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Effects of a virtual reality and treadmill training on gait of subjects with multiple sclerosis: a pilot study.

Short title for running head: VR based gait training for MS subjects.

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Abstract

Gait and cognitive deficits are common in multiple sclerosis (MS) and are negatively affected during dual-task walking. Treadmill (TM) training has been previously used to preserve locomotor activity in MS. Virtual reality (VR) engages the user in cognitive and motor activities simultaneously. A training combining TM and VR has been successfully adopted in several neurological diseases, but not in MS. This study aims at investigating the feasibility of a TM- and VR-based rehabilitation intervention on gait of subjects with MS.

Eight persons with relapsing-remitting MS were recruited to participate in a six-week TM- and VR-based training. Gait analysis was performed both in single and dual task conditions. Clinical tests were used to assess walking endurance and obstacle negotiation. All the evaluations were performed before, immediately and one month after the training. Gait speed and stride length improved in dual task post-intervention and were retained at follow-up. An improved ability in negotiating obstacles was found across the evaluations. TM- and VR-based training is feasible and safe for MS subjects with moderate disabilities and may positively affect gait under complex conditions, such as dual tasking and obstacle negotiation.

Key words: dual task, gait, multiple sclerosis, rehabilitation, relapsing-remitting, treadmill, virtual reality.

INTRODUCTION

Multiple sclerosis (MS) is a progressive degenerative disease involving impairments in the motor, sensory and cognitive systems (O'Sullivan & Schmitz 1988). Common motor symptoms in MS include muscle weakness, ataxia, stiffness and muscle spasms (LaRocca 2011). Compared to normal gait, MS individuals frequently show reduced stride length and gait speed, prolonged double limb support duration and greater variability in the lower limb kinematics (Crenshaw et al. 2006; Socie & Sosnoff 2013a). Approximately 75% of individuals with MS report mobility problems (Lord et al. 1998; Swingler & Compston 1992) and experience fatigue, that severely affects walking endurance (Krupp et al. 1988; Socie & Sosnoff 2013b; Fisk et al. 2005). Cognitive impairments are observed in processing speed and attention, which affect performance in executive functions and memory (Chiaravalloti & DeLuca 2008). Recently, some studies explored the relationship between cognitive aspects and gait impairments in people with MS, reporting deteriorations in their gait when walking while performing a secondary attention-demanding task (Sosnoff et al. 2011; Hamilton et al. 2009; Motl et al. 2014). Since daily life often requires walking with simultaneous cognitive demands, a gait rehabilitation intervention for MS individuals should include dual task paradigms.

Specific rehabilitation treatments for gait dysfunction in MS mostly include muscle-strengthening exercises, gait and balance control techniques (O'Sullivan & Schmitz 1988; Cameron & Wagner 2011). Among them, treadmill (TM) training has been recently applied to MS individuals (Beer et al. 2012; Swinnen et al. 2012) and has shown to improve gait speed and endurance (Giesser et al. 2007; Pilutti et al. 2011; Van Den Berg et al. 2006; Newman et al. 2007).

Virtual reality (VR) is a relatively new intervention tool in rehabilitation and allows to simultaneously engage the subject in cognitive and motor activities (dual tasking). VR has shown to enhance motor learning, through the provision of multisensory feedback, and to improve patients' motivation during rehabilitation, decreasing the perception of exertion (Thornton et al. 2005; Burdea 2002). Gait rehabilitation interventions based on the combined use of VR and TM demonstrated improvements in gait quality in individuals post-stroke (Fung et al. 2006; Yang et al. 2008; Walker et al. 2010; Jaffe et al. 2004) and in patients with Parkinson's disease (Mirelman et al. 2011).

Although TM- and VR-based training programs have shown promising results in neurological diseases, there is little evidence of its utility in MS. In a case report study, Fulk used TM and VR for training a person with MS (Fulk 2005). The study investigated the effects of the TM training on walking, while a separate VR-based intervention was used to train balance. Improvements were observed in the subject's gait speed, balance, and endurance. However, a combined TM and VR-based intervention in MS was never explored.

The aim of this study was to assess the feasibility of using a combined TM and VR-based intervention to improve gait and endurance in subjects with MS. The effects of a six-week TM- and VR-based intervention were assessed through both a clinical evaluation and a full instrumental gait analysis.

MATERIALS AND METHODS

Study Design

This study employed a repeated measures design. A group of MS individuals attended the TM and VR-based intervention and was evaluated in three experimental sessions: 1) before the beginning of the training (Pre); 2) immediately after the completion of the training (Post) and 3) after four weeks from the completion of the training (F-Up).

