Intensity-dependent clinical effects of an individualized technologysupported task-oriented upper limb training program in Multiple Sclerosis: A pilot randomized controlled trial

Peer-reviewed author version

LAMERS, Ilse; RAATS, Joke; SPAAS, Jan; MEULEMANS, Iris; Kerkhofs, Lore; Schoutenden, Sofie & FEYS, Peter (2019) Intensity-dependent clinical effects of an individualized technologysupported task-oriented upper limb training program in Multiple Sclerosis: A pilot randomized controlled trial. In: Multiple Sclerosis and Related Disorders, 34, p. 119-127.

DOI: 10.1016/j.msard.2019.06.014
Handle: http://hdl.handle.net/1942/28926

Intensity-dependent clinical effects of an individualized technology-supported task-oriented upper limb training program in Multiple sclerosis: a pilot randomized controlled trial

Ilse Lamers[1, 2] PhD, Joke Raats[1] MSc, Jan Spaas [1] MSc, Michaël Meuleman [1] MSc, Lore Kerkhofs [2] BSc, Sofie Schouteden [2] BSc, Peter Feys[1] PhD

[1] *REVAL Rehabilitation Research Center, BIOMED Biomedical Research Institute, Faculty of Rehabilitation Sciences, Hasselt University, Martelarenlaan 42, 3500 Hasselt, Belgium*

[2] *Rehabilitation and MS center, Boemerangstraat 2, 3900 Overpelt, Belgium*

Corresponding author

Ilse Lamers

+3211286939 (office) or +32474242486 (mobile)

Email: ilse.lamers@uhasselt.be

Address: Hasselt University, Martelarenlaan 42, 3500 Hasselt, Belgium

Number of words abstract: 205

Number of words manuscript: 4227

Number of tables: 2

Number of figures: 5

Supplementary material: 2 tables

Number of references: 37

Declaration of Interest

Ilse Lamers has received teaching honoraria from Sanofi Genzyme Europe. Peter Feys is steering committee member of Neurocompass, participated to advisory board meetings of BIOGEN IDEC, and received teaching honoraria for EXCEMED and PARADIGMS. The devices used in this study were given in loan by the Tyromotion and Symbio Therapy.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Research data

Raw data of the pre and post testing can be shared (coded) on request and after approval of Medical Ethics and privacy committee of the involved parties. The personal data collected in this study remains confidential and would not be shared.

Abstract

Background: Task-oriented training promotes functional recovery in Multiple Sclerosis (MS). Know-how to determine an individualized training intensity and intensity-dependent effects are, however, unknown. The objective of the study was to investigate the feasibility and the clinical effects of a task-oriented upper limb training program at different individualized training intensities with conventional occupational therapy.

Methods: People with MS (n=20, EDSS range 4-8) were divided into three groups, receiving task-oriented training at 100% (n=7) or 50% (n=8) of their individual maximal number of repetitions, or conventional occupational therapy (n=5). Effects were evaluated using different upper limb capacity and perceived performance measures on activity level, and measures on body functions and structures level.

Results: Mixed model analyses revealed significant improvements ($p<0.05$) over time on the Box and block test (BBT), Action Research Arm Test and the Manual Ability Measure-36. Significant interaction effects (group*time) in favor of the task-oriented group training at the highest intensity were found for BBT and static fatigue index during a maximal sustained handgrip strength test.

Conclusion: All participants were able to perform the task-oriented training at their individualized intensity without any adverse effects. Several improvements over time were found for all intervention groups, however the results suggest a superiority of task-oriented training at 100%.

Clinical trial registration number on clinicaltrials.gov = NCT02688231

Highligths

- PwMS were able to perform an intense task-oriented upper limb training program without any adverse effects.
- The procedures to individualize and determine the therapy content and dosage were easy to use.
- Several significant improvements were found for the intervention and control group.
- No clear intensity-dependent effects during task-oriented training were found.

Keywords: Multiple Sclerosis, Upper Extremity, Rehabilitation, Task-oriented, Technology-supported, Intensity

1. Introduction

Multiple Sclerosis (MS) is a chronic disease of the central nervous system that results in sensorimotor, visual, cognitive and autonomous impairments.[1] These sensorimotor deficits may cause impaired manual dexterity or upper limb dysfunction. According to Kister et al.[2], 60% of people with MS (pwMS) report a diminished hand function in the first year after diagnosis. The number of patients experiencing impaired upper limb function increases considerably as the disease progresses. In addition, upper limb dysfunction may present bilaterally in pwMS, even in patients in an early stage of the disease.[3] Given that an impaired manual dexterity acts as a predictor of overall activity limitations and participation restrictions[4], the performance of activities of daily life and the quality of life can be hampered significantly.

Despite this large impact of upper limb dysfunction on the daily life activities, rehabilitation strategies targeting the upper limb are needed. To date, only a limited number of studies targeted specifically the upper limb in MS, however indicating a clear potential for substantial upper limb improvements after rehabilitation.[5] In other neurological diseases such as stroke, several reviews[6] and practical guidelines[7] have indicated the beneficial clinical and neural effects after upper limb rehabilitation. Verbeeck et al.[7] concluded that there is strong evidence for interventions favoring intensive high repetitive task-oriented and task-specific training in all poststroke phases. In MS, studies investigating the effects of task-oriented training are scarce. Only Bonzano et al.[8] investigated the clinical and neural effects after a task-oriented upper limb motor rehabilitation program in pwMS and found indications that a task-oriented upper limb rehabilitation improved not only the upper limb motor function but also could preserve the white matter microstructure (diffusion MRI) in the brain.

