ORIGINAL COMMUNICATION

Treadmill training with virtual reality to enhance gait and cognitive function among people with multiple sclerosis: a randomized controlled trial

Irina Galperin[1,2] · Anat Mirelman[1,3,4] · Tanja Schmitz-Hübsch[5,6,7] · Katherine L. Hsieh[8] · Keren Regev[9] · Arnon Karni[3,4,9] · Marina Brozgol[1] · Pablo Cornejo Thumm[1] · Sharon G. Lynch[10] · Friedemann Paul[5,6,7] · Hannes Devos[11] · Jacob Sosnoff[11] · Jeffrey M. Hausdorff[1,4,12,13]

Abstract

Background Motor and cognitive impairments impact the everyday functioning of people with MS (pwMS). The present randomized controlled trial (RCT) evaluated the benefits of a combined motor–cognitive virtual reality training program on key motor and cognitive symptoms and related outcomes in pwMS.

Methods In a single-blinded, two-arm RCT, 124 pwMS were randomized into a treadmill training with virtual reality (TT + VR) group or a treadmill training alone (TT) (active-control) group. Both groups received three training sessions per week for 6 weeks. Dual-tasking gait speed and cognitive processing speed (Symbol Digit Modalities Test, SDMT, score) were the primary outcomes. Secondary outcomes included additional tests of cognitive function, mobility, and patient-reported questionnaires. These were measured before, after, and 3 months after training.

Results Gait speed improved ($p < 0.005$) in both groups, similarly, by about 10 cm/s. The TT + VR group ($n = 53$ analyzed per-protocol) showed a clinically meaningful improvement of 4.4 points (95% CI 1.9–6.8, $p = 0.001$) in SDMT, compared to an improvement of only 0.8 points in the TT ($n = 51$ analyzed per-protocol) group (95% CI 0.9–2.5 points, $p = 0.358$) (group X time interaction effect $p = 0.027$). Furthermore, TT + VR group-specific improvements were seen in depressive symptoms (lowered by 31%, $p = 0.003$), attention (17%, $p < 0.001$), and verbal fluency (11.6% increase, $p = 0.002$).

Discussion These findings suggest that both TT and TT + VR improve usual and dual-task gait in pwMS. Nonetheless, a multi-modal approach based on VR positively impacts multiple aspects of cognitive function and mental health, more than seen after treadmill-treading alone. Trial registered at ClinicalTrials.Gov NCT02427997.

Keywords Gait · Treadmill training · Dual task · Virtual reality · Multiple sclerosis

Introduction

Gait abnormalities are a hallmark of multiple sclerosis (MS) and a major cause of disability and reduced health-related quality of life. People with multiple sclerosis (pwMS) walk more slowly than age-matched controls, with a lower cadence and increased stride-to-stride variability [1, 2]. Intervention trials have shown that treadmill-training improves gait speed, endurance, and balance in pwMS [3, 4]. However, MS difficulties extend beyond these motor

problems. Cognitive dysfunction affects 40–70% of pwMS [5] and frequently leads to impaired information processing speed and deficits in verbal and visual memory [6, 7]. The cognitive deficits also negatively impact many aspects of quality of life [8] and walking during everyday activities [9], especially during challenging conditions like dual-tasking [10, 11]. These deficits in gait, cognitive function, and dual-tasking are associated with an increased risk of falls [12, 13] and disability [14, 15] and suggest the need for combined motor-cognitive rehabilitation approaches that address the multiple symptoms and challenges that are faced by pwMS [16].

To meet this need, several recent studies among pwMS combined motor and cognitive training into one treatment program [17, 18]. Progressive, integrated dual-tasking

✉ Jeffrey M. Hausdorff
jhausdor@tlvmc.gov.il

Extended author information available on the last page of the article

training led to significantly greater improvement in dual-tasking gait compared to single-task training [17]. Exercises delivered via virtual reality (VR) and conventional balance exercises improved balance and mobility in pwMS, while VR-based training also improved cognitive–motor performance [18]. One advantage of VR technology is that it can provide multidimensional, personalized rehabilitation while mimicking real-world environments in a controlled, game-like manner. Several studies reported that VR-based training improves mobility in older adults and people with neurological impairments [19–22]. Two systematic reviews also reported the potential of VR-based training to improve impaired cognitive domains and reduce depressive symptoms and anxiety in healthy older populations and patients with neurological impairment [23, 24]. Furthermore, in a small, open-label pilot study among pwMS, a 6-week VR-based treadmill training intervention enhanced dual-task walking, and the effects were maintained 1 month later [25]. These studies suggest that adding VR-based challenges that incorporate cognitive as well as motor demands to treadmill training may enhance dual-task walking abilities and certain aspects of cognitive function. Nonetheless, among pwMS, evidence from well-powered randomized controlled trials regarding the added value of treadmill training with VR, compared to treadmill training alone, is lacking [16], and there is a need for evidence-based, clinically feasible interventions to treat cognitive deficits [7].

The goal of the present work was to address this gap. We identified three specific aims: (1) To assess the benefits of using treadmill-training, augmented with virtual reality (TT + VR) on key MS symptoms, specifically dual-tasking gait speed and cognitive processing speed, i.e., the two primary outcomes, compared to treadmill training (TT) alone; (2) to evaluate the transfer of the training effects to non-trained tasks and other MS symptoms (e.g., depressive symptoms); and (3) to assess retention effects of using TT + VR, compared to TT alone, at 3 months post-training.

Methods

Study design

This multi-site study was a single-blinded, 2-arm RCT that took place at four clinical sites: Tel Aviv Sourasky Medical Center (TASMC), the University of Illinois at Urbana-Champaign (UIUC), University of Kansas Medical Center (UKMC), and NeuroCure Clinical Research Center (NCRC), Charité-Universitätsmedizin in Berlin. The study was registered at clinicaltrials.gov (NCT02427997). The first patient entered the study on August 5, 2016, enrollment finished on January 15, 2021, and the last patient was assessed on June 4, 2021; the decision to stop the study was made after weighing COVID-19 and funding considerations and becoming sufficiently close to the proposed sample size. The study protocol, hypotheses, sample size justification (the original target was to enroll 144 participants), and methods were published previously [26]. Here, we briefly summarize key elements.

Participants

The key criteria for inclusion were: (a) physician confirmed diagnosis of relapsing–remitting MS (RRMS) following McDonnald's criteria, (b) relapse-free in the last 30 days, c) between 20 and 65 years of age, (d) gait limitations due to MS (based on the first question of the Multiple Sclerosis Walking Scale), and (e) score between 2.0 and 6.0 on the Expanded Disability Status Scale (EDSS). Key exclusion criteria included: (a) inability to walk unassisted (excluding cane) for 5 min or follow safety or training instructions, (b) another neurological disorder, (c) any cardiovascular, orthopedic, or other problems that may interfere with walking, or diagnosed active psychiatric problems (e.g., severe depression), and (d) currently participating in an intensive exercise program.

Procedures

After providing informed written consent, subjects underwent a baseline assessment. Then, participants were randomized to either a treadmill training (TT) alone group (active-control comparison group) or treadmill training with VR (TT + VR; i.e., the experimental) group; training took place at one of four clinical sites, as mentioned above. The subjects were informed that the purpose of the study was to compare the impact of two forms of treadmill training on symptoms; in that sense, they were blinded to the specific study hypotheses, and this can, to some degree, be considered a double-blind study.

Randomization was performed by center and by gender to ensure gender balance across the two intervention and control arms in blocks of four with the goal of 1:1 allocation to the two study arms. The randomization sequence was generated in Matlab® by EG and was only shared with the trainers on a rolling, as-needed basis. The trainers accessed the randomization file one subject at a time; trainers or study coordinators informed the participants about the intervention arm. The assessors did not have access to this file.

All randomized subjects received 13–18 (maximum) sessions (3/week × 6 weeks) of training. The VR system and the training protocol were previously described (GaitBetter, Ramat Gan, Israel) [21, 26] and are also detailed in the protocol paper [26]. All study sites used the same software, and the treadmill, computer screen, and safety harness were similar at all sites, as described previously) [21, 26].