Participants

Eight subjects with relapsing-remitting MS (Polman et al. 2011) were recruited from the Operative Unit of the Neurology unit at the Sassari University Hospital (7 f; mean age±std: 44.3±8.1 y.o.). Inclusion criteria included an expanded disability status scale (EDSS) score between 3 and 6 (Kurtzke 1983) and an Ambulation Index between 3 and 5 (Rose et al. 2006), which reflect mild to moderate impairment (to assess the feasibility of using such intervention on a wide range of MS subjects). Subjects were included if they also had a mini-mental state examination score equal or higher than 24 (to ensure no dementia) and stable medical conditions with no apparent relapses in the six months prior to the study. Exclusion criteria included chronic medical illnesses, severe visual deficits (assessed using the visual acuity tests), severe ataxia during gait and major depression (DSM-IV-TR criteria, American Psychiatric Association, 2000). Subjects who had received botulinum toxin injection within the past four months or functional surgery in the past six months were also excluded from the study.

During the study, participants did not receive concurrent physical therapy treatments. All participants provided an informed written consent, approved by the local ethics committee, prior to the study.

Training equipment

A TM , a safety harness and a head mounted display (Emagin, Z800) – or, alternatively, an LCD screen (LG, Lw550t, 32”; resolution:1366x768 pixels) – were used for the training sessions (Figure 1a). The head mounted display was used to deliver a VR environment purposely developed. Two magneto-inertial measurement units (Xsens, MTx) were attached to the subject's shoes and used to reproduce their motion in the VR environment in real time (Figure 1b). An additional unit was placed on the subject’s head to monitor its rotation in the horizontal plane and to move the VR accordingly. Further details on the experimental set-up used in this study may be found elsewhere (Peruzzi et al. 2013).

Figure 1 a) The experimental set-up used to provide the rehabilitation intervention; b) a screen-shot of the VR environment delivered to the subject while walking on the TM, during a training session.

Intervention

The participants walked on the TM while watching a VR environment representing a tree-lined trail. Subjects were required to pass obstacles (puddles and logs) appearing on the trail. The specific simulation was chosen to address specific gait problems, common in MS (i.e., decreased foot clearance, obstacle avoidance, and problems with planning). Successful and unsuccessful passes, as determined by the inertial measurements, were rendered to the subject during the trial with visual and auditory feedbacks. A cognitive concurrent task was added by asking subject to memorize the route to follow, which was shown to them prior to the trial. Several dynamic distractors were also added to the virtual environment to challenge subject's attention.

The intervention was administered twice a week for six weeks by a physical therapist who also provided verbal instructions to assist in motor learning. Training sessions were scheduled at similar times during the day in a temperature-controlled training room. Each training session lasted about 45 minutes (3x10-minute training bout + 5-minute rest between each bout). Subjects reported their perceived level of exertion using an *ad-hoc* scale before and after each bout (Borg 1982).

Training progression was based on a protocol of intensive progressive individualized TM training with VR for neurological subjects (Mirelman et al. 2011). Walking progression was based on subjects' overground gait speed, calculated from the 10-meter walk test performed prior to the training. In the first session, TM speed was set at 80% subject's gait speed. Then, TM speed was increased by 10% each week. The frequency and size of the virtual obstacles were adjusted during the intervention to increase task complexity and progress training difficulty. Cognitive challenges were introduced in the second week and were gradually increased each week based on the subjects' performance.

Evaluation

Subjects were asked to walk overground in the gait analysis laboratory under two conditions: a) at comfortable speed (single task condition - ST); and b) while serially subtracting the number "3" from a predefined 3-digit number (dual task condition - DT). Testing conditions were fixed for all subjects in all evaluations.

A stereo-photogrammetric system (six-camera Vicon, T20; video rate: 100 frames/s) and two force platforms (AMTI, OR6-7; sampling at 1000 Hz) were used to collect marker trajectories and ground reaction forces. The Vicon Plug-in Gait protocol (Davis et al. 1991) was adopted for the estimate of spatial-temporal parameters, lower limb joint kinematics and kinetics. Selected joint kinematic parameters (peak values of the kinematic curves) (Benedetti & Pignotti 1998) and kinetic parameters (maximum values of the joint moments and power during gait phases) were then extracted. Three gait cycles were acquired for ST and DT. The evaluations in the DT condition were performed after those in ST. Patients were allowed to rest after each trial. Instrumented gait analysis was carried out by an experienced bioengineer and a physical therapist.

