Multiple Sclerosis and Related Disorders 48 (2021) 102713

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

How may patients with MS benefit from using music assisted therapy? A case-control feasability study investigating motor outcomes and beyond.

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ARTICLE INFO

Keywords:
gait training
music therapy
neurological disorders
acoustic cue

ABSTRACT

Motor impairment is the most common symptom in multiple sclerosis (MS), as gait and balance dysfunction are reported in more than 85% of the patients, with considerable consequences on the patient's activities of daily living and psychological status. This study aimed at evaluating the feasibility and potential efficacy of a novel treatment involving music plus treadmill in patients with MS. Ten patients affected by secondary progressive MS were submitted to a specific training using the Gait Trainer (GT) 3, a platform that integrates gait training via a treadmill and rhythmic auditory stimulation. The 30 minutes training was performed three times per week for eight weeks (24 sessions in total). The enrolled patients were compared with a control group (CG) of 10 patients with MS matched for age, gender, disease duration, and EDSS stage. The CG received the same amount of treatment, but using conventional overground gait training. All patients completed the training without reporting any side effects. At the end of the training, CG improved in static and dynamic balance and in mood. Instead, in the EG a significant improvement in static and dynamic balance, walking speed, and mobility, as well as in mood, and perception of quality of life (QoL), both for physical and mental well-being, was found. This exploratory study suggests that GT3 might be a feasible and potentially useful approach for MS gait rehabilitation, thanks to patients' high motivation and good acceptance of the music assisted therapy.

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disease that causes widespread demyelination and degeneration of the central nervous system (Ghasemi, et al., 2017; Katz Sand, 2015). This disease has a prevalence of about 15 / 100,000 to 250 / 100,000 and it can occur at any age, although it is mainly diagnosed between the ages of 20 and 40 (Milo and Miller, 2014; Burridge and Hughes 2010). Clinically, MS exhibits multiple symptoms, such as motor disability (i.e. weakness, spasticity, and tremor), sensory disturbances (i.e. pain), visual dysfunction (i.e. diplopia and optic neuritis), sphincter dysfunction, neuropsychiatric symptoms, and cognitive impairment (i.e., impaired behavior or mood, attention, memory and learning). Symptoms progressively worsen, having a negative impact on the quality of life (QoL) of patients and their families (Manuli et al., 2020). In particular, motor impairment is the most common symptom in MS, as gait and balance dysfunction are reported in more than 85% of the patients (Panitch and Applebee, 2011; Morrison and Mayer, 2017), with considerable consequences on the patient's activities of daily living and psychological status. The aims of MS therapies are to improve gait speed, cadence, and stride length in order to increase independence and reduce the risk of falls. In recent years, it has been shown that in the field of rehabilitation, technological innovations, such as robotics, PC based training and virtual reality (VR), alone or combined, can offer a cost-effective way to improve the outcomes of neurorehabilitation (Calabrò et al., 2016, Maggio et al., 2018, De luca et al., 2018, Maresca et al., 2018). It was shown that effects of robot-assisted training were even more when combining it with music therapy. Music-assisted therapy (MAT) may be

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https://doi.org/10.1016/j.msard.2020.102713
Received 14 November 2020; Received in revised form 10 December 2020; Accepted 19 December 2020
Available online 24 December 2020

considered an effective strategy to improve motor (with regard to gait) and behavioral outcomes in patients with MS (Impellizzeri et al., 2020). It has been shown that training associated with auditory stimulation, such as music and the rhythmic impulses of the metronome, significantly reduce fatigue in MS patients compared to rehabilitation without the use of music (Moumdjian et al., 2019). In fact, rhythm can activate various motor areas of the central nervous system, the cerebellum, the spinal tract, and the cortex. The auditory-motor coupling also facilitates the rhythmicity of the step, favoring the cadence, the speed of the gait and the length of the step, and reducing the risk of falls (Moumdjian et al., 2019; Conklyn et al., 2010). The method uses external auditory stimulation to support gait initiation and continuation. Temporally predictable auditory cues have an immediate beneficial effect on gait by increasing speed, stride length, and improving symmetry as well as stability. Benefits can generalize to non-cued gait after an extensive period of training with auditory cues, resulting in increased mobility and enhanced QoL (Moumdjian et al., 2019). Thus, rhythmic auditory stimulation (RAS) represents a neurological therapy strategy, based on music and rhythm, aiming to improve the intrinsic rhythmicity of the gait, non-pharmacologically (De Luca et al., 2020; Calabrò et al., 2019, Naro et al., 2020). MAT-Studies conducted among Parkinson's disease (PD) patients have shown positive effects on motor (Calabrò et al., 2019; Frazzita et al., 2009; Studer et al., 2017) and non-motor symptoms in PD (De Luca et al., 2020; Calabrò et al., 2019; Frazzitta et al., 2009; Studer et al., 2017; Gooßes et. al., 2020). Particularly, various aspects of gait seem to benefit from MAT-approaches (Calabrò et al., 2019; Studer et al., 2017; Frazzitta et al., 2009) or RAS strategies (Bella et al., 2017). However, the effects of MAT are believed to depend on patients' musicality.