Briefly, the treadmill speed was set based on the participant's over-ground walking speed at baseline, and then, it was measured weekly. The treadmill speed and the session duration increased gradually, and hand support decreased. This was similar in both groups. Subjects in the TT + VR group navigated through a virtual environment projected on a TV screen while walking on the treadmill and receiving feedback from the system in real-time (Fig. 1). Motor and cognitive challenges in both groups were individualized to the participant's level of performance. Training protocols within each group were specified in advance. After the 6-week intervention, participants returned within 10 days for a post-assessment identical to the baseline assessment and completed an identical follow-up assessment 3 months later. To isolate the effects of the interventions, participants were instructed not to start any new activity or receive additional therapy during the training period.

Outcome measures

All outcome measures were evaluated by treatment-blinded assessors who were experts in collecting mobility and cognitive data in pwMS. The two primary outcome measures were: (1) dual-tasking gait speed, as measured when the subject walked while performing a word list generation task;

(2) scores on the Symbol Digit Modalities Test (SDMT), a widely used measure that reflects information processing speed and attention [27] as evaluated after completion of the 6 weeks of the intervention. The number of correctly matched symbols within 90 s was the outcome score for the SDMT. A change of 4 points is considered clinically meaningful among pwMS [28].

Secondary outcome measures included functional gait tests, cognitive function, daily-living mobility, and patient-reported questionnaires. Functional tests included the Timed 25-Foot Walk (T25FW) and the 6-Minute Walk (6 MW) test [29]. Gait under usual-walking (UW) and dual-task walking (DTW) conditions were quantified, while participants were walking back and forth over a 12-m walkway for 1 min while wearing sensors (Opals, APDM, Portland, OR) placed on each wrist, on the lateral malleolus of each leg and the lower back. Only straight-line segments were studied. Extracted parameters included gait speed, cadence, and step regularity [30]. Step regularity reflects the regularity (and consistency) of the stepping pattern between consecutive steps. Low step regularity indicates that there is low regularity between steps or asymmetry between the left and the right leg (higher values indicate greater symmetry). To evaluate the impacts of TT and TT + VR training on daily-living physical function and daily-living gait, a small, light-weight,

Fig. 1 The training setup illustration. **a** The study training arms. Treadmill training alone (TT) on the left vs. TT with the addition of virtual reality (TT + VR) on the right. All participants were wearing a harness during the training. The VR is projected on the TV screen in front of the participant in the TT + VR group. The markers are attached to each foot captured by the camera, which is located below the TV screen. **b** Visualization of the VR environment include in movement of the participant's virtual feet as they negotiate virtual obstacles with positive (green) and negative (red) feedback. The VR setup is similar to that described in the V-Time study (Mirelman et al. [20])
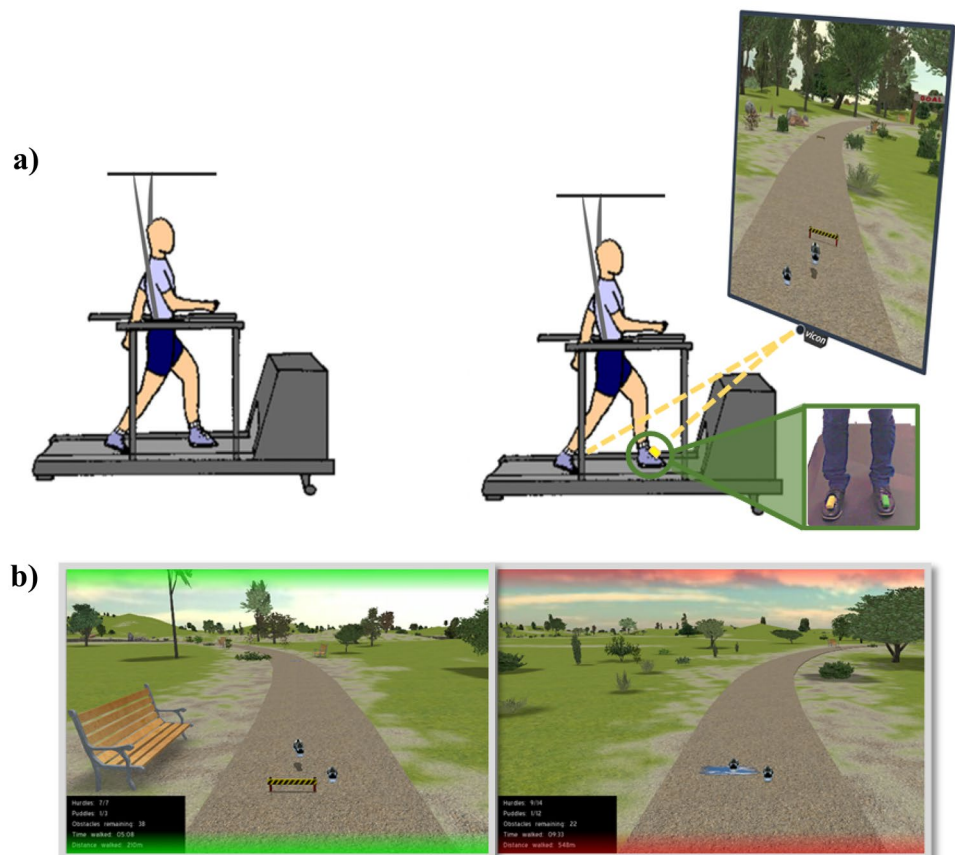
water-proof tri-axial accelerometer (Axivity AX3, York, UK; $23.0 \times 32.5 \times 7.6$ mm; weight: 11 g; 100 Hz sampling rate) was worn on the back (at the level of the fifth lumbar vertebrae) for 7 days at each assessment time point [31]. Participants were asked to wear the device continuously for 1 week and to continue their daily activities as usual. Upon completion of the 1-week recording, participants removed the device and sent it back to the local clinical site. Data were included in the analysis if the recording was longer than three days. For gait quality, walking bouts that were at least 30 s long were evaluated. The extracted measures included the amount of walking (step counts per day), total daily-living physical activity (sum of signal vector magnitude, SVM, during the day), and three measures (cadence, gait speed, and regularity) that reflect the quality of daily-living gait (i.e., "typical", the subject's median value across the week) and "best" (i.e., the subjects 90% value across the week) [31].

A standard battery of neuropsychological tests, the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), comprising the California Verbal Learning Test-II (CVLT-II), the revised Brief Visuospatial Memory Test (BVMTR), and the Word List Generation (WLG) tests, evaluated cognitive outcomes [27]. The Trail Making Test (TMT) A and B evaluated attention and executive function, respectively [32].

Patient-reported outcomes included: (a) The Multiple Sclerosis Walking Scale-12 (MSWS-12), a reflection of perceived walking impairment [33]; (b) Subscales of quality of life (e.g., physical function, emotional well-being) and overall quality of life via the MS QOL-54 (MSQOL54) [34]; and (c) The Patient Health Questionnaire-9 (PHQ-9), a measure of depressive symptoms [35, 36].

Statistical analyses

Demographic and clinical characteristics were summarized as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables and as frequencies (percentage) for categorical variables. The Kolmogorov–Smirnov/Shapiro–Wilk test was used to test for normal distributions. Differences in demographic and clinical characteristics among the groups were evaluated using t tests and General Linear Models (GLM) with adjustment for age and gender, or Mann–Whitney tests, and Pearson's Chi-square for dichotomous variables (i.e., gender). Significant outliers (median $\geq$ 3SDs) were removed before the repeated-measures procedure. The effects of time (Baseline versus Post-training assessment and baseline versus 3-months follow-up) and treatment were evaluated using repeated-measures (RM) ANOVA and Wilcoxon test for repeated measures (for categorical and bi-nominal variables). We also examined the role of the study site (center)

as a covariate (TASMC $n = 49$; UIUC = 29; UKMC = 17; NCRC = 9); it was not significant in any of the analyses, and hence, the results are reported without adjustment of this covariate. The level of significance was set at $p \leq 0.05$. Post hoc comparisons with Bonferroni corrections were performed for within-group pairwise comparisons (adjusting for the number of tests within a domain). Mean differences and 95% confidence intervals (CI) are also reported for normally distributed outcome measures. Partial eta-squared (η^2) is used to estimate effect sizes ($\geq 0.0.06$ and 0.14 is considered medium and large, respectively). Statistical analyses were performed using SPSS (Version 27.0 for Windows, SPSS Inc., Chicago, IL). For the primary outcomes, we report the results based on a "per protocol" analysis, using the complete case analysis (CCA) method (i.e., subjects with pre-post assessments) and a modified intention-to-treat analysis (using an imputation approach that replaces missing post-training assessment values with an individual's baseline assessment values and assuming no training effect for dropouts). For the other outcomes, results are reported without imputation using the available data. In addition, we conducted a sensitivity analysis of the baseline values of those who finished the intervention period and completed the post-assessment and dropouts using t tests.

