54 ± 21,76	81,86 ± 21,08	0.944 (–0.070)	–0.21	0.886 (–0.169)	–0.06
	RAGT group	88,75 ± 28,32	84,75 ± 34,78	83,63 ± 33,25	0.499 (–0.676)		0.600 (–0.524)	
Stride (cm)	RAGT-VR group	84,27 ± 20,90	84 ± 18,82	87,34 ± 23,05	0.575 (–0.560)	–0.39	1.000 (–0.000)	–0.09
	RAGT group	89,38 ± 26,77	92,17 ± 23,37	89,03 ± 14,61	0.237 (–1.183)		0.463 (–0.734)	
Single Support (sec)	RAGT-VR group	0,49 ± 0,11	0,46 ± 0,07	0,45 ± 0.04	0.401 (–0.840)	0.12	0.499 (–0.676)	–0.26
	RAGT group	0,43 ± 0,07	0,45 ± 0,09	0,47 ± 0,10	0.236 (–1.185)		0.046 (–1.992)	
Double Support (sec)	RAGT-VR group	0,69 ± 0,32	0,72 ± 0,38	0,65 ± 0,34	0.575 (–0.560)	–0.08	0.866 (–0.169)	–0.09
	RAGT group	0,64 ± 0,49	0,76 ± 0,57	0,69 ± 0,48	0.866 (–0.169)		0.917 (–0.105)	
Stabilometric assessment								
Length of CoP (mm)								
Eyes opened	RAGT-VR group	247 ± 62,98	184,12 ± 43,31	249,12 ± 89,62	0.012 (–2.524)*	–0.24	0.726 (–0.350)	–0.12
	RAGT group	253,86 ± 58,65	195 ± 47,75	239,14 ± 69,46	0.012 (–2.524)*		0.398 (–0.845)	
Eyes closed	RAGT-VR group	374,25 ± 161,95	308,38 ± 108,16	404,71 ± 127,29	0.327 (–0.980)	–0.11	0.612 (–0.507)	0.04
	RAGT group	343,14 ± 166,76	320,86 ± 121,08	397,67 ± 204,73	0.401 (–0.840)		0.866 (–0.169)	
Sway Area ($mm^{2)}$								
Eyes opened	RAGT-VR group	213 ± 118,25	154,75 ± 90,51	200,88 ± 122,77	0.012 (–2.521)*	0.12	0.779 (–0.280)	0.01
	RAGT group	202,43 ± 92,8	145,14 ± 67,29	200,33 ± 80,51	0.012 (–2.524)*		0.398 (–0.845)	
Eyes closed	RAGT-VR group	381,88 ± 143	279,88 ± 113,04	372,43 ± 136,49	0.262 (–1.122)	–0.27	1.000 (–0.00)	0.34
	RAGT group	375,71 ± 219,91	311,28 ± 122,72	427,83 ± 190,45	0.327 (–0.980)		0.917 (–0.105)	

Abbreviations: SD = Standard Deviation; FU = follow-up; *p* value (Z) = *p*-value and corresponding Z-value identified from the Wilcoxon test; RAGT-VR: Robot-assisted Gait Training combined with Virtual Reality; RAGT: Robot-assisted Gait Training; 2MWT: Two Minutes Walking Test; 10MWT: Ten Meters Walking Test; BBS: Berg Balance Scale; CoP: Center of Pressure. *Statistically significant at $P \leq 0.025$.

Peruzzi et al., 2017). To our knowledge, the effects of RAGT + VR on cognitive function and the relationship between motor rehabilitation and cognition in MS are yet to be fully explored (Postigo-Alonso et al., 2018; Varalta et al., 2018; De Keersmaecker et al., 2019). Calabrò and colleagues reported that, compared to over-ground training and body weight support treadmill training, RAGT + VR may be safely used as a tool to improve walking function in MS patients (Calabrò et al., 2017). Authors concluded that the significant contribution of VR to RAGT may depend on improvement in either attention/motivation or mood. They stated that if the patients are motivated by experiencing a varied and stimulating environment through the VR, they would get an improvement in attention with potentially better functional outcomes, maybe thanks to the reactivation/boosting of brain neurotransmission, including the cholinergic and dopaminergic system.