Thus, the purpose of this study was to evaluate the feasibility of a novel treatment involving music plus treadmill, provided using the GT3, in patients with MS. Moreover, we sought to evaluate the efficacy of this innovative approach on motor and behavioral outcomes, as well as on QoL.

2. Materials and Methods

2.1. Study population and setting

Ten MS-patients affected by Secondary Progressive MS (3 males and 7 females; mean age of 45.3 ± 9.7 years) attending the inpatient Robotic and Behavioral Neurorehabilitation Service of the IRCCS Centro Neurolesi Bonino-Pulejo (Messina, Italy) from May 2019 to December 2019 were evaluated for inclusion in this study.

Inclusion criteria were: i) MS diagnosis (secondary progressive form) according to Lublin criteria; ii) an Expanded Disability Status Scale (EDSS) between 3 and 6; iii) to love/enjoy music, either performed instrumentally or listened; iv) absence of disabling sensory alterations (i.e., hearing and visual loss); v) no change in disease-modifying drugs treatment in the previous six months.

Exclusion criteria as follows: i) age > 65 years; ii) presence of severe medical and psychiatric illness potentially interfering with the MAT; iii) personal history of neoplasms and other neurological conditions; iv) presence of moderate-severe cognitive decline (MOCA < 21) v) neurologic music therapy in the last three months.

The enrolled patients were compared with a control group of 10 patients with MS matched for age, gender, disease duration, and EDSS stage. Given the exploratory nature of the present study, the main aim of which was to provide evidence that could allow planning of further confirmatory studies, we focused on the usability and efficacy of the training on specific functional outcomes. Therefore, the sample size was determined without any *a priori* formal statistical hypothesis.

2.2. Outcome measures

Each participant was evaluated by a neuropsychologist, neurologist and physiotherapist before (T0) and immediately after the end of the training (T1).

Motor evaluation consisted of the Berg Balance Scale (BBS) to determine patient's balance; the Timed Up and Go Test (TUG) to assess patients' mobility; and the 10-metre Walk Test (10MWT) to register walking speed (m/s) over a short distance.

The neuropsychological battery included: Beck Depression Inventory II (BDI-II) to assess mood; Multiple Sclerosis Quality of Life-54 (MSQOL-54) to investigate patients' QoL-perception of life; Goal attainment scaling (GAS) for evaluating the extent to which the patient believes that individual goals during the intervention were achieved.

Finally, patients completed the System Usability Scale (SUS), to evaluate the usability of the MAT with GT3.

2.3. Procedures

The included patients were submitted to the same amount of conventional physiotherapy (i.e., stretching, muscle strength and occupational therapy, provided twice a day, each session lasting about 45 minutes), as per our standard research and clinical protocol. Only the type of gait training was different: group 1 (EG) was trained with the GT3 device, whereas group 2 (CG) performed conventional overground gait training. The gait rehabilitation protocol consisted of a total of 40 training sessions (i.e. five times a week for 8 weeks, as per our standard research and clinical protocol) lasting about one hour for each group.

2.4. GT3 Training

GT3 treadmill is an extension of common therapy and training treadmills, since it has an integrated RAS function and a visual feedback option (Fig. 1).

For the RAS the device is equipped with a library of different metronome sounds and music written and recorded by music therapists, the RAS library of the GT3 incorporates carefully chosen musical elements to expand rhythm-based therapy using spatial, temporal, and force cues (Young, 2017). The RAS (metronome/ music) of the GT3 can be adapted to patients' potential in terms of pace and complexity.