Results

As summarized in Fig. 2, 139 participants were enrolled in the study, 124 participants were randomly assigned to one of the training groups, and 108 completed the training program and the post-training assessment (52 in the TT and 56 in the TT + VR groups). Eighty-four participants completed the 3-month follow-up assessment. Four more subjects were excluded from the analysis. Reasons for exclusions and dropouts are described in Fig. 2. Thus, per-protocol analysis was based on 104 individuals who completed the 6-week intervention and participated in the before and after assessments. These subjects were 49.0 ± 9.8 years old, with a median EDSS score of 3.5 (2–6), and 72.2% were female. Participants who were allocated into the two training groups had similar age, gender, height, weight, and EDSS at baseline (Table 1), and also showed similar performance in the primary outcomes at baseline: SDMT scores ($p = 0.751$) and dual-tasking gait speed ($p = 0.616$) (see also below). Forty-eight percent of the subjects completed all 18 sessions (53% in the TT and 44% in the TT + VR groups). The number of training sessions that were completed was similar ($p = 0.771$) in the TT and TT + VR groups. The median number of sessions in those trained with TT was 18 (range: 13–18), and in those trained with TT + VR, it was 17 (range: 15–18).
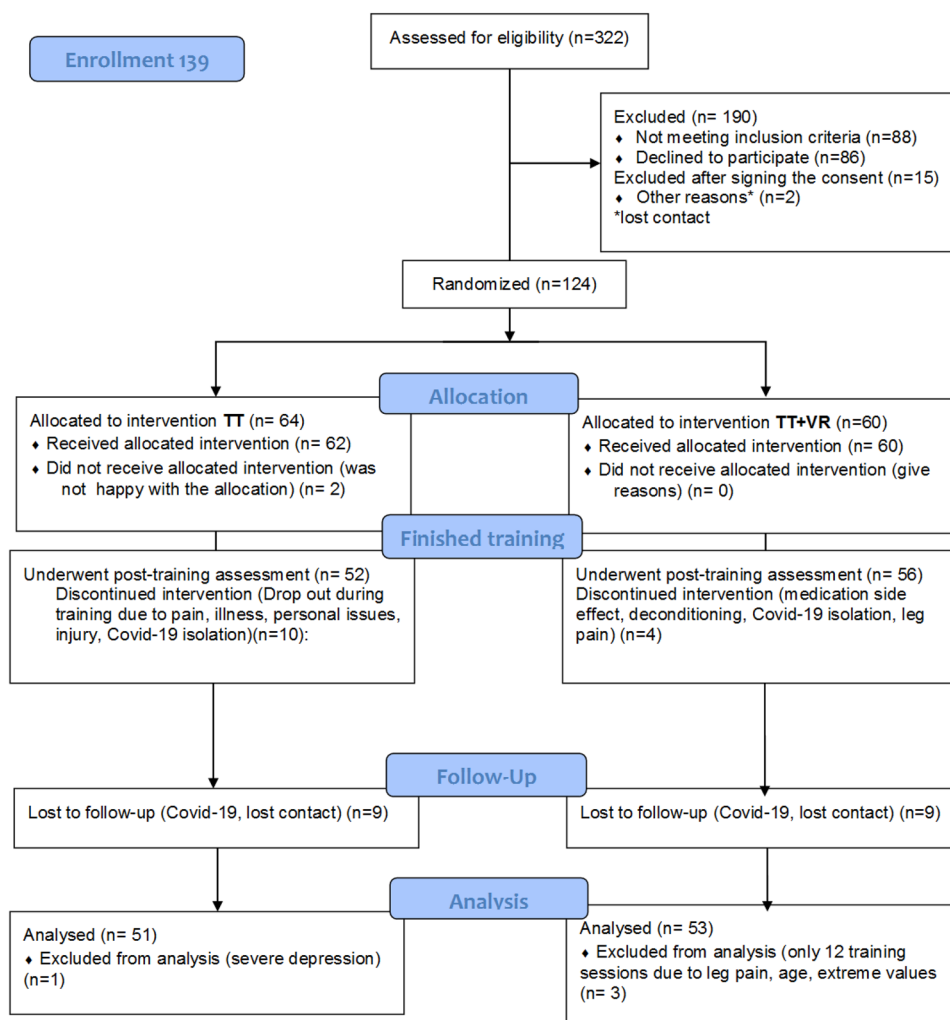
Fig. 2 Study CONSORT Flow

Training effects on the primary outcomes

In per-protocol analyses, SDMT scores improved in both training groups (time effect: $p = 0.004$, $\eta^2 = 0.108$) after the intervention. A timeXtreatment-group interaction ($p = 0.027$, $\eta^2 = 0.051$) revealed that subjects in the TT + VR group improved more than those in the TT. Within-group analysis showed that the participants who trained with TT improved their SDMT score by 0.8 points (95% CI 0.9–2.5 points, $p = 0.358$, $\eta^2 = 0.037$). In contrast, subjects who trained with TT + VR improved by 4.4 points (CI 1.9–6.8, $p = 0.001$, $\eta^2 = 0.105$) (Fig. 3). Three months post-training, SDMT values were 3 points higher than the baseline values in the TT + VR group ($p = 0.005$) and 1.8 points higher than baseline values in the TT group ($p = 0.06$).

Dual-tasking gait speed increased (time effect: $p = 0.001$, $\eta^2 = 0.219$) in both groups. It increased by 10.4% (10.7 cm/s, CI 4.5–17.0 cm/s, $p = 0.001$, $\eta^2 = 0.219$) in the TT group and by 8.7% (10.5 cm/s, CI 4.4–16.7 cm/s, $p = 0.001$, $\eta^2 = 0.227$) in the TT + VR group. The time X treatment-group

Table 1 Subject characteristics in the two training groups at baseline

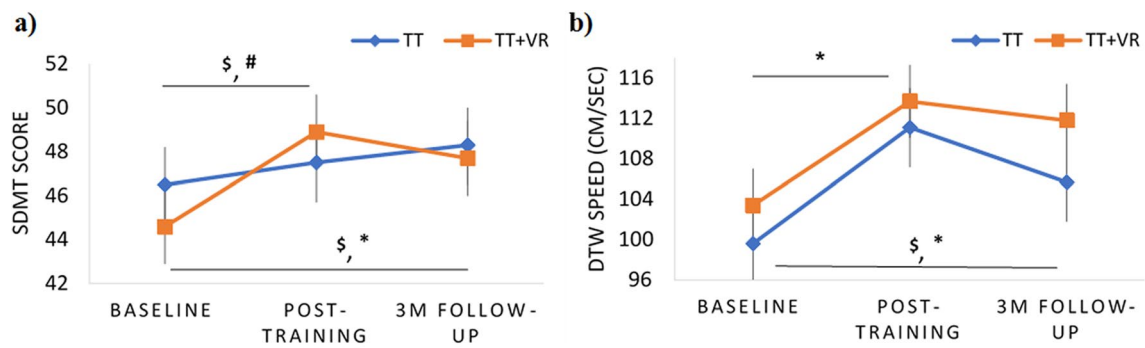|	TT group	TT + VR group	p value
Age (years)	49.1 ± 9.7	49.0 ± 10.0	0.960
Gender (% female)	72.2 (%)	72.3 (%)	0.956
Height (cm)	167.5 ± 9.6	169.8 ± 9.7	0.182
Weight (kg)	76.3 ± 19.1	76.8 ± 23.0	0.713
MoCA	26.6 ± 2.0	25.6 ± 2.4	0.230
Education (years)	15.5 ± 2.5	15.6 ± 3.1	0.571
EDSS (score)	3.5 [2–6]	3.5 [2–6]	0.845

Results are presented as percentages for categorical variables and mean ± standard deviation (SD) or median interquartile range [IQR] for continuous variables. p values based on Pearson's Chi-square (for gender), independent-samples t test (for age, height, weight, MoCA, and education), and Mann–Whitney for EDSS

EDSS expanded disability status scale; *MoCA* montreal cognitive assessment

Fig. 3 The primary outcomes at baseline, post-training, and 3-month follow-up. **a** SDMT-cognitive processing speed; **b** gait speed walk under dual-task condition. *Significant main time effect ($P < 0.05$). # time X training significant interaction. $Within-group significant time effect for TT + VR group only

interaction effect was not significant ($p = 0.670$), indicating that the improvements were similar in the two training groups. Dual-tasking gait speed remained higher than baseline 3 months after the intervention (time effect: $p = 0.008$) (Fig. 3). The within-group effect at this time point was only significant in the TT + VR group (8.4 cm/s; CI 7.0–10.0 cm/s; $p = 0.035$) (Table 6).