In our study, within-group analysis of motor ability scores showed that both groups gained in gait ability and balance performance. We hypothesize that the improvements obtained in gait endurance result from training with the device. RAGT performed on an end-effector device such as the GE-O System presents several advantages: task-oriented exercise for gait training and practice in gait-like movement with minimal assistance by means of a partial-body weight system. Before each session, patients are positioned on two footplates, the plate movements simulate stance and swing gait phases in a highly physiological manner. Our results are in line with previous studies (Calabrò et al., 2017; Russo et al., 2018).

Our findings also showed significant improvement in balance ability. As mentioned by Gandolfi and colleagues, RAGT can be considered "task-specific balance training" (Gandolfi et al., 2014). As such, RAGT may stimulate central integrative centers in the brain stem and spinal cord by reinforcing neuronal circuits, leading to improved postural control. Since the GE-O device allows for performing more steps than in standard physiotherapy, patients are able to train at higher volume and intensity for a fixed time in a single session of physiotherapy (Hesse et al., 2013). Given these advantages, RAGT can be considered a useful approach to address proprioceptive and central integration deficits. Our results are in line with previously studies in which RAGT coupled to 2D VR may be a valuable tool for promoting neural plasticity and that it could be considered as induction therapy to improve walking ability and balance performance in MS patients (Russo et al., 2018; De Keersmaecker et al., 2019).

In addition to investigating cognitive and motor effects, the present study demonstrated significant improvement in quality of life in both groups. The functional consequences of MS-related impairments can be debilitating, with a multidimensional impact on activities of daily living. The gain in quality of life can be attributed to the positive effects of RAGT. Our findings are in line with a previously studies (Straudi et al., 2016, Fanciullacci et al. 2017) and support the hypothesis that, by inducing functional recovery, RAGT can influence the subjective perception of functional outcomes (Feistein et al., 2015).

This pilot, randomized controlled trial has several limitations that restrict the strength of its conclusions. First, the sample size is small. Based on sample size calculation, 100 patients (50 per group) are required to detect a significant improvement on the PASAT test (power of 95%). Because this study is a part of larger project, to further validate our present findings, a multicenter randomized controlled is needed to increase the number of subjects. Second, fully immersive VR may provide a complete simulated experience through the support of multiple sensory output devices to enhance stereoscopic view of the environment through movement of the user's head, as well as audio and haptic devices; this could be more interactive for immersing the patient in reality. Third, the lack of a follow-up assessment at 3 or more months after training is needed to further assess the persistence of the training effect.

In conclusion, greater positive effects on gait ability were noted after RAGT engendered by VR than RAGT alone. VR-enhanced training may influence cognitive functions in MS patients and provide a therapeutic alternative and a motivational and effective enrichment of traditional motor rehabilitation.

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Conflicts of interest

The authors declare that they have no conflict of interest related to the publication of this manuscript.

References

Baram, Y., & Miller, A. (2010). Glide-symmetric locomotion reinforcement in patients with multiple sclerosis by visual feedback. *Disability and Rehabilitation: Assistive Technology*, *5*(5), 323-326.

Benedict, R.H.B., & Zivadinov, R. (2011). Risk factors for and management of cognitive dysfunction in multiple sclerosis. *Nature Reviews Neurology*, *7*(6), 332-342.

Bisht, B., Darling, W.G., White, E.C., White, K.A., Shivapour, E.T., Zimmerman, M.B., & Wahls, T.L. (2017). Effects of a multimodal intervention on gait and balance of subjects with progressive multiple sclerosis: a prospective longitudinal pilot study. *Degenerative Neurological and Neuromuscular Disease*, *7*, 79-93.