Besides the content of an upper limb training program, the training dosage is as equally important. According to Page et al.[9] the training dosage covers different aspects such

as intensity, frequency and duration. The frequency and duration of a training are easy to measure and standardize, while this is more difficult for intensity of training especially in task-oriented training programs. In stroke, Lohse et al. recommended to report on the active time or repetitions of an exercise for a more accurate representation of the dose since the time scheduled for therapy may not accurately reflect the actual practice time.[10] After the publication of this meta-analysis of Lohse et al. several RCT's investigating the effects of task-oriented training used the number of repetitions performed as a measure of intensity.[11-13] Remarkably, in the latter studies they did not individualize the intensity of training but used fixed number of repetitions for all the included participants in each intervention group. Despite the ambiguity about the intensity of task-oriented upper limb training in stroke and whether the intensity of training should be individualized, the literature suggests a positive relationship between the therapy dosage and the therapy outcomes[1] and recommends intensive high repetitive training in all phases of stroke. [7]

In MS, the most optimal therapy dosage for upper limb rehabilitation is unknown. However, based on the findings from a review[5], some suggestions regarding therapy dosage can be made. It seemed that intervention programs of 8 weeks or more with a frequency of 2 to 5 days per week and training sessions of 30 to 60 minutes were effective on one or more upper limb outcome measures. The intensity of the upper limb training program was however rarely reported and only individualized in studies using strength and/or endurance training, as these types of intervention allowed controlling of and documentation of the number of repetitions and training intensity. The need for individualized intensity of training is likely even more important in MS than in stroke, as motor performance can be largely influenced by perceived fatigue and the presence of motor fatigability, which are frequently reported and disabling symptoms in MS.[14, 15]

In order to individualize the intensity of a task-oriented upper limb training program, we developed a specific procedure to define maximal performance and consequently individualize the intensity of a task-oriented upper limb training program. In this pilot RCT, we aimed to investigate the feasibility and the clinical effects of a task-oriented upper limb training program at different individualized training intensities in comparison with conventional occupational therapy.

2. **Material and Methods**

2.1. *Participants*

The participants were recruited in the Rehabilitation and MS centre Overpelt, Belgium. The inclusion criteria were: a definite diagnose of MS according to the McDonald criteria[16], age >18y, minimal-to-severe self-reported upper limb dysfunction (six-point Likert scale). Participants were excluded if they had a relapse or relapse-related treatment within the last three months, complete paralysis of both upper limbs, severe cognitive or visual deficits interfering with testing and training, or other medical conditions interfering with upper limb function (orthopedic or rheumatoid impairment). All participants were informed about the study design and gave their written consent. This pilot study was conducted in 2016 and was registered at clinicaltrials.gov (NCT02688231). All procedures were approved by the Medical Ethics Committee of the University of Leuven, Hasselt University and 'Mariaziekenhuis Noord-Limburg' (17/12/2015).

2.2. Study procedure

Participants in all groups were stratified into three blocks according to their upper limb disability level (mild, moderate, severe) using the procedure displayed in figure 1. To ensure homogeneous distribution of upper limb disability levels, the participants were blocked

randomized into the 2 groups receiving task oriented training. During a period when no task-oriented training sessions were given, data from control subjects was collected (not randomized).

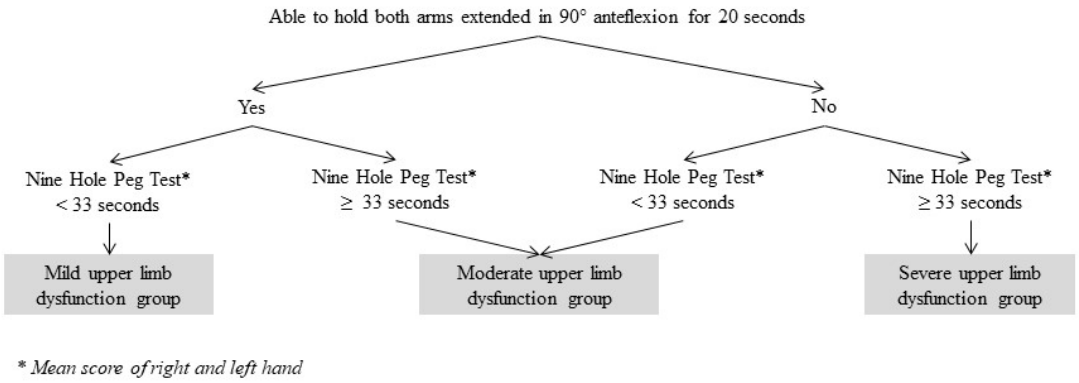

Figure 1. Determination of the participants' upper limb disability level.

2.3. Intervention

Both the task-oriented training groups and the control group received training for 8 weeks at a frequency of 5 days per week and with a duration of 1 hour for each training session. In addition to this upper limb training program, all participants received usual physical therapy sessions at the rehabilitation center, focusing on lower limb rehabilitation (gait and balance).

Task-oriented training at 100% or 50% of the individual maximum number of repetitions.