In modified intention-to-treat analyses, the results for dual-tasking gait speed and SDMT were similar to those for the per-protocol analyses described above. For dual-tasking gait speed, a significant time effect was observed (8.0 cm/s, CI 4.7–11.3 cm/s, $p < 0.001$), regardless of intervention (time X treatment-group interaction effect $p = 0.956$). For the SDMT scores, a time effect was observed ($p = 0.007$),

and, as before, a time X treatment-group ($p = 0.010$) interaction effect was also seen. The TT group improved by 0.7 points (CI 0.7–2.0 points, $p = 0.358$), and the TT + VR group improved by 4.0 points (CI 1.8–6.3 points, $p = 0.001$).

Secondary outcomes

Gait

Other aspects of gait significantly improved after training in both groups (Table 2). For example, usual-walking gait speed significantly increased in both groups following the intervention ($p < 0.001$) (recall Table 2). This improvement persisted 3 months later. Similarly, cadence

Table 2 Gait before and after training in the TT and TT + VR groups

	TT group			TT + VR group			
	Baseline	Post-training	Within-group effect (MD, 95%CI, p value)	Baseline	Post-training	Within-group effect (MD, 95%CI, p value)	Main effect of time (p value)
DTW speed (cm/s)	104 ± 41	114 ± 42	10.3, 4.2, 16.3, $p = 0.001$[a,b]	104 ± 32	115 ± 31	11.0, 4.8, 17.3, $p = 0.001$[a,b]	<0.001[a,b]
UW speed (cm/s)	118 ± 40	123 ± 41	11.2, 5.9, 16.5, $p < 0.001$[a,b]	120 ± 36	134 ± 39	14.2, 7.8, 20.7, $p < 0.001$[a,b]	<0.001[a,b]
DTW cadence (steps/min)	94 ± 21	99 ± 18	4.8, 2.0, 7.5, $p = 0.011$[a]	97 ± 15	102 ± 16	5.3, 3.0, 7.6, $p < 0.001$[a,b]	<0.001[a,b]
UW cadence (steps/min)	102 ± 18	106 ± 17	3.2, 0.8, 5.5, $p = 0.011$[a]	104 ± 14	108 ± 15	4.6, 2.0, 7.3, $p = 0.001$[a,b]	<0.001[a,b]
DTW step regularity (unitless)	0.48 ± 0.25	0.56 ± 0.23	0.07, 0.02, 0.12, $p = 0.005$[a,b]	0.54 ± 0.20	0.57 ± 0.18	0.03, 0.03, 0.08, $p = 0.277$	0.004[a,b]
UW step regularity (unitless)	0.58 ± 0.25	0.61 ± 0.23	0.03, 0.06, 0.01, $p = 0.182$	0.59 ± 0.19	0.61 ± 0.20	0.02, 0.02, 0.06, $p = 0.405$	0.131

Variables mean values ± standard deviation (SD) are presented

MD mean difference, *DTW* dual-task controlled for the number of words generated during the 1-min walk), *UW* usual walk

[a]Significant pairwise time effect. Significance was set to 95% in all tests

[b]Significant p value after adjustment to multiple comparisons $p < 0.008$. For all repeated ANOVA measures, the estimated marginal means were controlled for age and gender

and dual-tasking step regularity increased post-training (time effect: $p < 0.001$). Within-group analysis showed that dual-tasking step regularity improved only in the TT group (adjusted), while usual and dual-tasking cadence improved in the TT + VR group (adjusted). However, these improvements did not persist at the 3-month follow-up. Additional gait and cognitive outcome measures at the 3-month follow-up are presented in Table 6.

Functional tests of mobility

Time to complete the T25FW decreased by 2.9% (95% CI − 7.6 to − 1.7%) in the TT group and by 7.7% (95% CI − 11.5 to − 3.8%) in the TT + VR group following the interventions (Fig. 4). This time effect was statistically significant in the TT + VR group ($p < 0.001$) but not in the TT group ($p = 0.176$). Endurance, i.e., the distance walked in 6 min, increased in both groups (time effect: $p = 0.005$), with no significant interaction effect of time X treatment group ($p = 0.620$). However, a significant within-group-specific time effect was found in the TT group (20.7 m, 95% CI 3.2–38.2 m, $p = 0.021$), and only a trend in the TT + VR group was seen (14.4 m, 95% CI 2.5–31.4 m, $p = 0.093$) (Fig. 4).

Cognitive function

Both groups showed significant improvements on the CVLT tests. The time to complete TMT A was significantly better, as was world list generation and the number of words generated during the dual-task gait test in the TT + VR group, while those who trained with TT only showed only trends for these cognitive outcomes (Table 3). Moreover, several cognitive improvements were preserved after 3 months in the TT + VR group (see also Table 6).

Patient-reported outcomes

Compared to baseline values, scores on self-report of physical quality of life (MSQOL-54) were higher after training (Table 4) in both groups, with a stronger trend seen in the TT group ($p = 0.031$ unadjusted). TT + VR subjects reported improvements ($p = 0.010$) in mental components of quality of life (MSQOL-54) and fewer ($p = 0.003$) depressive

Fig. 4 Functional tests at baseline and post-training. **a** 25 foot walk at fast speed; **b** maximal distance covered in 6 min. *Pre–post-significance in TT + VR group according to Wilcoxon repeated signed test. #pairwise significant time effect according to RM ANOVA
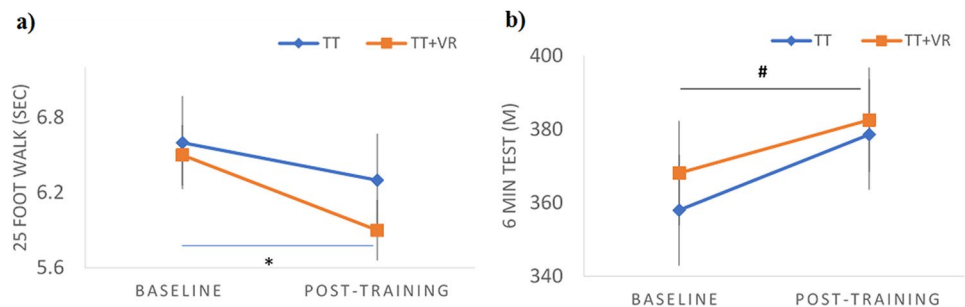
Table 3 Secondary cognitive outcomes before and after training in the TT and TT+VR groups

	TT group			TT + VR group		
	Baseline	Post-training	Within-group effect (p value)	Baseline	Post-training	Within-group effect (p value)
DT words	11 (2–24)	12 (4–25)	0.022[a]	13 (3–25)	14 (3–33)	< 0.001[a,b]
TMT A	48.1 (17.5–180.5)	44.1 (18.7–187.2)	0.099	49.8 (19.0–122.0)	41.28 (22.4–212.0)	< 0.001[a,b]
TMT B	95.5 (40.3–360.6)	91.6 (39.0–286.7)	0.050	92.9 (35.2–304.8)	90.2 (37.5–302.9)	0.012[a]
WLG	35 (14–77)	33 (14–66)	0.028[a]	36 (9–62)	38 (12–61)	0.002[a,b]
CVLT	53 (24–73)	59 (35–75)	< 0.001[a,b]	55 (26–78)	61 (29–80)	< 0.001[a,b]
BVMT	10 (2–12)	10 (2–12)	0.294	9 (1–12)	10 (2–12)	0.055

Results are presented as percentages for categorical variables and mean ± standard deviation (SD) or median interquartile range [IQR] for continuous variables. Note that the change in the WLG scores among the TT group reflects deterioration (not an improvement)

DT dual task, *TMT A&B* The Trail Making Test (TMT) A and B, *WLG* word list generation, *CVLT* California verbal learning test, *BVMT* brief visuospatial memory test