Brütsch, K., Koenig, A., Zimmerli, L., Mérillat-Koeneke, S., Riener, R., Jäncke, L., van Hedel, H.J., & Meyer- Heim, A. (2011). Virtual reality for enhancement of robot-assisted gait training in children with central gait disorders. *Journal of Rehabilitation Medicine*, *43*(6), 493-499.

Bryant, T.N., Machin, D. (1997). Statistical methods. In B.A. Wilson & D.L. McLellan, (Eds), Rehabilitation Studies Handbook (pp. 189-204). Cambridge, Enlgland: Cambridge University Press.

Calabrò, R.S., Russo, M., Naro, A., De Luca, R., Leo, A., Tomasello, P., Molonia, F., Dattola, V., Bramanti, A., & Bramanti, P. (2017). Robotic gait training in multiple sclerosis rehabilitation: can virtual reality make the difference? Findings from a randomized controlled trial. *Journal of the Neurological Sciences*, *377*, 25-30.

Cameron, M.H., Fitzpatrick, M., Overs, S., Murchison, C., Manning, J., & Whitham, R. (2014). Dalfampridine improves walking speed, walking endurance, and community participation in veterans with multiple sclerosis: a longitudinal cohort study. *Multiple Sclerosis Journal*, *20*(6), 733-738.

Cameron, M., Mazumder, R., Murchison, C., & King, L. (2014). Mini Balance Evaluation Systems Test in people with multiple sclerosis: reflects imbalance but may not predict falls. *Gait & Posture*, *39*(1), 669.

Casuso-Holgado, M.J., Martín-Valero, R., Carazo, A.F., Medrano-Sánchez, E.M., Cortés-Vega, M.D., & Montero-Bancalero, F.J. (2018). Effectiveness of virtual reality training for balance and gait rehabilitation in people with multiple sclerosis: a systematic review and meta-analysis. *Clinical Rehabilitation*, *32*(9), 1220-1234.

Cattaneo, D., Jonsdottir, J., Zocchi, M., & Regola, A. (2007). Effects of balance exercises on people with multiple sclerosis: a pilot study. *Clinical Rehabilitation*, *21*(9), 771-781.

Cattaneo, D., Regola, A., & Meotti, M. (2006). Validity of six balance disorders scales in persons with multiple sclerosis. *Disability and Rehabilitation*, *28*(12), 789-795.

Ciaramelli, E., Serino, A., Benassi, M., & Bolzani, R. (2006). Standardizzazione di tre test di memoria di lavoro. *Giornale Italiano di Psicologia*, *33*(3), 607-624.

Wechsler, D. (1955). Manual for the Wechsler Adult Intelligence Scale. Oxford, England: Psychological Corp.

De Keersmaecker, E., Lefeber, N., Geys, M., Jespers, E., Kerckhofs, E., & Swinnen, E. (2019). Virtual reality during gait training: does it improve gait function in persons with central nervous system movement disorders? A systematic review and meta-analysis. *NeuroRehabilitation*, *44*(1), 43-66.

Eldridge, S.M., Chan, C.L., Campbell, M.J., Bond, C.M., Hopewell, S., Thabane, L., Lancaster, G.A., & PAFS consensus group. (2016). CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *British Medical Journal*, *355*, i5239.

Fanciullacci, C., Straudi, S., Basaglia N., & Chisari, C., (2017). The role of psychological well-being in multiple sclerosis rehabilitation. *European Journal of Physical and Rehabilitation Medicine*, *53*(1), 105-113.

Feinstein, A., Freeman, J., & Lo, A.C. (2015). Treatment of progressive multiple sclerosis: what works, what does not, and what is needed. *Lancet Neurology*, *14*(2), 194-207.

Folstein, M.F., Folstein, S.E., & McHugh, P.R. (1975). Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*, 189-198.