The procedure consisted of 5 steps explained in figure 2 and table 1 and 2 in supplementary material. In the first step the participant selected 1 unilateral and 2 bilateral tasks to train on. In the second step the participant was asked to perform each task 3 times in the same manner and with the same objects as they wish to perform the task in their daily life. For each task the initial task difficulty was determined by increasing or decreasing the difficulty by providing antigravity support or if needed downgrading the task. When a patient was not able to perform the task without compensations, assistance or aids, we first provided antigravity support

instead of downgrading the task immediately. We preferred the antigravity support because it allowed training of the complete task in their preferred context. During the determination of the initial task difficulty level the therapist searched for a the task difficulty level which was challenging, but not over- or underwhelming, the motor capabilities of the participant. In step 3 the individual maximum number of repetitions for each task was determined. The participant started with performing a Box and Block test (BBT) with both hands to have a starting point. Secondly the participant was asked to perform as many task repetitions as possible. After every 25 repetitions, the participant gave a BORG score and performed the BBT again. The individual maximum number of repetitions was reached if at least one of the following criteria were met: 1) a BORG score ≥17, 2) a decrease ≥ 25% on the BBT, 3) abnormal compensations were present during the upper limb task performance such as abnormal trunk and head compensations or abnormal scapular movements (therapist judgement). These abnormal compensations were avoided to decrease the risk for discomfort, pain or even injury during the high-intense and repetitive execution of upper limb tasks. Step 2 and 3 were repeated for each task and a time limit for step 3 for each task was set on 40 minutes. In step 4 the participants were blocked randomized (blinded) into two groups receiving task-oriented training at 50% or 100% of their individual maximum number of repetitions. During the 60 minutes of training the participants performed their 3 selected tasks in random order at the initial task difficulty level (20 minutes for each task). The aim was to reach their individual number of repetitions. The number of repetitions were always registered by the technology used. During the training standardized rules for up-and downgrading of the difficulty levels were used (step 5 – presented in table 2 in supplementary material). Both the procedure and the training were performed by one therapist.

To perform this task-oriented training two technology-supported rehabilitation devices (figure 3) were used to facilitate the implementation of motor learning components such as

'knowledge of results', 'part and whole practice', 'training with real life objects' and 'individualization of the training', which can be important to guide the training and maintain patient motivation and involvement. The TagTrainer (Symbio Therapy) is a sensor-based tabletop device which allows unilateral or bilateral upper limb training with real-life objects in an individually adaptable workspace.[17-19] The TagTrainer was used in all participants enrolled in the task-oriented training programs and supported the therapist and patient by displaying the current and target number of repetitions during each training session. The DIEGO (Tyromotion) is a robotic upper limb support and was used only in participants who required upper limb weight compensation (anti-gravity support[20]) during the performance of different upper limb tasks. The device provides assistance-as-needed during 3-dimensional unilateral and bilateral task-oriented upper limb training with real-life objects for the entire workspace. The device set-up time (5 minutes) was not included in the therapy sessions. Both devices were selected as they allowed training with limited supervision of the therapist or could be used during group sessions in the future.