A battery of clinical tests was also carried out for ancillary evaluations by a clinician. The six minute walk test (6MWT) was used to assess walking endurance (American Thoracic Society 2002). The Four Square Step Test (FSST), a timed test consisting of stepping over an obstacle (Dite & Temple 2002) was used to evaluate obstacle negotiation (Mirelman et al. 2011; Blennerhassett & Jayalath 2008). The EDSS was assessed at each evaluation session by the same physician.

Data analysis

Data from both the most and the least affected side were analyzed separately. The percentage change $\Delta x_{\%}$ of each selected parameter at Post and at F-Up, respect to Pre, was computed ($\Delta x_{\%} = 100 \cdot (x_{post} - x_{pre}) / x_{pre}$). Moreover, percentage dual task cost (DTC) of walking (Hamilton et al. 2009), for gait speed, stride time and stride length, between ST and DT was calculated (DTC = 100 * |(ST-DT)/ST|). Descriptive statistics (mean and std) were computed, across subjects, for gait parameters, DTC of walking of the selected gait parameters, motor test and EDSS scores.

The Friedman test was used to assess the effects of the intervention. For significant findings, pairwise comparisons were performed between Post and Pre and between F-Up and Pre, using Wilcoxon signed ranks test. The level of significance was determined using the Holm-Bonferroni correction for adjusted p-values (alpha=0.05). The statistical analysis was performed using SPSS (v. 21, IBM).

RESULTS

All the participants completed the training and tolerated the training sessions well. No adverse effects or medical treatment interferences were reported (the drug was taken at least 24 hours before each training session). None of the subjects reported falls throughout the entire study period. A summary of the subjects characteristics are shown in Table 1. One subject used crutches to walk. Subjects were similar in regards to education years and cognitive function.

Subject	Age (years)	Gender	Disease Duration (years)	EDSS	AI	MMSE	Clinical involvement (Most affected side)
P01	40	F	17	5	3	29	unilateral (left)
P02	60	F	17	5.5	4	30	unilateral (right)
P03	38	F	5	3.5	3	28	unilateral (left)
P04	43	F	5	4	3	29	unilateral (right)
P05	34	F	5	6	5	29	bilateral (left)
P06	50	F	18	4	3	30	unilateral (right)
P07	42	F	11	6	4	27	bilateral (left)
P08	48	M	15	4.5	3	24	bilateral (left)
mean±std	44.4±7.6	-	11.6±5.5	4.8±0.9	3.5±0.7	28.3±1.9	-

Table 1 Participants' characteristics.

In the first training session, the average TM speed was 0.53 m/s, all subjects walked while holding the handrails, and often hit the obstacles (only 18% successful passes). As training progressed, TM speed and the number of negotiated obstacles increased. At the final session average TM speed was 0.81 m/s (with an average success rate of 67% in obstacle negotiation) and the use of handrails diminished (five subjects were able to walk on the TM without hand support). The Borg scores provided by the subjects across the training sessions revealed no excessive exertion (Peruzzi et al. 2013).

Since one subject could not walk autonomously during the gait assessment, force platform data for that subject were not recorded. Hence, lower limb joint kinetic data were analyzed for seven subjects.

Gait spatial-temporal parameters

No significant increases were observed in ST condition. Gait speed increased, by 10% at Post and 11% at F-Up (p=0.197, Table 2). Stride length increased by 7% at Post and by 11% at F-Up . In the DT condition, gait speed significantly increased by 18% at Post and by 26% at F-Up (Table 2). Stride length significantly increased by 10% at Post and by 16% at F-Up. DTC of walking decreased, although not significantly, at Post (DTC for gait speed from 12±23% to 10±12%, DTC for stride time from 15±21% to 7±10% and DTC for stride length from 4±12% to 5±6%) and at F-Up (DTC for gait speed to 6±13%, DTC for stride time to 7±12% and DTC for stride length to 1±7%).

	Parameter	Pre	Post	F-Up	p-value
ST	**Gait speed [m/s]**	0.79 ± 0.27	0.87 ± 0.26	0.88 ± 0.23	0.197
	Stride time [s]	1.34 ± 0.45	1.27 ± 0.32	1.28 ± 0.28	0.197
	Stride Length [m]	0.97 ± 0.22	1.04 ± 0.20	1.08 ± 0.16	0.135
DT	**Gait speed [m/s]**	0.65 ± 0.19	0.77 ± 0.24*	0.82 ± 0.21*	0.021
	Stride time [s]	1.50 ± 0.35	1.35 ± 0.29	1.36 ± 0.30	0.034
	Stride Length [m]	0.91 ± 0.15	1.00 ± 0.21*	1.06 ± 0.1*	0.008

Table 2 Spatial-temporal parameters values (mean ± standard deviation) at Pre, Post and F-Up in single task (ST) and dual task (DT) condition. The asterisk (*) indicates a significant change (alpha = 0.05) of the parameter at Post and F-Up with respect to Pre.