Fonte, C., Smania, N., Pedrinolla, A., Munari, D., Gandolfi, M., Picelli, A., Varalta, V., Benetti, MV., Brugnera, A., Federico, A., Muti, E., Tamburin, S., Schena, F., &Venturelli, M. (2019). Comparison between physical and cognitive treatment in patients with MCI and Alzheimer's disease. *Aging*, *11*(10), 3138-3155.

Fulk, G.D. (2005). Locomotor training and virtual reality-based balance training for an individual with multiple sclerosis: a case report. *Journal of Neurologic Physical Therapy*, *29*(1), 34-42.

Gandolfi, M., Geroin, C., Picelli, A., Munari, D., Waldner, A., Tamburin, S., Marchioretto, F., & Smania, N. (2014). Robot-assisted vs. sensory integration training in treating gait and balance dysfunctions in patients with multiple sclerosis: a randomized controlled trial. *Frontiers in Human Neuroscience*, *8*, 318.

Gijbels, D., Eijnde, B., & Feys, P. (2011). Comparison of the 2- and 6-minute walk test in multiple sclerosis. *Multiple Sclerosis Journal*, *17*(10), 1269-1272.

Givon, U., Zeilig, G., & Achiron, A. (2009). Gait analysis in multiple sclerosis: characterization of temporal- spatial parameters using GAITRite functional ambulation system. *Gait & Posture*, *29*(1), 138-142.

Goodman, A.D., Brown, T.R., Edwards, K.R., Krupp, L.B., Schapiro, R.T., Cohen, R., Marinucci, L.N., Blight, A.R., & MSF204 Investigators. (2010). A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Annals of Neurology*, *68*(4), 494-502.

Goodman, A.D., Brown, T.R., Krupp, L.B., Schapiro, R.T., Schwid, S.R., Cohen, R., Marinucci, L.N., Blight, A.R., & Fampridine MS-F203 Investigators. (2009). Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. *Lancet*, *373*(9665), 732-738.

Gunn, H.J., Newell, P., Haas, B., Marsden, J.F., & Freeman, J.A. (2013). Identification of risk factors for falls in multiple sclerosis: a systematic review and meta-analysis. *Physical Therapy*, *93*(4), 504-513.

Guyatt, G.H., Pugsley, S.O., Sullivan, M.J., Thompson, P.J., Berman, L., Jones, N.L., Fallen, E.L., Taylor, D.W. (1984). Effect of encouragement on walking test performance. *Thorax*, *39*(11), 818-822.

Hesse, S., Schattat, N., Mehrholz, J., & Werner, C. (2013). Evidence of end-effector based gait machines in gait rehabilitation after CNS lesion. *NeuroRehabilitation*, *33*(1), 77-84.

Hesse, S., Tomelleri, C., Bardeleben, A., Werner, C., & Waldner, A. (2012). Robot-assisted practice of gait and stair climbing in nonambulatory stroke patients. *Journal of Rehabilitation Research & Development*, *49*(4), 613-622.

Higginson, C.I., Arnett, P.A., & Voss, W.D. (2000). The ecological validity of clinical tests of memory and attention in multiple sclerosis. *Archives Clinical Neuropsychology*, *15*(3), 185-204.

Jongen, P.J., Ter Horst, A.T., & Brands, A.M. (2012). Cognitive impairment in multiple sclerosis. *Minerva Medica*, *103*(2), 73-96.

Khan, F., & Amatya, B. (2017). Rehabilitation in multiple sclerosis: a systematic review of systematic reviews. *Archives of Physical Medicine and Rehabilitation*, *98*(2), 353-367.

Krause, I., Kern, S., Horntrich, A., & Ziemssen, T. (2013). Employment status in multiple sclerosis: impact of disease-specific and non-disease-specific factors. *Multiple Sclerosis Journal*, *19*(13), 1792-1799.

Kurtzke, J.F. (1983). Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*, *33*(11), 1444-1452.