[a]Significant time effect Baseline-post-assessment according to related-sampled Wilcoxon Signed-Rank test. Significance was set to 95% in all tests

[b]Significant p value after adjustment to multiple comparisons $p < 0.008$

Table 4 Patient-reported outcomes: quality of life, depression, and mobility disability based on self-report at baseline and post-training in the TT and TT+VR groups

	TT group			TT + VR group		
	Baseline	Post-training	Within-group effect (*p* value)	Baseline	Post-training	Within-group effect (*p* value)
PHQ	4.8 ± 7.2	5.5 ± 6.3	0.25	5.0 ± 6.5	3.7 ± 3.9	0.003[a,b]
MSWS-12	37.28 ± 30.51	33.78 ± 31.21	0.017[a]	31.74 ± 41.48	31.21 ± 31.10	0.42
MFIS sum	61.31 ± 39.50	61.12 ± 37.42	0.47	91.02 ± 39.14	37.35 ± 19.26	0.23
MSQOL-54 overall	67.76 ± 54.71	68.70 ± 92.17	0.97	65.50 ± 81.33	66.80 ± 71.34	0.23
MSQOL-54 physical health	15.5 ± 57.1	20.0 ± 60.5	0.031[a]	18.9 ± 57.5	20.0 ± 59.3	0.07
MSQOL-54 mental health	17.3 ± 68.17	17.8 ± 70.6	0.26	21.2 ± 67.4	19.5 ± 71.1	0.08[a,b]

Results are presented as percentages for categorical variables and mean ± standard deviation (SD) or median interquartile range [IQR] for continuous variables

MSWS-12 The Multiple Sclerosis Walking Scale-12, *MSQOL54* overall quality of life via the MS QOL-54, *PHQ-9* Patient Health Questionnaire-9 (a measure of depressive symptoms), *MFIS* Modified Fatigue Impact Scale

[a]Indicates a statistical significance according to the related-sampled Wilcoxon Signed-Rank test ($p < 0.05$)

[b]Significant *p* value after adjustment to multiple comparisons using a threshold of $p \leq 0.008$

symptoms (PHQ-9); these changes were not seen in the TT group ($p > 0.25$). Conversely, patients who trained with TT reported fewer walking problems according to MS Walking Scale-12 scores ($p = 0.017$ unadjusted), while those who trained with TT + VR did not (see Table 4). After the adjustment for multiple comparisons, these TT group advantages did not persist.

Daily-living physical activity

Total daily-living physical activity did not change in either group (time effect: $p = 0.520$; timeX treatment-group effect: $p = 0.124$). Step count also did not change after training (time effect: $p = 0.326$) (Table 5). Conversely, certain aspects of the quality of daily-living walking became higher, reflecting an improvement after training. "Best" daily-living gait speed improved (time effect $p = 0.032$) in both groups (timeX treatment-group interaction effect: $p = 0.890$), as did usual (time effect $p = 0.012$) and best daily-living step regularity (time effect: $p = 0.002$). This change was more pronounced in the TT + VR group ($p = 0.016$) than in the TT group ($p = 0.066$).

Training effects as a function of disease stage

To evaluate the role of disease severity, in exploratory analysis, we divided the subjects into those with mild-moderate disease (EDSS < 4) and those with more advanced disease (EDSS ≥ 4). The time X EDSS group X treatment-group interaction was significant ($p = 0.023$) for SDMT scores. When exploring each EDSS group separately (adjusted to age and gender), the time effect on SDMT scores persisted within both the lower EDSS

($p = 0.046$) and the higher EDSS ($p = 0.009$) subgroups with an advantage to the TT + VR training. Among those with lower EDSS, in the TT group, SDMT scores increased by 0.5 points (95% CI − 2.3 to 3.3) and by 4.1 points (95% CI 1.3–6.9) in the TT + VR group. Among those with higher EDSS, in the TT group, SDMT score increased by 1.3 points (95% CI − 1.9 to 4.5) versus 4.6 points (95% CI 1.5–7.6) in the TT + VR group. For dual-tasking gait speed, a significant time effect was also observed among both low ($p = 0.005$) and high ($p < 0.001$) EDSS levels regardless of training group (interaction effect: $p = 0.350$); In the lower EDSS level, dual-tasking gait speed increased by 12.4 cm/s (95% CI 4.0–20.0 cm/s) in the TT group, and by 8.1 cm/s (95% CI − 1.4 to 17.7 cm/s) in the TT + VR group. In the higher EDSS level, dual-task gait speed increased by 7.0 cm/s (95% CI − 2.5 to 16.5 cm/s) in the TT group and by 9.7 cm/s (95% CI 0.7–18.6 cm/s) in the TT + VR group.

Dropouts and loss to follow up

Fourteen subjects who were assessed at baseline were not assessed after the interventions (recall Fig. 2). The subjects who were and were not evaluated post-training were similar in the two primary outcomes at baseline. No significant differences were found in SDMT scores (in the TT group, $p = 0.742$ and the TT + VR group, $p = 0.368$) or in dual-tasking walking speed (in the TT group, $p = 0.367$ and the TT + VR group, $p = 0.634$). This suggests that there were no systematic differences among those who were and were not assessed after the intervention and that the data may be considered missing at random (MAR).

Table 5 Metrics of daily-living activity and daily-living gait at baseline and post-training

	TT group			TT + VR group			Main effect of time
	Baseline	Post-training	Within-group effect (MD, 95%CI, p value)	Baseline	Post-training	Within-group effect (MD, 95%CI, p value)	
Daily-living usual gait speed (cm/s)	93 ± 26	96 ± 27	2.7, − 2.8, 8.3, $p = 0.327$	92 ± 15	95 ± 17	2.5, − 2.20, 7.20, $p = 0.287$	0.174
Daily-living best (90%) speed (cm/s)	108 ± 32	113 ± 31	4.9, 1.51, 11.21, $p = 0.130$	107 ± 17	112 ± 24	4.8, 1.21, 10.89, $p = 0.113$	0.033[a]
Daily-living cadence (steps/min)	96 (30–125)	100 (42–128)	1.6, $p = 0.112$	100 (28–141)	101 (63–138)	1.81, $p = 0.070$	0.012[b]
Daily-living best (90%) cadence (steps/min)	103 (44–134)	108 (48–138)	1.4, $p = 0.148$	108(66–140)	108 (69–150)	1.5, $p = 0.231$	0.069
Daily-living step Regularity usual (unitless)	0.47 ± 0.19	0.51 ± 0.21	0.042, 0.002, 0.078, $p = 0.034$[a]	0.481 ± 0.12	0.518 ± 0.12	0.04, 0.01, 0.08, $p = 0.124$	0.012[a]
Daily-living step Regularity Best (90%) (unitless)	0.60 ± 0.19	0.629 ± 0.20	0.030, 0.002, 0.06, $p = 0.066$	0.59 ± 0.12	0.65 ± 0.12	0.05, 0.01, 0.10, $p = 0.016$[a]	0.002[a,c]
Total physical activity SVM (mg)	109,872 ± 32,670	13,668 ± 31,262	3796, − 4197, 11,788, $p = 0.341$	122,327 ± 36,797	118,484 ± 38,781	− 3843, − 9914, 2228, $p = 0.207$	0.635
Step counts	9030 ± 4190	9371 ± 4512	$p = 0.996$	9806 ± 4020	9537 ± 3874	$p = 0.022$[a]	0.277

Variables mean ± standard deviation (SD) are presented for normally distributed variables. Otherwise median (minimal, maximal) are presented

[a]Significant pairwise time effect

[b]Significant time effect Baseline-post-assessment according to related-sampled Wilcoxon singed-rank test. Significance was set to 95% in all tests

[c]Significant p value after adjustment to multiple comparisons $p < 0.006$. For all repeated ANOVA measures, estimated marginal means controlled for age and gender. Total physical activity based on signal vector magnitude (SVM)

Retention effects

The effects of the interventions at the follow-up (secondary time point) are summarized in Table 6. As described above, several benefits persisted at this time point, while others were weakened or vanished.

Discussion

This RCT evaluated the impact of cognitive–motor virtual reality training on cognitive processing speed, dual-tasking gait speed, and other aspects of mobility, cognition, patient-reported outcomes, real world, daily-living activity, and quality of life, and compared its effects to those of an active-control intervention: conventional treadmill training alone.