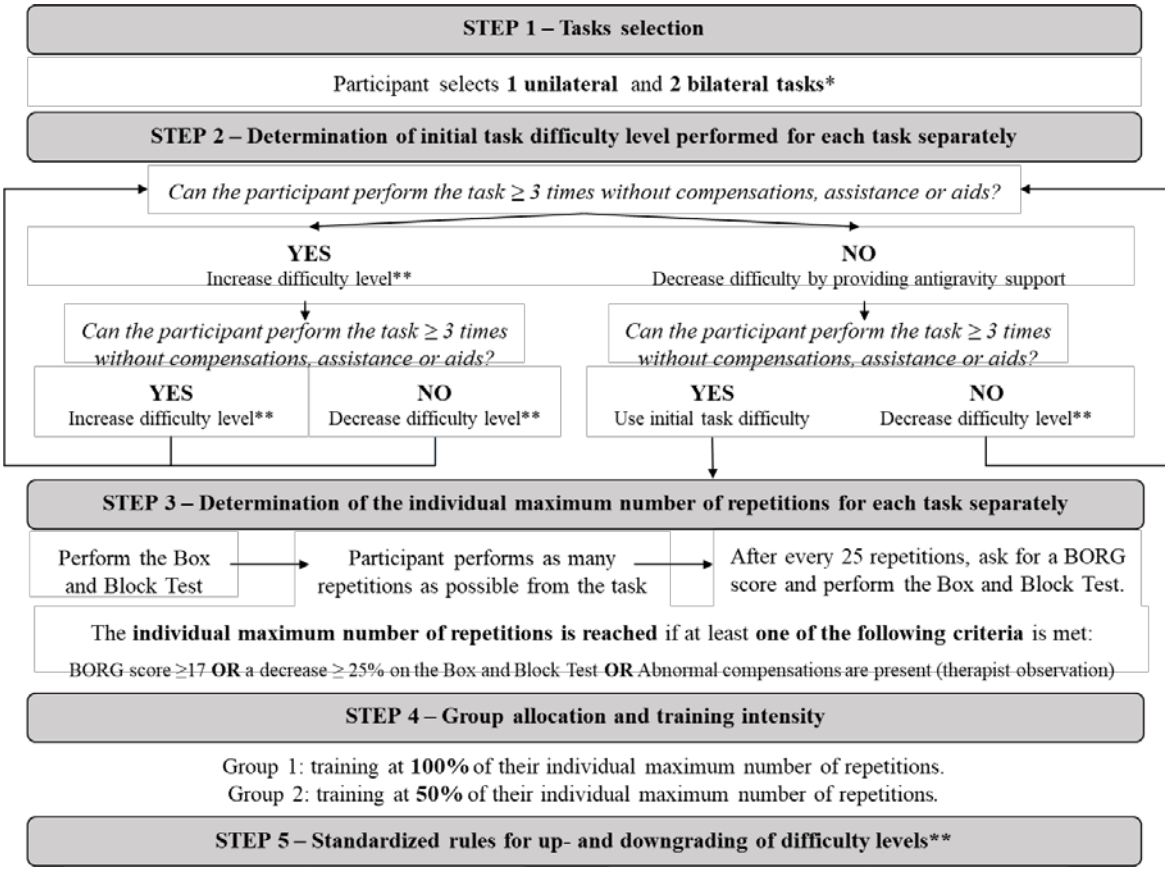

Figure 2. Procedure of task selection, initial task difficulty level, determination of the individual maximum number of repetitions, group allocation and standardized rules for up- and downgrading. ** see table 1 in supplementary material, ** see table 2 in supplementary material.*

Figure 3. Training set-up with the DIEGO (Tyromotion) and TagTrainer (Symbio Therapy).

Control intervention.

The control group received conventional occupational therapy focusing on upper limb rehabilitation using different rehabilitation strategies such as NDT-Bobath concept, Perfetti method, passive mobilizations, scapula settings, (functional) upper limb strength training, task-oriented training and rehabilitation technology (ReJoyce, E-Link). There were no instructions to therapists on the intensity of the interventions.

2.4. Descriptive measures

Age, gender, the Expanded Disability Status Scale (EDSS)[21], type of MS and disease duration since diagnosis determined by neurologists were retrieved from the medical records. Hand dominance was established with the Edinburgh Handedness Inventory[22] and participants were asked by a single question to indicate their most impaired hand. Intention tremor during the finger-nose test was evaluated using the Fahn Tremor Rating Scale (5-point scale; 0=none and 4=severe amplitude).[23] Muscle tone (spasticity) in the upper limb was evaluated with the Modified Ashworth Scale (0=no increased muscle tone and 5=rigid; maximum score=15).[24] The Modified Fatigue Impact Scale (0= no impact of fatigue and 84= highest impact of fatigue) was used to describe the impact of physical, cognitive and psychosocial fatigue.[25] The Symbol Digit Modalities Test (SDMT) was used to assess working memory, information processing speed and sustained attention.[26]

2.5. Outcome measures

An assessor blinded for group allocation recorded all assessments within one week before and after the intervention. The sequence of the assessments was randomized to avoid order effects. Unilateral tests were completed separately with both upper limbs. Outcome measures on the

activity level and body functions and structures level of International Classification of Functioning, Disability and Health were conducted to evaluate the effects.

Primary outcome measures on activity level

The nine hole peg test (NHPT) was used to assess fine manual dexterity, by recording the time needed (seconds) to place and remove 9 pegs.[27] The BBT evaluates gross manual dexterity by recording the number of blocks transported from one box to another in 1 minute.[28] The Action Research arm Test (ARAT) addresses unilateral arm-hand function with four subscales (grasp, grip, pinch, gross arm movements) with a maximum score of 57.[28] The Test d'Évaluation des Membres Supérieurs des Personnes Âgées (
TEMPA) measures the amount of difficulty (score 0, -1, -2, -3) observed while performing different standardized unilateral and bilateral tasks.[29] Perceived upper limb performance was evaluated using the Manual Ability Measure (MAM-36) by asking the participant to score 36 unilateral and bilateral tasks using a four-point scale.[30] The summed score of all tasks was subsequently calibrated and converted to a manual ability score (Rasch analysis) with 0 indicating lowest manual ability and 100 indicating perfect manual ability.

Secondary outcome measures on body functions and structures level

Overall upper limb muscle strength (pinch grip, elbow flexion, and shoulder abduction) was evaluated with the Motricity Index (MI) (normal score=100).[31] Maximal isometric hand, key, 3jaw and pinch grip strength (kilograms) were measured with the hand-held and pinch dynamometer of the E-link (Biometrics Ltd.). The average force produced during three trials of three seconds maximum voluntary contraction was used.[32] A Static Fatigue Index (SFI) during a maximal sustained handgrip strength test of 30 seconds was calculated as described by Surakka et al.[33] A higher SFI value (expressed as 0-100%) indicates a greater decline in

grip strength over time, and thus more motor fatigability. Five Semmes-Weinstein monofilaments (Smith & Nephew Inc, Germantown, Wisconsin) with different diameters (2.83, 3.61, 4.31, 4.56, and 6.65) were used to test tactile sensitivity in the fingertip of the thumb[34, 35] in accordance with the testing procedure described by Cuypers et al.[36] Scores on this test ranged from 1= normal sensation; 6= loss of sensation. Vibration sense was assessed with a 128-Hz Rydel Seiffer Tuning fork at the distal interphalangeal articulation of the index finger (dorsal side) and on the ulnar styloid (dorsal side).[37] A score of 0 indicates absence of vibration sense while a score 8 indicates an intact vibration sense.