Larocca, N.G. (2011). Impact of walking impairment in multiple sclerosis: perspectives of patients and care partners. *Patient*, *4*(3), 189-201.

Laver, K.E., Lange, B., George, S., Deutsch, J.E., Saposnik, G., & Crotty, M. (2017). Virtual reality for stroke rehabilitation. *Cochrane Database Of Systematic Reviews*, *11*, CD008349.

Lehrer, N., Chen, Y., Duff, M., L Wolf, S., & Rikakis, T. (2011). Exploring the bases for a mixed reality stroke rehabilitation system, Part II: design of interactive feedback for upper limb rehabilitation. *Journal of NeuroEngineering and Rehabilitation*, *8*, 54.

Leocani, L., Comi, E., Annovazzi, P., Rovaris, M., Rossi, P., Cursi, M., Comola, M., Martinelli, V., & Comi, G. (207). Impaired short-term motor learning in multiple sclerosis: evidence from virtual reality. *Neurorehabilitation Neural Repair*, *21*(3), 273-278.

Loitfelder, M., Fazekas, F., Koschutnig, K., Fuchs, S., Petrovic, K., Ropele, S., Pichler, A., Jehna, M., Langkammer, C., Schmidt, R., Neuper, C., & Enzinger, C. (2014). Brain activity changes in cognitive networks in relapsing-remitting multiple sclerosis - insights from a longitudinal FMRI study. *PLoS One*, *9*(4), e93715.

Maggio, M.G., Russo, M., Cuzzola, M.F., Destro, M., La Rosa, G., Molonia, F., Bramanti, P., Lombardo, G., De Luca, R., & Calabrò, R.S. (2019). Virtual reality in multiple sclerosis rehabilitation: A review on cognitive and motor outcomes. *Journal of Clinical Neuroscience*, *65*, 106-111.

Massetti, T., Trevizan, I.L., Arab, C., Favero, F.M., Ribeiro-Papa, D.C., & de Mello Monteiro, C.B. (2016). Virtual reality in multiple sclerosis – A systematic review. *Multiple Sclerosis and Related Disorders*, *8*, 107-112.

Menz, H.B., Latt, M.D., Tiedemann, A., Mun San Kwan, M., & Lord, S.R. (2004). Reliability of the GAITRite walkway system for the quantification of temporo-spatial parameters of gait in young and older people. *Gait & Posture*, *20*(1), 20-25.

Mondini S, Mapelli D., Alec Vestri, A., Arcara, G., Bisiacchi, P.S. (2011). Esame neuropsicologico breve 2. Una batteria di test per lo screening neuropsicologico. Milan, Italy: Raffaello Cortina Editore.

Ortiz-Gutiérrez, R., Cano-de-la-Cuerda, R., Galán-del-Río, F., Alguacil-Diego, I.M., Palacios-Ceña, D., & Miangolarra-Page, J.C. (2013). A telerehabilitation program improves postural control in multiple sclerosis patients: a Spanish preliminary study. *International Journal of Environmental Research and Public Health*, *10*(11), 5697-5710.

Paltamaa, J., West, H., Sarasoja, T., Wikström, J., & Mälkiä, E. (2005). Reliability of physical functioning measures in ambulatory subjects with MS. *Physiotherapy Research International*, *10*(2), 93-109.

Peruzzi, A., Zarbo, I.R., Cereatti, A., Della Croce, U., & Mirelman, A. (2017). An innovative training program based on virtual reality and treadmill: effects on gait of persons with multiple sclerosis. *Disability and Rehabilitation*, *39*(15), 1557-1563.

Postigo-Alonso, B., Galvao-Carmona, A., Benítez, I., Conde-Gavilán, C., Jover, A., Molina, S., Peña-Toledo, M.A., & Agüera, E. (2018). Cognitive-motor interference during gait in patients with Multiple Sclerosis: a mixed methods Systematic Review. *Neuroscience & Biobehavioral Reviews*, *94*, 126-148.