Furthermore, the GT3 offers real-time visual feedback for patients' gait quality (step-length, weight bearing on each leg) on an LCD display, so that patients can monitor their gait pattern. The target step length is visualized by a marked corridor in between two green lines. Patients' alternating steps for right and left foot were shown and patients were provided with the visual, but also written feedback (e.g. "good job" or "longer step right/left") via the monitor. Furthermore, patients received a feedback on the step symmetry by the percentage of weight bearing on each foot shown as a bar graph.

By combining treadmill training with RAS and visual biofeedback the GT3 allows repetition of correct movement to promote neuroplasticity by creating new and retraining old neural pathways helping neurologic patients to regain motor function.

During the gait training several gait parameters can be monitored and recorded for off-line analysis.

In our protocol patients were at first trained to synchronize their footsteps to the beat of the music (beats per minute, bpm), which was analog to their baseline gait performance (steps per minute). Then, the bpm was progressively increased up to the target of 120bpm (on the average) within the first three sessions. This target frequency was then applied during the remaining training sessions, according to the patient's needs and performance.

2.5. Statistical analysis

The clinical records of 10 MS patients treated with GT3 and 10 patients with MS who performed TT were examined. We assigned them to one of two groups: EG and CG. To reduce the selection bias, we matched age, sex, duration of the disease and EDSS score. The data were analyzed

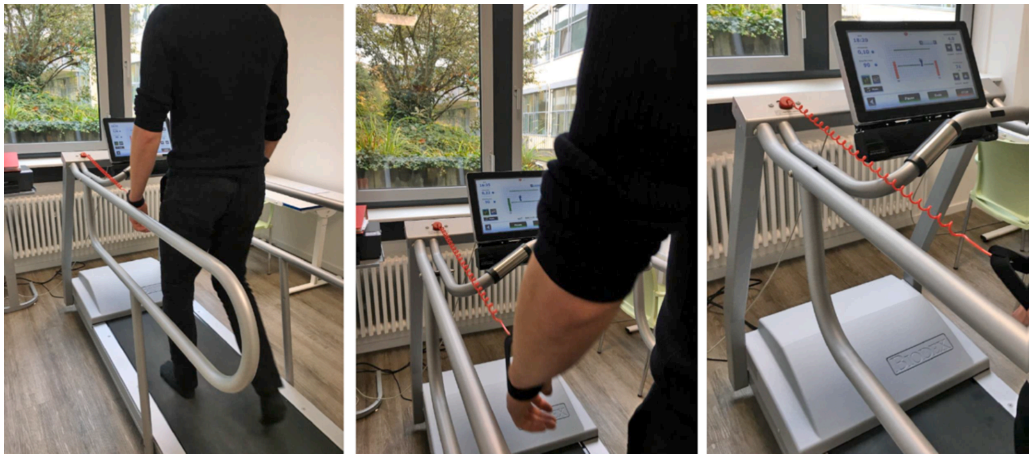

Figure 1. shows a patient with MS during the training with the GT3 device.

using SPSS version 16.0 (Armonk, NY), considering a $p<0.05$ as statistically significant. Continuous variables were expressed as mean ± standard deviation or median ± first-third quartile, as appropriate. The categorical variables were expressed as frequencies and percentages. Due to the small sample size, and since the Kolmogorov–Smirnov test showed irregular distributions for many variables, a nonparametric analysis was performed. The Mann–Whitney U test was used to compare the two groups (inter-group analysis) and the Wilcoxon signed-rank test was used to compare each group between baseline and the end of the training (intra-group analysis).

3. Results

All patients completed the training, and both groups underwent the same amount of treatment. As the two groups were matched for age, sex, disease duration and EDSS score (Table 1), no significant differences were found in the age ($p = 1.00$), in the education level ($p = 1.00$), in disease duration and EDSS score ($p = 1.00$) and in the proportion of gender ($p = 1.00$). Moreover, at baseline, no significant differences emerged between the outcome scores of two groups. The results of Wilcoxon's tests (table 3) showed significant differences in all of the domains that we evaluated (Table 2), underlining that the scores of some tests were influenced by the type of treatment. CG showed significant improvement in static and dynamic balance (BBS: p 0.004) and in mood (BDI: p 0.004). Instead, EG showed significant improvement in the pre-post comparisons in static and dynamic balance (BBS $p < 0.002$), walking speed (10mWT $p < 0.002$), and mobility (TUG $p < 0.002$). Moreover, we observed an improvement in mood (BDI $p < 0.002$), and the QoL-perception, both physical (MSQOL-PH $p < 0.002$) and mental health (MSQOL-MH $p < 0.001$), as well as in the perception of the therapeutic goal achievement (GAS $p < 0.002$). In particular, it was noticed that the majority of the sample chose the goal: "walking with a better balance" (51.2%) and "increasing the awareness/feeling well" (27.4%). The Mann–Whitney U test confirmed the results, showing that the effect of the two treatments was significantly different at T1 in all the outcomes, except for BBI and BDI-II (table 3).