2.6. Data analysis

Statistical analyses were performed with SAS JMP Pro 12.2.0. The significance level was set at 0.05. The dominant and non-dominant test scores of unilateral tests were analyzed together. Before the analyses, the residuals were calculated and normality of the residuals was checked by visual inspection of the normal quantile plots. As the assumption was not met for the NHPT and the ARAT subtest grasp data, a log transformation was performed after which normal distribution was achieved. Baseline characteristics of the three groups were compared using the Kruskal-Wallis test for continuous variables and the Fisher Exact test for categorical variables. For the experimental measures, a mixed model analysis was performed to investigate time, group and the group*time interaction as fixed effects. The participant was added as a random effect to account for repeated measurements. The side (dominant vs. non-dominant hand) was nested within the random effect of the participant to account for the presence of two scores on unilateral tests (scores of the dominant and non-dominant hand). Multiple comparisons (Tukey HSD) were performed on all outcome measures to test the evolution of scores within each group.

Results

2.7. Participants

Participant characteristics are shown in table 1. At baseline, no significant differences between the descriptive measures of the different groups were found. Furthermore, there were also no significant differences ($p>0.05$) found for the experimental measures at baseline except for the maximum isometric key grip strength ($p=0.023$), where post-hoc testing indicated significantly higher values in the control group compared to task-oriented training at 100% group. One participant with moderate upper limb disability level dropped out of task-oriented training at 50% group after seven weeks due to a relapse, unrelated to the intervention. Nineteen participants completed the post measurements (figure 4). Available data from the drop-out was included to apply intention-to-treat analysis.

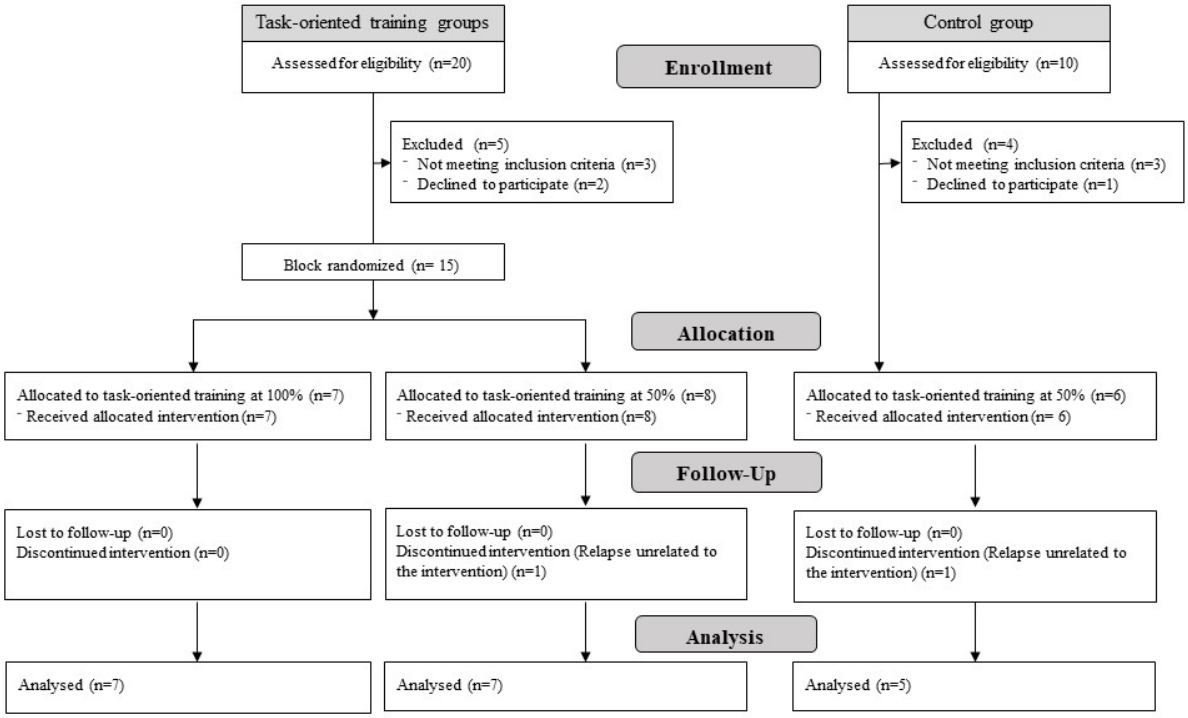

Figure 4. CONSORT flow chart

2.8. Feasibility of a task-oriented upper limb training program at different individualized training intensities

All participants in the task-oriented groups were able to perform the high-intense one-hour sessions for 8 weeks with a frequency of 5 days per week. No adverse effects were reported. Each participant trained on average 5 different tasks during the 8 weeks rehabilitation program. The number of task repetitions performed during one training session varied considerably between different participants and different tasks. The median total number of repetitions performed per participant after 8 weeks was 1569 repetitions [IQR 1134-2353] in the task-oriented training at 100% group and 1035 repetitions [IQR 588-1706] in the task-oriented training at 50% group. Participants in the 50% group reached on average 88% of the time their target number while participants in the 100% group on average 72% of the time. Two participants with severe upper limb dysfunction (one from each task-oriented group) initially needed antigravity support from the DIEGO (Tyromotion) but were able to train unassisted after two to seven weeks.

2.9. Effect of training

The effect of the different training interventions on the primary outcome measures are displayed in table 2a. The mixed model analyses revealed significant improvements over time for all groups for ARAT total score (p=0.001), ARAT subset grasp (p=0.015), grip (p=0.006) and pinch (p=0.001), BBT (p=0.001) and MAM-36 (p=0.044). No main effect of group was found. However, a significant group*time interaction effect on the BBT (p=0.026) was found in favor of the task-oriented training at 100% group (figure 5a). Other group*time interactions indicated no significant differences in response to training between the three interventions.