The impact on cognitive processing speed was greater after TT + VR training than after TT alone, consistent with our hypothesis. In contrast, dual-tasking gait speed improved similarly after both TT and TT + VR. We observed specific benefits to TT alone (MSWS-12 and MSQOL physical functioning) and multiple benefits specifically to TT + VR for several aspects of cognitive function, quality of life, and depressive symptoms, in addition to improvements in the SDMT. This positive impact on cognitive function addresses an important, previously identified gap regarding treating cognitive deficits in pwMS [7].

In contrast to an earlier RCT that reported no improvement in SDMT scores after 12 weeks of stepping training (in place) among 44 pwMS [37], cognitive processing speed became faster in both training groups following the training. The slight improvement (< 1 point) that was observed in the

Table 6 Study outcomes at baseline and at the 3-month follow-up in both groups

	TT group			TT + VR group			
	Baseline	Follow-up (p value)	Within-group effect (p value)	Baseline	Follow-up (p value)	Within-group effect (p value)	Overall retention effect (p value)
Gait							
DTW speed (cm/s)	101 ± 7.8	108 ± 6.4	0.117	102 ± 5.4	110 ± 5.1	0.035[a]	< 0.008[a,c]
UW speed (cm/s)	119 ± 6.8	124 ± 6.6	0.117	121 ± 6.7	130 ± 6.5	0.027[a]	< 0.001[a,c]
DTW cadence (steps/min)	93.8 ± 3.6	96.2 ± 3.0	0.133	96.1 ± 2.5	98.7 ± 2.5	0.152	0.033[a]
UW cadence (steps/min)	102.4 ± 2.8	104.2 ± 2.6	0.226	105.0 ± 2.7	107.0 ± 2.5	0.086	0.043[a]
DTW step regularity (unitless)	0.462 ± 0.044	0.563 ± 0.038	0.065	0.511 ± 0.038	0.530 ± 0.029	0.502	0.059
Cognition							
SDMT	47.0 ± 11.2	49.0 ± 11.7	0.058	43.9 ± 1.9	47.2 ± 11.8	0.005[a,c]	0.001[a,c]
DT words	11 (2–24)	13 (2–29)	0.010[b]	12 (3–25)	14 (3–22)	< 0.001[b,c]	< 0.001[b,c]
TMT A (s)	50.0 (20–142)	42.7 (34.6–205.6)	< 0.001[b,c]	52.8 (27.1–122.0)	45.2 (21.0–203)	0.001[b,c]	< 0.001[b,c]
TMT B (s)	93.0 (40.3–360.6)	89.4 (44.2–196.7)	0.307	97.0 (49.4–304.8)	95.4 (45.3–355.3)	0.013[b]	0.010[b]
WLG (words)	35 (14–62)	37 (16–57)	0.137	34 (9–62)	37 (13–66)	0.004[b,c]	0.002[b,c]
CLVT (words)	55 (24–73)	64 (16–79)	< 0.000[b,c]	51 (26–78)	62 (34–80)	< 0.001[b,c]	< 0.001[b,c]
Daily-living activity							
Daily-living best (90%) speed (cm/s)	115.5 ± 6.4	111.7 ± 6.4	0.146	108.9 ± 3.2	107.4 ± 3.2	0.459	0.115
Daily-living cadence	100.0 ± 24.6	98.0 ± 23.7	0.374	103.6 ± 15.7	102.0	0.170	0.137
Daily-living step regularity usual	503 ± 0.033	516 ± 0.036	0.562	503 ± 0.034	484 ± 0.037	0.435	0.844
Daily-living step regularity best (90%)	627 ± 0.040	633 ± 0.045	0.730	605 ± 0.024	603 ± 0.029	0.908	0.903
Patent-reported outcomes							
PHQ	5 (0–18)	4.5 (0–21)	0.636	4 (1–17)	6 (0–13)	0.750	0.615
MSWS-12	38.2 ± 13.7	36.0 ± 12.3	0.124	31.5 ± 14.4	33.0 ± 13.4	0.394	0.673
MSQOL physical health	58.4 ± 16.2	57.3 ± 16.4	0.792	52.0 ± 20.7	60.0 ± 20.3	0.367	0.382
MSQOL mental health	68.5 ± 17.1	67.9 ± 20.25	0.815	61.7 ± 23.0	69.6 ± 21.5	0.264	0.584

Variables mean values ± standard error presented

DTW dual-task controlled for the number of words generated during the 1-min walk. *UW* Usual walk. *SDMT* Symbol Digit Modalities Test *CVLT-II* California Verbal Learning Test-II, *WLG* Word List Generation. *TMT A&B* The Trail Making Test A & B. *MSWS-12* The Multiple Sclerosis Walking Scale-12. *MSQOL54* overall quality of life via the MSQOL-54. *PHQ-9* Patient Health Questionnaire-9 (a measure of depressive symptoms)

[a]Significant pairwise time effect. Significance was set to 95% in all tests. For all repeated ANOVA measures, the estimated marginal means controlled for age and gender are presented

[b]Significant time effect according to related-sampled Wilcoxon repeated signed test

[c]Significant p value after adjustment to multiple comparisons $p < 0.008$

TT group could be a result of a practice effect [38]. Conversely, the TT + VR subjects showed clinically meaningful improvements [28] (mean increase of 4.4 points). Improved attention and verbal fluency (better scores on TMT A and the WLG test), cognitive functions critical for everyday life, also improved specifically in the TT + VR group, consistent with the SDMT findings. These improvements emphasize the added value of augmenting VR to treadmill training to enhance cognitive function in pwMS. In general, these findings extend previous work, which recommends VR to target cognitive function among older adults and patients with neurological impairments [19, 22, 23]; here, we provide novel RCT evidence among pwMS.

Several aspects of gait became larger (better) following the intervention, under usual and dual-task conditions, some after TT, some after TT + VR, and some after both treatments (e.g., gait speed). These findings are consistent with previous studies that used treadmill-based rehabilitation in pwMS with moderate EDSS [3, 25]. Similar to those previous reports [3, 25], in our study, gait speed improved by about 10% following treadmill training, and dual-tasking gait speed increased by about 10 cm/s, often considered the minimum clinically important difference for gait speed [39, 40]. However, in contrast to our expectations, the addition of VR to the treadmill training did not further enhance dual-tasking gait speed, beyond that seen with TT alone. Perhaps, subjects in the TT group spent less cognitive effort focusing on the motor task after the intervention, allowing for more cognitive resources to be available to attend to the motor task. Regardless of the exact mechanism, this finding is similar to that of a recent RCT in 39 pwMS, which showed that both conventional balance training and balance training with VR improved balance and mobility in pwMS, although each showed unique advantages [18]. However, to the best of our knowledge, our study is the first and the largest RCT study in pwMS to examine the impact of adding VR to treadmill training on cognitive functioning and gait measured overground in a laboratory setting and during daily-living.

Following the intervention, subjects from both groups showed improvement in several aspects of daily-living mobility measures, e.g., "best" gait speed and daily-living step regularity [41]. These findings suggest that the treadmill training benefits transferred to certain aspects of over-ground walking in real-world, everyday settings. Nonetheless, the interventions did not change the subject's "typical" values of these measures during daily-living or daily-living step counts—perhaps because they are influenced by other behavioral and environmental factors, while the "top" performance during daily-living did improve. This "best" performance may reflect capacity, suggesting that this ability improved, consistent with the in-lab results. TT + VR tended to have a better effect on step regularity (greater symmetry) during daily-living.

This might be a reflection of the multi-modal intervention. Treadmill training with VR can positively impact certain aspects of daily-living ambulation, dual-tasking, and cognitive function. Thus, in the future, it would be interesting to examine if this intervention reduces the risk of falls, a common problem among pwMS that has been related to cognitive and motor deficits, and disability [12–15]. In addition, the results suggest that to change everyday behavior and increase daily-living physical activity, treadmill training should, perhaps, be combined with some form of behavioral intervention that promotes physical activity.

Three months after training, SDMT scores tended to be higher than the baseline values in both groups (recall Fig. 3). However, only the TT + VR group maintained the improvement in most of the cognitive tests. These findings align with recent studies showing the potential of VR to promote cognitive rehabilitation among older adults [42] and executive and visual–spatial abilities in pwMS [43]. Furthermore, previous studies that used motor–cognitive training in pwMS reported improvement in functional tests [44]. Consistent with that, we observed greater improvement in the functional short, fast walk test (T25FW) in the combined training group (TT + VR), which was retained after the follow-up period, apparently slowing the reported natural annual deterioration of 1.8 s on the T25FW [45], at least for 3 months. Yet, the improvements achieved in the T25FW and the 6MWT cannot be considered clinically meaningful [46], suggesting perhaps that treadmill training improved gait quality, but that other approaches are needed to significantly impact cardiovascular function and endurance.