Finally, results from the System Usability Scale revealed that patients perceived high usability of robotic devices, which were well tolerated (SUS mean 86.05 ± 5.1). The robot training was feasible for all patients, as the training did not cause any negative side effects, including fatigue. Furthermore, nearly all patients found the device easy to use and the training enjoyable.

Table 1
Clinical - Demographic characteristics of the sample at baseline.

	Experimental Group	Control Group
Patients	10 (100%)	10 (100%)
Females; Males (% Female)	3; 7 (70.0%)	4; 6 (60%)
Age (years)	45.3 ± 9.7	45.3 ± 9.5
Education	12.09 ± 2.1	12.09 ± 2.0
MS course		
Relapsing-remitting	5 (50%)	5 (50%)
Primary progressive	5 (50%)	5 (50%)
Secondary progressive	0	0
Disease duration, years Median EDSS	17.7 ± 5.3	17.7 ± 5.4
	4.7 ± 1.5	4.8 ± 1.3

Mean ± standard deviation was used to describe continuous variables; proportions (numbers and percentage) were used to describe categorical variables.
Legend: EDSS:Expanded Disability Status Scale; MS: Multiple Sclerosis.

4. Discussion

To the best of our knowledge, this is the first study assessing the feasibility of MAT with the GT3 in MS patients rehabilitation. Our study showed that MAT using GT3 is an effective neurorehabilitation approach to increase MS patients engagement in and motivation for treatment, with a positive effect on the QoL. All the patients in the EG found the device easy to use and the training useful and enjoyable, as per SUS; in addition, they reached their planned goal, as per GAS. In both groups, we found a good perception of the results achieved, but only in the EG this was statistically significant. In our opinion, MAT training with the GT3 allows us to customize the exercise according to the characteristics and preferences of MS-patients, encouraging the perception of motor and mental well-being. The patient's perception of the use of innovative tools is poorly considered in the literature. In a recent study, Manuli et al. (2020) have observed that investigating users' perceptions in the field of neurorehabilitation can be fundamental in reaching rehabilitation goals, as patient's motivation is a good predictor of his/her long-term changes. In fact, patients who find rehab devices useful and motivational have better performance during exercises, greater therapy adherence, and better outcomes (Hughes et al., 2011; Grahn et al., 2000). In our sample, we observed the active participation of MS-patients, who enjoyed the training with good behavioral outcomes. In line with our findings, Resquin et al. (2016) suggested that patients who find robotic rehabilitation useful and motivational tend to adopt an active attitude without feeling pressured or stressed. There is evidence to suggest that music is able to evoke and alter emotional reactions that promote motivation. In particular, some studies (Hodgens, 2010; Hodgens and Sebald, 2011) have shown that music is not only able to evoke emotional reactions, including emotional peak experiences, but also can alter mood, emotions, and the attitude of the patients. Furthermore, responses to music are accompanied by persistent physiological changes, likely due to the music capacity to

Table 2
Statistical Analysis of motor neuropsychological evaluation.