No significant effects of time and group were found for the outcome measure on body functions and structures level (table 2b). There was only one significant group*time

interaction for the SFI ($p<0.001$) (figure 5b). The task-oriented training at 100% group demonstrated a significantly lower SFI compared to baseline, while the scores in the task-oriented training at 50% group and the control group worsened or remained stable.

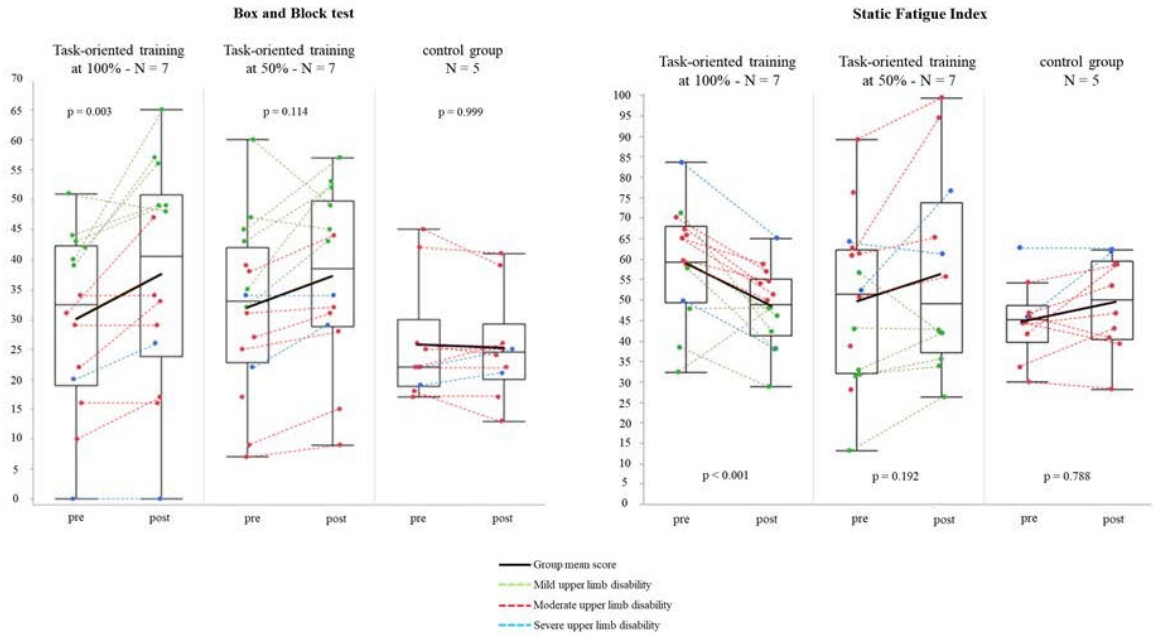

Figure 5. Boxplot (median and interquartile range) showing the group and individual results on a) the Box and Block test and b) the Static Fatigue Index for the task-oriented training groups and the control group.

Table 1. Overview of participant descriptive characteristics at baseline.

	Task-oriented training at 100%	**Task-oriented training at 50%**	**Control intervention**	**p-value**
Number of participants	7	8	5	
Drop-out	0	1	0	
Upper limb disability level				0.583
Mild	3	3	0	
Moderate	3	4	4	
Severe	1	1	1	
Gender (male/female)	3/4	2/6	2/3	0.848
Age (years)	57 [42-69]	55 [43-62]	64 [47-78]	0.501
Type of MS (RRMS/SPMS/PPMS)	4/1/2	3/4/1	3/2/0	0.601
Time since diagnosis (years)	19 [7-29]	10.5 [6.5-20.5]	21 [10-40]	0.389
EDSS (0-10)	7 [5-7]	7 [5.6-7.9]	6.5 [6-7.5]	0.659
Hand dominance (R/L/A)	5/0/2	6/2/0	4/0/1	0.338
Most impaired hand (R/L/R&L)	4/3/0	6/1/1	3/1/0	0.783
Fahn's tremor rating scale				0.380
Score 0, none	9	12	5	
Score 1, slight	3	4	2	
Score 2, mild	0	0	1	
Score 3, marked	1	0	2	
Score 4, severe	1	0	0	
Modified Ashworth Scale †				0.455
Score 0	11	13	10	
Score 1	2	3	0	
Score 2	1	0	0	
Score 3 -5	0	0	0	
Modified Fatigue Impact Scale				
Physical subscale (0-36)	26 [19-31]	25 [17-28]	20 [14.5-29.5]	0.793
Cognitive subscale (0-40)	25 [13-29]	19 [8-26]	22 [16-30]	0.764
Psychological subscale (0-8)	6 [3-6]	3.5 [0.3-5.5]	4 [2-6.5]	0.376
Total score (0-84)	51 [36-62]	46 [30.8-58.5]	47 [32.5- 65.5]	0.756
SDMT (n° correct response)	28 [26-35]	37 [21.5-49.5]	16.5 [10.8-40.3]	0.329

Continuous data are presented as Median [IQR]. Continuous variables were compared with the Kruskal-Wallis test, categorical variables with the Fisher Exact test. RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary progressive multiple sclerosis, PPMS: primary progressive multiple sclerosis, EDSS: Expanded Disability Status Scale, R: right, L: left, A: ambidextrous. † mean score of shoulder adductors, elbow flexors and wrist flexors, SDMT: Symbol Digit Modalities Test.