Joint kinematics and kinetics

Joint kinematic and kinetic parameters during ST did not show significant changes in the most affected side, with the exception of the maximum value of the hip extension angle at terminal stance (Figure 2). The same parameter showed a similar trend, in the least affected side (Pre: 14.3 ± 5.2 deg, F-Up: 16.9 ± 5.9 deg). In the least affected side, the maximum value of the ankle plantar-flexion angle during the pre-swing phase significantly (p=0.03) increased between Pre and Post (Figure 2).

In DT, the maximum value of hip extension at terminal stance in the most affected side showed an increase, although not significant, between Pre and F-Up (Pre: 14.5 ± 5.1 deg, F-Up: 18.2 ± 5.4 deg; p = 0.07). The maximum ankle plantar-flexion during the pre-swing phase increased in the least affected side (Pre: 6.4 ± 6.9 deg, Post: 12.6 ± 7.2 deg, F-Up: 11.8 ± 7.2 deg; p = 0.07). For the most affected side, the maximum power generated by the ankle significantly increased between Pre and Post (p = 0.04) and the gain was retained also in F-Up (p = 0.04), whereas, the maximum absorbed power showed a significant increase (p = 0.04) between Pre and F-Up (Figure 2).

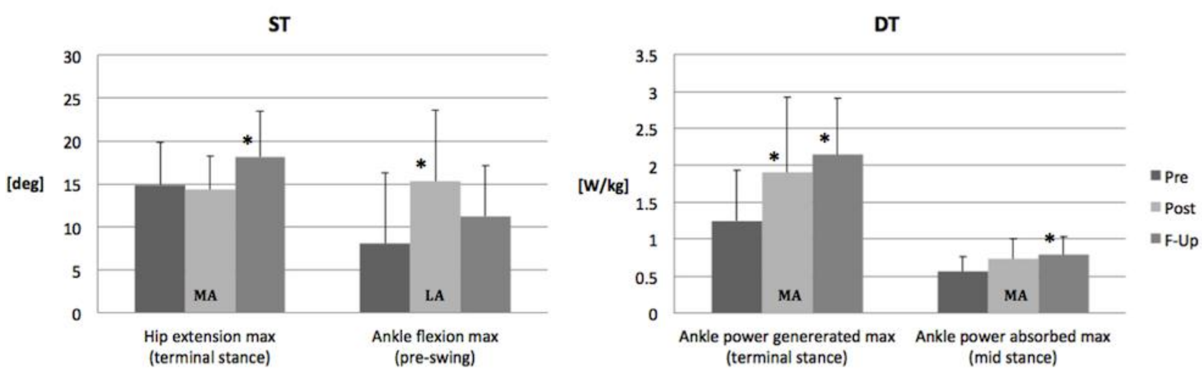

Figure 2 Relevant lower limb joint kinematic and kinetic parameters (mean and standard deviation) for most affected (MA) and least affected side (LA) at Pre, Post and F-Up. The asterisk (*) indicates a significant change (alpha = 0.05) of the parameter.

Performance and impairment -based measures

The distance walked during the 6MWT tended to increase by 8% at Post and by 23% at F-Up (Table 3), which reflects improved endurance. Time to execute the FSST significantly decreased by 22% at Post (p = 0.02) and by 37% at F-Up (p = 0.02).

The mean value of the EDSS significantly decreased by 12% at Post and the change was retained at F-Up (Table 3).

Parameter	Pre	Post	F-Up	p-value
6MWT [m]	301±83	324±77	372±67	0.093
FSST [s]	23±10	18±6*	14±4*	0.001
EDSS	4.8±1.0	4.2±1.2*	4.3±1.1*	0.042

Table 3 Motor tests scores (mean ± standard deviation) at Pre, Post and F-Up. The asterisk (*) indicates a significant change (alpha = 0.05) of the parameter at Post and F-Up with respect to Pre.

DISCUSSION

Our findings demonstrate that a six-week TM- and VR-based training is safe and well tolerated by subjects with MS, and showed some beneficial effects on their gait. The eight participants concluded the rehabilitation program without difficulties, reporting enjoyment, and seven of them would have liked to continue the training after the end of the study (Peruzzi et al. 2013).