CLINICAL SCALE	Statistical Analysis		*Mean (DS)*	*p-value*
Motor Scores				
BBS	**Between groups**	**EG - T0 / CG - T0**	31.0 (29.5-35.7) - 32.1 (29.0-33.0)	0.80
		EG - T1 / CG- T1	38.0 (35.0-40.7) - 36.3 (34.0-39.0)	0.19
	Within group	**EG - T0 / EG - T1**	31.0 (29.5-35.7) -38.0 (35.0-40.7)	**0.002**
		CG- T0 / CG- T1	32.1 (29.0-33.0) - 36.3 (34.0-39.0)	**0.004**
10mWT	**Between groups**	**EG - T0 / CG - T0**	23.5 (20.0-26.4) - 22.2 (20.8–25.4)	0.81
		EG - T1 / CG- T1	18.2 (12.6-23.0) - 21.7 (20.0-24.5)	**0.004**
	Within group	**EG - T0 / EG - T1**	23.5 (20.0-26.4) - 18.2 (12.6-23.0)	**0.002**
		CG- T0 / CG- T1	22.2 (20.8–25.4) - 21.7 (20.0-24.5)	0.250
TUG Left	**Between groups**	**EG - T0 / CG - T0**	18.4 (12.5-22.9) - 17.1 (10.4-21.8)	0.75
		EG - T1 / CG- T1	15.4 (10.5-19.4) - 16.6(10.0-23.2)	**0.001**
	Within group	**EG - T0 / EG - T1**	18.4 (12.5-22.9) - 15.4 (10.5-19.4)	**0.002**
		CG- T0 / CG- T1	17.1 (10.4-21.8) - 16.6(10.0-23.2)	0.064
TUG Right	**Between groups**	**EG - T0 / CG - T0**	17.7 (13.4-25.9) -18.4 (12.5-22.0)	0.92
		EG - T1 / CG- T1	15.7 (11.1-21.1) - 17.1 (22.5-31.0)	**0.003**
	Within group	**EG - T0 / EG - T1**	17.7 (13.4-25.9) -15.7 (11.1-21.1) 18.4 (12.5-22.0) - 17.1 (22.5-31.0)	**0.002**
		CG- T0 / CG- T1		0.071
Psychological parameters				
BDI-II	**Between groups**	**EG - T0 / CG - T0**	10.5 (7.7-16.5) - 9.7 (7.7-16.5)	0.25
		EG - T1 / CG- T1	4.5 (2.0-6.0) - 8.5 (4.0-10.0)	0.12
	Within group	**EG - T0 / EG - T1**	10.5 (7.7-16.5) - 4.5 (2.0-6.0)	**0.002**
		CG- T0 / CG- T1	9.7 (7.7-16.5) - 8.5 (4.0-10.0)	**0.004**
MSQOL PH	**Between groups**	**EG - T0 / CG - T0**	53.8 (42.3-78.5) - 53.6 (36.0– 76.0)	0.75
		EG - T1 / CG- T1	81.3 (54.9-129.0) - 56.6 (48.0-84.5)	**0.004**
	Within group	**EG - T0 / EG - T1**	53.8 (42.3-78.5) - 81.3 (54.9-129.0)	**0.002**
		CG- T0 / CG- T1	53.6 (36.0– 76.0) - 56.6 (48.0-84.5)	0.008
MSQOL MT	**Between groups**	**EG - T0 / CG - T0**	46.6 (35.6-60.3) - 42.1 (41.6-57.1) -	0.72
		EG - T1 / CG- T1	85.5 (77.7-93.9) - 43.7 (41.5-60.5)	**0.00**
	Within group	**EG - T0 / EG - T1**	46.6 (35.6-60.3) - 85.5 (77.7-93.9) 42.1 (41.6-57.1) - 43.7 (41.5-60.5)	**0.002**
		CG- T0 / CG- T1		0.078
GAS	**Between groups**	**EG - T0 / CG - T0**	37.7 (36.0-38.2) - 37.7 (37.6 - 37.6)	0.78
		EG - T1 / CG- T1	61.6 (55.7-67.2) - 56.3 (43.1-60.5)	**0.002**
	Within group	**EG - T0 / EG - T1**	37.7 (36.0-38.2) - 61.6 (55.7-67.2)	**0.002**
		CG- T0 / CG- T1	37.7 (37.6 - 37.6) - 56.3 (43.1-60.5)	0.012

Legend: BBS: Berg Balance Scale; BDI-II: Beck Depression Inventory-II; GAS: Goal attainment scaling; MSQOL: Multiple Sclerosis Quality of Life-54; PH: Physical health; MT: Mental Health; TUG: Timed Up and Go Test; 10mWT: 10 m Walking Test.
*Significant differences are in bold ($p < 0.005$). Results are expressed in median (first-third quartile).