Table 2a. Results of the different task-oriented training and control interventions on the outcome measures at activity level.

	Task-oriented training at 100%		Task-oriented training at 50%		Control intervention		Mixed model analysis		
	Pre	Post	Pre	Post	Pre	Post	Time	Group	Group* Time
NHPT, time (s)	35.6 [26.6-155.4]	40.9 [23.5-213]	37.5 [29.4-136.9]	41.6 [23.8-97.6]	60.4 [51.7-77.4]	70 [55.2-87]	0.767	0.899	0.104
ARAT									
total score (0-57)	45.5 [36.8-52.3]	53 [44-55]	49 [25.5-53.8]	54 [39-56]	45 [41.8-49.2]	47 [41-52.5]	**0.001**	0.738	0.386
grasp (0-18)	16 [13.5-18]	18 [16.75-18]	16 [8.25-18]	17.5 [15-18]	16 [13-18]	17 [14.8-18]	**0.015**	0.476	0.600
grip (0-12)	9 [7.5-11.3]	10.5 [7.5-12]	10 [6.25-11]	11 [9-11.3]	8.5 [8-10]	9.5 [8-10]	**0.006**	0.973	0.482
pinch (0-18)	13.5 [9.8-15]	15 [12-18]	14.5 [4.3-15.8]	17 [6-17.3]	12 [11-13.5]	12.5 [11-15.3]	**0.001**	0.580	0.361
gross movement (0-9)	8 [7-9]	9 [8-9]	8.5 [8-9]	9 [8-9]	9 [8.8-9]	9 [7-9]	0.920	0.464	0.098
BBT (n° blocks)	32.5 [19-42.3]	40.5 [23.8-50.8]	33 [22.8-42]	38.5 [28.8-49.8]	22 [18.8-30]	24.5 [20-29.3]	**0.001**	0.245	**0.026**
TEMPA									
total score (-39-0)	-2 [-20- -1]	0 [-4-0]	-5.5 [-10.5- -2]	0 [-5-0]	-9 [-23.5- -4.5]	-16 [-19.5- -6.5]	0.226	0.409	0.549
unilateral score (-12-0)	-1 [-4.8-0]	0 [-1-0]	-1.5 [-5-0]	0 [-1.75-0]	-3 [-7- -0.8]	-4 [-5.3- -1.5]	0.065	0.472	0.470
bilateral score (-15-0)	0 [-6-0]	0 [-3-0]	-1.5 [-2.8-0]	0 [0-0]	-4 [-10- -3]	-7 [-8.5- -4]	0.471	0.096	0.427
MAM-36 (0-100)	50.5 [38-54.5]	54.5 [43-57.5]	50.2 [40.4-62.8]	55 [53-63]	49.5 [48.5-57]	54.5 [48-57.5]	**0.044**	0.773	0.694

Data reported are continuous and presented as Median [Interquartile range] or p-values found in the mixed model analysis. NHPT: Nine Hole Peg Test, ARAT: Action Research Arm Test, BBT: Box and Block Test, TEMPA: Test d'Évaluation des Membres Supérieurs des Personnes Âgées, MAM-36: Manual Ability Measure-36.

Table 2b. Results of the different task-oriented training and control interventions on the outcome measures at body functions and structures level.

	Task-oriented training at 100%		Task-oriented training at 50%		Control intervention		Mixed model analysis		
	Pre	Post	Pre	Post	Pre	Post	Time	Group	Group* Time
Max. isometric grip strength (kg)									
Hand	15.3 [9.4-21.5]	16.7 [11.6-19.5]	15.5 [9-26.8]	21.3 [10-23.2]	22.6 [14.5-31.1]	22.4 [15.5-33.5]	0.166	0.153	0.557
Key	3.65 [2.3-4.4]	3.9 [2.4-5]	4.2 [1.9-5.4]	4.3 [3.2-6.4]	5.9 [4.7-6.9]	5.5 [4.4-7]	0.695	0.197	0.354
3-jaw	3.8 [1.7-5.3]	3.3 [2-5.4]	3.5 [1-4.8]	3.9 [2-5.8]	4.5 [2-5.3]	4.4 [2.5-6]	0.060	0.825	0.137
Pinch	2.9 [1.5-4]	2.5 [1.5-4]	2.5 [0.8-3.3]	2.5 [1.7-3.9]	3.3 [2.6-4.7]	3.1 [2.8-4.4]	0.425	0.285	0.227
Static Fatigue Index (0-100%)	59.2 [49.3-68]	49 [41.2-55.2]	51.5 [32-62.4]	49.1 [37.1-73.8]	45.2 [39.6-48.7]	50.1 [40.4-59.5]	0.846	0.522	**<0.001**
Motricity Index (0-100)	80.5 [63-88.8]	76.5 [68.5-85]	88 [67-91]	83 [70-91]	79.5 [73.5-91.3]	76 [70.5-84]	0.136	0.545	0.922
Monofilaments (1-6)									
thumb	3 [2-3.3]	3 [1-3]	3 [2-3]	2 [1.8-3]	2 [1-4]	2.5 [2-3]	0.163	0.987	0.354
index finger	2 [2-3]	2.5 [1.8-3]	3 [2-4]	2 [1.8-3]	2 [1-4]	2.5 [1.8-3.3]	0.413	0.891	0.486
Vibration sense (0-8)									
DIP	7 [6-7.6]	7 [5-8]	7 [5.1-8]	7.5 [5-8]	6.5 [5.8-8]	7.3 [6-8]	0.271	0.537	0.504
Ulnar styloid	6.8 [4.8-8]	6.8 [5.5-8]	6.5 [5-7.8]	6.3 [4.9-8]	5.5 [5-7.3]	6.3 [5-7.1]	0.233	0.893	0.275

Data are continuous and presented as Median [Interquartile range] or p-values found in the mixed model analysis. DIP: distal interphalangeal articulation of the index finger.