Consistent with other work [47], treadmill training alone—but not TT + VR—slightly improved self-perceptions of mobility (MSWS-12). Perhaps, focusing on the gait pattern (without the VR interference) translated to a better physical self-perception. Nonetheless, the TT + VR group showed improvements in the mental component of QOL and a substantial reduction in depressive symptoms; these changes were not seen after TT alone. These positive effects of VR training on mood and depression are supported by previous studies in older adults [42], in people with neurological disorders (e.g., stroke) [48], and, recently, in pwMS [43]. Our results underscore the links between physical function, cognition, and mental aspects of quality of life.

Interestingly, both subjects with mild and more advanced disease benefited from the training. This question should be further explored in larger cohorts of pwMS with more advanced disease. The disparate effects of TT and TT + VR on SDMT suggest that the improvement in cognitive processing speed among those who trained with the TT + VR was not simply related to dual-task gait improvements. This is parallel to cross-sectional findings [49]. In that regard, it would be interesting to perform

mediation analyses to examine the relationships between improvements in SDMT, gait, and other outcomes like mental health.

This study has several limitations. For example, we attempted to match the training in both groups, except for the VR addition; however, during the TT sessions, the participants in the TT group had more time to concentrate on their gait in the absence of the VR component. This may have masked some of the VR advantages. The emergence of the COVID-19 pandemic made recruitment and training challenging, causing dropouts and limited retention for follow-up. Moreover, the pandemic likely affected daily-living activity and may have reduced the effects of the interventions, especially on real-world ambulation. Hence, the impact of the treadmill training with and without VR addition on daily-living gait in pwMS should be further explored. In the future, it may also be informative to evaluate the effects of treadmill training with and without VR on brain structure and function and other markers of disease burden in pwMS and to assess whether the impact of TT and TT + VR on dual-tasking gait speed depends on the specifics of the dual-task [49]. The present work sets the stage for these future studies.

In summary, to the best of our knowledge, this is the largest RCT among pwMS to demonstrate that treadmill training with or without the addition of a VR component positively affects several aspects of gait and mobility. The results of this RCT support the idea that treadmill training, with or without VR, should be recommended to people with relapsing–remitting MS, across a range of disability levels to improve their gait. Further, the addition of VR appears to confer important benefits for cognitive function and mental health. Thus, the present RCT results underscore the idea that both motor and cognitive function can be improved among pwMS, even among patients with relatively advanced disease. Future studies should further explore the long-term effects of this combined motor-cognitive training, perhaps as a disease-modifying therapy [50], and the possibility of slowing down or reversing the natural course of the disease in mild and more advanced patients.

Data availability statement Data will be made available by reasonable request from any qualified investigator.

Declarations

Conflicts of interest JJS reports funding from the National Institute of Health (R21AG073892, R21AG064308-01), National Multiple Sclerosis Society (MB-1807-31633, RG-1701-26862), ownership in Sosnoff Technologies, LLC, speaking fees from BrainWeek, and consulting fees from Xavor, Inc. AM and JMH report have submitted a patent application on the use of virtual reality, the intellectual property rights for which are held by the Tel Aviv Medical Center. None of the other authors have potential conflicts of interest to be disclosed.

Standard protocol approvals, registrations, and patient consents The trial was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidance Good Clinical Practice, the 1964 Declaration of Helsinki and its later amendments, local applicable law and regulatory requirements, was approved by institutional review boards and ethical committees of each participating center, and was registered in ClinicalTrials.gov (NCT02427997). All patients provided written informed consent before any study procedure was performed.

References

1. Gunn H, Creanor S, Haas B et al (2013) Risk factors for falls in multiple sclerosis: an observational study. Mult Scler J 19:1913–1922. https://doi.org/10.1177/1352458513488233
2. Comber L, Galvin R, Coote S (2017) Gait deficits in people with multiple sclerosis: a systematic review and meta-analysis. Gait Posture 51:25–35. https://doi.org/10.1016/j.gaitpost.2016.09.026
3. Robinson AG, Dennett AM, Snowdon DA (2019) Treadmill training may be an effective form of task-specific training for improving mobility in people with Parkinson's disease and multiple sclerosis: a systematic review and meta-analysis. Physiother (UK) 105:174–186. https://doi.org/10.1016/j.physio.2018.11.007
4. Ahmadi A, Arastoo AA, Nikbakht M (2010) The effects of a treadmill training programme on balance, speed and endurance walking, fatigue and quality of life in people with multiple sclerosis. Int Sport J 11:389–397
5. Chiaravalloti ND, DeLuca J (2008) Cognitive impairment in multiple sclerosis. Lancet Neurol. https://doi.org/10.1016/S1474-4422(08)70259-X
6. Patti F, Amato MP, Trojano M et al (2009) Cognitive impairment and its relation with disease measures in mildly disabled patients with relapsing-remitting multiple sclerosis: baseline results from the Cognitive Impairment in Multiple Sclerosis (COGIMUS) study. Mult Scler. https://doi.org/10.1177/1352458509105544
7. Sumowski JF, Benedict R, Enzinger C et al (2018) Cognition in multiple sclerosis. Neurology. https://doi.org/10.1212/wnl.0000000000004977
8. Amato MP, Ponziani G, Pracucci G et al (1995) Cognitive impairment in early-onset multiple sclerosis: pattern, predictors, and impact on everyday life in a 4-year follow-up. Arch Neurol. https://doi.org/10.1001/archneur.1995.00540260072019
9. Wajda DA, Sosnoff JJ (2015) Cognitive-motor interference in multiple sclerosis: a systematic review of evidence, correlates, and consequences. Biomed Res Int. https://doi.org/10.1155/2015/720856
10. Learmonth YC, Dlugonski DD, Pilutti LA et al (2013) The reliability, precision and clinically meaningful change of walking

assessments in multiple sclerosis. Mult Scler J. https://doi.org/10.1177/1352458513483890

11. Learmonth YC, Ensari I, Motl RW (2017) Cognitive motor interference in multiple sclerosis: insights from a systematic quantitative review. Arch Phys Med Rehabil 98:1229–1240

12. Wajda DA, Motl RW, Sosnoff JJ (2013) Dual task cost of walking is related to fall risk in persons with multiple sclerosis. J Neurol Sci. https://doi.org/10.1016/j.jns.2013.09.021

13. Etemadi Y (2017) Dual task cost of cognition is related to fall risk in patients with multiple sclerosis: a prospective study. Clin Rehabil. https://doi.org/10.1177/0269215516637201

14. Rooney S, Ozkul C, Paul L (2020) Correlates of dual-task performance in people with multiple sclerosis: a systematic review. Gait Posture 81:172

15. Merlo D, Stankovich J, Bai C et al (2021) Association between cognitive trajectories and disability progression in patients with relapsing-remitting multiple sclerosis. Neurology. https://doi.org/10.1212/WNL.0000000000012850

16. Wajda DA, Mirelman A, Hausdorff JM, Sosnoff JJ (2017) Intervention modalities for targeting cognitive-motor interference in individuals with neurodegenerative disease: a systematic review. Expert Rev Neurother 17:251–261

17. Veldkamp R, Baert I, Kalron A et al (2019) Structured cognitive-motor dual task training compared to single mobility training in persons with multiple sclerosis, a multicenter RCT. J Clin Med 8:1–16. https://doi.org/10.3390/jcm8122177

18. Molhemi F, Monjezi S, Mehravar M et al (2021) Effects of virtual reality vs conventional balance training on balance and falls in people with multiple sclerosis : a randomized controlled trial. Arch Phys Med Rehabil 102:290–299. https://doi.org/10.1016/j.apmr.2020.09.395

19. Holden MK (2005) Virtual environments for motor rehabilitation: review. Cyberpsychol Behav 8:212–219

20. Mirelman A, Maidan I, Herman T et al (2011) Virtual reality for gait training: Can it induce motor learning to enhance complex walking and reduce fall risk in patients with Parkinson's disease? J Gerontol Ser A. https://doi.org/10.1093/gerona/glq201