activate the ventral tegmental area and stimulate the production of dopamine (Blum et al., 2017). The positive influence of music on mood and emotional status could be - at least partly- the reason why it may be effective in neurological disorders, such as MS, in which emotional and behavioral disturbances are often present and can negatively impact on motor outcomes (Impellizzeri et al., 2020; Skokou et al., 2012; Koch et al., 2015). In fact, according to Galinska (2015), music can be a means of helping patients to consider therapeutic experiences with affective and motivational aspects, encouraging therapeutic compliance. In addition, growing evidence has pointed out that music can foster the activation of "echo-mirror neurons" during the execution of music-related movements (as in gait training) by encouraging a better execution of the movements themselves (Hou et al., 2017). In line with these aspects, our study revealed higher psychological and emotional well-being levels after music-assisted treadmill training, confirming its greater involvement in patients' activities and motivation. Recent studies have observed that the use of MAT (especially RAS) can be considered as part of the multidimensional approach to improve gait and gait-related activities for patients with neurological disorders (Ashoori et al., 2015; Calabrò et al., 2019). Moreover, some authors have highlighted the positive effect of MAT not only on motor function (bradykinesia, gait, gait freezing), but also on emotional and psychological functioning, coping strategies, and QoL in neurological patients (De Luca et al., 2020; Calabrò et al., 2019; Gooßes et. al., 2020).

In our exploratory study, after the GT3 training, patients showed a significant improvement in static and dynamic balance (BBS), walking speed and balance (10WT and TUG), further supporting how MAT may positively affect motor outcomes, leading to better results than conventional overground training. Moreover, an improvement in mood and perception of QoL was observed, suggesting the idea that MAT might also be effective on behavioral and cognitive outcomes, as demonstrated in individuals submitted to robotic training (Goda et al., 2020; Bragoni et al 2013). In fact our study, in line with previous data (De Luca et al., 2020), showed that training with the treadmill plus music actively potentiated the ability to walk "normally", leading to positive repercussions on physical, psychological and emotional aspects. Nonetheless, this issue deserves further attention and validation.

The positive effects of music as a rehabilitative tool has been extensively investigated in different neurological disorders (Magee et al., 2017; Sihvonen et al., 2017), particularly in patients with PD (Barnish and Barran, 2020; Zhang et al., 2017; De Bartolo et al., 2020). The rationale underlying the use and effectiveness of MAT in PD lays on the intrinsic features of the disease. Indeed, PD is characterized by a deficiency of dopamine in the basal ganglia, leading to a reduction in spontaneous movements, including gait. GT3 may improve motor and cognitive performance by boosting the altered circuities. Indeed, in response to MAT, the deficiency of basal ganglia may be: i) compensated by the premotor, parietal, anterior cingulate, and supplementary motor areas, or ii) substituted by the cerebellum-thalamus-cortical circuits (which process and synchronize perceptual stimuli), as the latter are less affected by the disease (Della Bella et al., 2015; Nombela et al., 2013). Compared to PD, patients with MS have multiple demyelinating lesions potentially affecting many neural pathways involved in motor control (both planning and execution circuities). It is possible that coupling treadmill training with music may have acted as a sort of paired associative stimulation (i.e. bottom up stimulation through the treadmill and top-down stimulation thanks to the acoustic stimulation) with a potentiation of neural plasticity of the dysfunctional pathways and thus better outcomes, as demonstrated in PD.

The main limitation of the study is the small sample, so the work should be considered as a preliminary study with promising results to be confirmed in further randomized controlled trials (RCT). However, the sample used was homogeneous regarding MS type and was compared to a matched control group, so to provide information on the potential efficacy of the tool. Additionally, we included several variables in the study analysis, and the duration of the effect remains indefinite due to the lack of a follow-up period. Further RCTs should be conducted using larger samples and follow up to evaluate if and to what extent the functional gain is maintained. Furthermore, we did not consider other factors, which could have affected patients' mood and training results. For future trials, it would also be recommendable to evaluate the potential cognitive effects of this training and to investigate the neurological circuits underpinning the functional recovery.

In conclusion, our results suggest that GT3 could be a feasible and potentially useful approach for the gait rehabilitation of MS-patients, thanks to patients' high engagement and good acceptance of the MAT.

Disclosure

The authors have nothing to disclose

CRediT authorship contribution statement

Maria Grazia Maggio: Conceptualization, Writing - original draft, Formal analysis. **Daniele Tripoli:** Data curation, Investigation. **Bruno Porcari:** Visualization, Investigation. **Alfredo Manuli:** Visualization, Data curation. **Serena Filoni:** Data curation, Validation. **Antonino Naro:** Data curation, Investigation, Methodology. **Mareike Eschweiler:** Methodology, Writing - review & editing. **Rocco Salvatore Calabrò:** Conceptualization, Writing - original draft, Methodology, Writing - review & editing, Validation.

Acknowledgment

The authors wish to thank Dr. Nicola Fiorente for his support in the development and management of the protocol.

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