Spatial-temporal parameters showed progressive improvements throughout the ST evaluations although these were not significant. Conversely, during the DT conditions, significant differences were observed after training, and these were further maintained at F-Up. Balance and performance-based measures, such as the FSST, also improved. The trend of improvement in the 6MWT reflects more endurance and functional capacity. The average increase in the distance walked during the 6MWT was 71 meters at F-Up, which is a meaningful clinical change resulting from the training [Newman et al. 2007]. This result along with the participant’s commitment to the training program suggests that fatigue did not play a major role in this study.

Previous studies in MS have shown improvements in gait speed (Giesser et al. 2007; Pilutti et al. 2011) and endurance (Newman et al. 2007; Van Den Berg et al. 2006) after TM training alone. Our study demonstrated similar results but extended them to include also the beneficial effects on DT performance. The training introduced virtual obstacles, which required both the integration of balance strategies as well as planning, information processing and sensory integration. Thus, the significant improvement of the gait parameters in DT and of the time in performing the FSST across the evaluations can be directly related to training specificity (Blennerhassett & Jayalath 2008; Mirelman et al. 2011).

Since this is the first study to assess the effects of a combined TM- and VR-based training in MS, we compared our results to similar studies in other neurological populations. Some authors assessed the efficacy of VR interventions in subjects post stroke (Yang et al. 2008; Walker et al. 2010; Jaffe et al. 2004) reporting improvements in gait speed and endurance. Similarly, subjects with PD (Mirelman et al. 2011) demonstrated improvements in gait speed, stride length and endurance after six weeks of TM- and VR-based training and retention effects even up to one month post training. Despite the varying nature of the diseases and the differences in the methodology, previous studies presented similar findings, suggesting the benefits of combining motor and cognitive training for neurological subjects.

A thorough gait evaluation in terms of lower limb joint kinematics and kinetics analysis was performed to investigate the effects of the rehabilitation intervention on MS individuals. However, the examination of the joint kinematic and kinetic parameters did not reveal any consistent and clinically evident gait strategy change in ST. In DT, a significant progressive increase of the ankle power generated at terminal stance was observed in the most affected side. This increase may be related to the increased stride length observed after the training. It is speculated that the increased power generation in the ankle at push off and the increased, although not significant, hip extension at terminal stance facilitated the forward progression, enabling a longer stride. This, in turn, allowed for the increase in gait speed. This is consistent with earlier findings in post-stroke subjects (Mirelman et al. 2010), which, after a rehabilitation intervention, demonstrated improved foot placement and control, which enabled a more energy efficient gait pattern. During DT, the power generated by the ankle during the push-off at F-Up, reached values similar to those observed in ST, suggesting that the intervention created a functional change. This should be further assessed in a larger study. Interestingly, the main effects observed were in the more complex DT and not in ST. This could perhaps be related to the increased complexity and specificity of the training. The intervention was focused on DT tasks and was designed to train the subjects to improve their DT abilities. The results suggest a transfer effect to untrained tasks, such as the FSST and gait during serial subtraction, demonstrating a learning effect. Since everyday life frequently requires walking while performing simultaneously both cognitive and additional motor tasks, the proposed training can potentially improve mobility and, therefore, the quality of life of trained people.

The pilot study has several limitations. First, the sample size was limited. This was partially due to the difficulties associated to the recruitment of a highly homogenous MS subject cohort (many inclusion and exclusion criteria to be contemporarily satisfied). Furthermore, since this was an open label pilot study intended to assess the feasibility of the use of VR for gait rehabilitation in MS, the interpretation of the effects of this intervention should be taken with caution.

It is worthwhile to underline that, during the assessments, the walking trials in ST were performed before the trials in DT. Nevertheless, to minimize possible influence of fatigue due to the execution of several consecutive gait trials, participants were allowed to rest between trials. In addition, the average of the total number of trials performed in each session was adequate (<20), the distance walked in each trial relatively short (10 m) and the velocity self-paced.

CONCLUSIONS

To our knowledge, this is the first study evaluating the effects of a rehabilitation intervention based on the combined use of VR and TM on gait and endurance of MS subjects. The results have to be considered preliminary due to the limited sample size and relatively homogenous sample. Nevertheless, the findings suggest that intensive and progressive TM with VR gait training may be a viable approach in MS and may positively affect complex gait conditions such as dual tasking and obstacle negotiation. Larger scale, randomized controlled studies with long term follow-up are needed to confirm efficacy and retention of TM and VR-based gait training on motor and cognitive aspects and quality of life of MS subjects.

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Highlights

- Intensive and progressive treadmill training with virtual reality is viable in MS.
- Spatial-temporal parameters improved in dual task after the intervention.
- The endurance and ability in negotiating obstacles improved after the intervention.
- The training positively affects complex gait conditions in MS.
- The training is an effective therapeutic option for MS subjects with impaired gait.