21. Mirelman A, Rochester L, Maidan I et al (2016) Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. Lancet. https://doi.org/10.1016/S0140-6736(16)31325-3

22. Valenzuela T, Okubo Y, Woodbury A et al (2018) Adherence to technology-based exercise programs in older adults: a systematic review. J Geriatr Phys Ther 41:49–61

23. Coyle H, Psych B, Traynor V et al (2015) Computerized and virtual reality cognitive training for individuals at high risk of cognitive decline: systematic review of the literature. Am J Geriatr Psychiatry 23:335–359. https://doi.org/10.1016/j.jagp.2014.04.009

24. Dockx K, Bekkers EMJ, Van den Bergh V et al (2016) Virtual reality for rehabilitation in Parkinson's disease. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD010760.pub2

25. Peruzzi A, Zarbo IR, Cereatti A et al (2017) An innovative training program based on virtual reality and treadmill: effects on gait of persons with multiple sclerosis. Disabil Rehabil 39:1557–1563. https://doi.org/10.1080/09638288.2016.1224935

26. Hsieh KL, Mirelman A, Shema-Shiratzky S et al (2020) A multimodal virtual reality treadmill intervention for enhancing mobility and cognitive function in people with multiple sclerosis: Protocol for a randomized controlled trial. Contemp Clin Trials 97:106122. https://doi.org/10.1016/j.cct.2020.106122

27. Langdon DW, Amato MP, Boringa J et al (2012) Recommendations for a brief international cognitive assessment for multiple sclerosis (BICAMS). Mult Scler J 18:891–898

28. Benedict RHB, Deluca J, Phillips G et al (2017) Validity of the symbol digit modalities test as a cognition performance outcome measure for multiple sclerosis. Mult Scler 23:721–733

29. Gijbels D, Dalgas U, Romberg A et al (2012) Which walking capacity tests to use in multiple sclerosis? A multi-centre study providing the basis for a core set. Mult Scler J. https://doi.org/10.1177/1352458511420598

30. Moe-Nilssen R, Helbostad JL (2004) Estimation of gait cycle characteristics by trunk accelerometry. J Biomech. https://doi.org/10.1016/S0021-9290(03)00233-1

31. Shema-Shiratzky S, Hillel I, Mirelman A et al (2020) A wearable sensor identifies alterations in community ambulation in multiple sclerosis: contributors to real-world gait quality and physical activity. J Neurol. https://doi.org/10.1007/s00415-020-09759-7

32. Tombaugh TN (2004) Trail making test A and B: normative data stratified by age and education. Arch Clin Neuropsychol. https://doi.org/10.1016/S0887-6177(03)00039-8

33. Hobart JC, Riazi A, Lamping DL et al (2003) Measuring the impact of MS on walking ability: the 12-item MS Walking Scale (MSWS-12). Neurology. https://doi.org/10.1212/WNL.60.1.31

34. Vickrey BG, Hays RD, Harooni R et al (1995) A health-related quality of life measure for multiple sclerosis. Qual Life Res. https://doi.org/10.1007/BF02260859

35. Kroenke K, Spitzer RL, Williams JBW (2001) The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 16:606

36. Williams KG, Sanderson M, Jette N, Patten SB (2020) Validity of the Patient Health Questionnaire-9 in neurologic populations. Neurol Clin Pract. https://doi.org/10.1212/cpj.0000000000000748

37. Hoang P, Schoene D, Gandevia S et al (2016) Effects of a home-based step training programme on balance, stepping, cognition and functional performance in people with multiple sclerosis: a randomized controlled trial. Mult Scler. https://doi.org/10.1177/1352458515579442

38. Roar M, Illes Z, Sejbaek T (2016) Practice effect in symbol digit modalities test in multiple sclerosis patients treated with natalizumab. Mult Scler Relat Disord. https://doi.org/10.1016/j.msard.2016.09.009

39. Stuck AK, Bachmann M, Füllemann P et al (2020) Effect of testing procedures on gait speed measurement: a systematic review. PLoS ONE. https://doi.org/10.1371/journal.pone.0234200

40. Bohannon RW, Glenney SS (2014) Minimal clinically important difference for change in comfortable gait speed of adults with pathology: a systematic review. J Eval Clin Pract 20:295–300

41. Hillel I, Gazit E, Nieuwboer A et al (2019) Is every-day walking in older adults more analogous to dual-task walking or to usual walking? Elucidating the gaps between gait performance in the lab and during 24/7 monitoring. Eur Rev Aging Phys Act. https://doi.org/10.1186/s11556-019-0214-5

42. Yen HY, Chiu HL (2021) Virtual reality exergames for improving older adults' cognition and depression: a systematic review and meta-analysis of randomized control trials. J Am Med Dir Assoc 22:995–1002. https://doi.org/10.1016/j.jamda.2021.03.009

43. Maggio MG, Russo M, Cuzzola MF et al (2019) Virtual reality in multiple sclerosis rehabilitation: a review on cognitive and motor outcomes. J Clin Neurosci 65:106–111. https://doi.org/10.1016/j.jocn.2019.03.017

44. Veldkamp R, Moumdjian L, Dun K et al (2021) Motor sequence learning in a goal-directed stepping task in persons with multiple sclerosis: a pilot study. Ann N Y Acad Sci. https://doi.org/10.1111/nyas.14702

45. Kalinowski A, Cutter G, Bozinov N et al (2021) The timed 25-foot walk in a large cohort of multiple sclerosis patients. Mult Scler J. https://doi.org/10.1177/13524585211017013

46. Baert I, Freeman J, Smedal T et al (2014) Responsiveness and clinically meaningful improvement, according to disability level,

of five walking measures after rehabilitation in multiple sclerosis: a European multicenter study. Neurorehabil Neural Repair. https://doi.org/10.1177/1545968314521010

47. Ahmadi A, Arastoo AA, Nikbakht M et al (2013) Comparison of the effect of 8 weeks aerobic and yoga training on ambulatory function, fatigue and mood status in MS patients. Iran Red Crescent Med J. https://doi.org/10.5812/ircmj.3597

48. Massetti T, da Silva TD, Crocetta TB et al (2018) The clinical utility of virtual reality in neurorehabilitation: a systematic review. J Cent Nerv Syst Dis 10:117957351881354. https://doi.org/10.1177/1179573518813541

49. Veldkamp R, Baert I, Kalron A et al (2021) Associations between clinical characteristics and dual task performance in Multiple Sclerosis depend on the cognitive and motor dual tasks used. Mult Scler Relat Disord. https://doi.org/10.1016/j.msard.2021.103230

50. Motl RW, Sandroff BM (2022) Physical exercise in multiple sclerosis is not just a symptomatic therapy: it has a disease-modifying effect—yes. Mult Scler J. https://doi.org/10.1177/1352458521 1061651

Authors and Affiliations

Irina Galperin[1,2] · Anat Mirelman[1,3,4] · Tanja Schmitz-Hübsch[5,6,7] · Katherine L. Hsieh[8] · Keren Regev[9] · Arnon Karni[3,4,9] · Marina Brozgol[1] · Pablo Cornejo Thumm[1] · Sharon G. Lynch[10] · Friedemann Paul[5,6,7] · Hannes Devos[11] · Jacob Sosnoff[11] · Jeffrey M. Hausdorff[1,4,12,13]

Irina Galperin
ira.galperin@gmail.com

[1] Center for the Study of Movement, Cognition and Mobility, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

[2] Miriam and Sheldon G. Adelson School of Graduate Studies, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[3] Department of Neurology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[4] Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel

[5] NeuroCure Clinical Research Center and Experimental and Clinical Research Center, Charité-Universitätsmedizin Berlin and Max Delbrueck Center for Molecular Medicine, Berlin, Germany

[6] Humboldt-Universität Zu Berlin, Berlin, Germany

[7] Berlin Institute of Health, NeuroCure Clinical Research Center, Berlin, Germany

[8] Department of Physical Therapy, Georgia State University Atlanta, Atlanta, GA, USA

[9] Neuroimmunology and Multiple Sclerosis Unit of the Neurology Division, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

[10] Department of Neurology, University of Kansas Medical Center, Kansas City, KS, USA

[11] Department of Physical Therapy, Rehabilitation Science, and Athletic Training, University of Kansas Medical Center, Kansas City, KS, USA

[12] Department of Physical Therapy, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[13] Rush Alzheimer's Disease Center and Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL, USA