Russo, M., Dattola, V., De Cola, M.C., Logiudice, A.L., Porcari, B., Cannavò, A., Sciarrone, F., De Luca, R., Molonia, F., Sessa, E., Bramanti, P., & Calabrò, R.S. (2018). The role of robotic gait training coupled with virtual reality in boosting the rehabilitative outcomes in patients with multiple sclerosis. *International Journal of Rehabilitation Research*, *41*(2), 166-172.

Schwartz, I., Sajin, A., Moreh, E., Fisher, I., Neeb, M., Forest, A., Vaknin-Dembinsky, A., Karusis, D., & Meiner Z. Robot-assisted gait training in multiple sclerosis patients: a randomized trial. *Multiple Sclerosis Journal*, *18*(6), 881-890.

Sepulcre, J., Vanotti, S., Hernández, R., Sandoval, G., Cáceres, F., Garcea, O., & Villoslada, P. (2006). Cognitive impairment in patients with multiple sclerosis using the Brief Repeatable Battery-Neuropsychology test. *Multiple Sclerosis Journal*, *12*(2), 187-195.

Shah, P. (2015). Symptomatic management in multiple sclerosis. *Annals of Indian Academy of Neurology*, *18*(1), S35-S42.

Solari, A., Filippini, G., Mendozzi, L., Ghezzi, A., Cifani, S., Barbieri, E., Baldini, S., Salmaggi, A., Mantia, L.L., Farinotti, M., Caputo, D., & Mosconi, P. (1999). Validation of Italian multiple sclerosis quality of life 54 questionnaire. *Journal of Neurology, Neurosurgery and Psychiatry*, *67*(2), 158-162.

Sosnoff, J.J., Sandroff, B.M., & Motl, R.W. (2012). Quantifying gait abnormalities in persons with multiple sclerosis with minimal disability. *Gait & Posture*, *36*(1), 154-156.

Straudi, S., Benedetti, M.G., Venturini, E., Manca, M., Foti, C., & Basaglia, N. (2013). Does robot-assisted gait training ameliorate gait abnormalities in multiple sclerosis? A pilot randomized-control trial. *NeuroRehabilitation*, *33*(4), 555-563.

Straudi, S., Fanciullacci, C., Martinuzzi, C., Pavarelli, C., Rossi, B., Chisari, C., & Basaglia N. (2016). The effects of robot-assisted gait training in progressive multiple sclerosis: A randomized controlled trial. *Multiple Sclerosis Journal*, *22*(3), 373-384.

Sumowski, J.F., Chiaravalloti, N., Wylie, G., & Deluca, J. (2009). Cognitive reserve moderates the negative effect of brain atrophy on cognitive efficiency in multiple sclerosis. *Journal of the International Neuropsychological Society*, *15*(4), 606-612.

Taylor, M., & Griffin, M. (2015). The use of gaming technology for rehabilitation in people with multiple sclerosis. *Multiple Sclerosis Journal*, *21*, 355-371.

Varalta, V., Fonte, C., & Munari, D. (2018) The influence of cognitive factors on balance and gait. In G. Sandrini, V. Homberg, L. Saltuari, N. Smania & A. Pedrocchi (Eds), Advanced technologies for the rehabilitation of gait and balance disorders (pp. 121-134). Switzerland AG: Springer Nature.

Yogev-Seligmann, G., Hausdorff, J.M., & Giladi, N. (2008). The role of executive function and attention in gait. *Movement Disorders*, *23*(3), 329-342.

You, S.H., Jang, S.H., Kim, Y.H., Hallett, M., Ahn, S.H., Kwon, Y.H., Kim, J.H., & Lee, MY. (2005). Virtual reality-induced cortical reorganization and associated locomotor recovery in chronic stroke: an experimenter-blind randomized study. *Stroke*, *36*(6), 1166-1171.