3. Discussion

This pilot RCT aimed to investigate the feasibility and clinical effects of a task-oriented upper limb training program at two different individualized training intensities in comparison with conventional occupational therapy for the upper limb. To individualize the intensity of a task-oriented upper limb training program, a specific procedure was developed to determine maximal intensity and evaluated in a small sample of pwMS with different levels of upper limb disability.

3.1. Feasibility of a task-oriented upper limb training program at different individualized training intensities

To our knowledge, this was the first study aiming to individualize the intensity of a task-oriented training program in MS. Studies in MS providing task-oriented training did not report on the intensity of training or the number of repetitions performed during the training. In the present study an individualized number of repetitions was introduced instead of imposing a fixed number of repetitions which is frequently used in the stroke studies.[11-13] The decision to individualize the intensity was based on the rehabilitation principles in other pathologies such as cardiovascular diseases, musculoskeletal impairments or even in the healthy population (sports) where guidelines recommend to individualize the training intensity by using percentages of maximum heartrate, VO_2Max or 1 repetition maximum for strength training. All other parameters influencing the dosage, such as training duration and frequency, were fixed in our study which is in contrast to the study investigating dose response in stroke.[14] The number of task repetitions performed during one training session in our pilot RCT varied considerably between different participants and the different tasks, which indicates the need for individualization of the intensity for each task.

The results of this study suggest that pwMS with different levels of upper limb disability were able to perform the intense task-oriented training program without any adverse effect. The procedure to determine the therapy content, the individualized number of repetitions and training progression were easy to use. Participants in the group training at 100% performed more repetitions per session but had more difficulties with reaching their target number of repetitions determined at baseline compared to participants training at 50%. It is assumed that fatigue, which was reported in the majority of participants (table 2 – MFIS) played an important factor why the target number of repetitions was not always reached. Even though the impact of fatigue in this study population, participants were able to reach the number of targets in more than 70% of the time, which indicates that both percentages of training intensity were challenging but feasible. Further research is however needed to compare directly the effects of an individualized task-oriented training versus non-individualized training and to identify the most optimal percentage of training intensity for task-oriented training programs in pwMS. For example it is unknown whether a 'minimal threshold' and/or a 'ceiling' exists with regard to training intensity and its effect on therapy outcome. This pilot RCT provides a procedure of individualizing the training intensity which can be further improved and used to investigate previous question.

3.2. Intensity-dependent effects of task-oriented training versus conventional occupational therapy

Several significant improvements on the capacity and perceived performance measures for both experimental groups and control group were found over time. Overall, the participants' ability to grasp and replace objects improved as indicated by the significant time effects on the BBT and ARAT. Several participants reported improvements in their upper limb performance, which was on a group level reflected in a significant improvement on the

MAM-36 questionnaire. There were however no intensity-dependent effects found, except for the BBT and SFI where the results indicate a superiority of task-oriented training at a higher intensity. As both the BBT and the SFI can be considered as endurance-related measures, this may suggest that a higher training intensity has an impact on endurance during movement and strength-related tasks. Even though the mixed model analysis did not show consistent statistical differences between groups, it seems plausible that the significant time effects found for the activity level measures were mainly influenced by the changes in the task-oriented training groups, and less by the changes in the control group for the following reasons: (1) the overall larger observable changes in the task-oriented groups; (2) the lower number of participants in the control group (n=5). In addition, it should be noted that most outcome measures included a mix of responders and non-responders. An explanation could be that rehabilitation content was adapted towards the individual's training preferences so the training program differed for every participant. According to the specificity of training principle, it is likely that participants improve on these aspects that were trained and do not transfer on other, unrelated, skills.

The results of our study are in line with the findings of previous upper limb rehabilitation research in MS. Bonzano et al.[8] found that both task-oriented training and passive mobilization of 8 weeks improved significantly the ARAT, NHPT and hand grip strength score. In our pilot study we found significant improvements of the ARAT, BBT and MAM-36 but not in the NHPT and hand grip strength in pwMS with higher overall and upper limb disability level. Mark et al. found significant long-term improvements on perceived upper limb performance measured with the Motor Activity Log and on a upper limb capacity measure (wolf motor function test) in favor of the constraint-induced movement therapy (CIMT) group in comparison with complementary and alternative medicine treatments. The findings of these previous published studies and the findings of our pilot study indicate that

task-oriented training improves upper limb capacity and performance in pwMS across upper limb disability levels. However, further research is necessary to investigate its superiority against other rehabilitation strategies and to further explore not only the clinical effects but also the neural effects as done in the study of Bonzano et al.[8]

3.3. Methodological considerations

Since this was a pilot study, the inclusion criteria were broad as we wanted to investigate the feasibility of the training program for pwMS with different upper limb disability levels. Participants were classified into three different upper limb disability levels to ensure balanced distribution among task-oriented training groups through even while the sample was small. Unfortunately, the group composition was not completely balanced. The blocked randomization resulted in an equal distribution of upper limb disability between the task-oriented groups but not in the control group. Due to the small sample size in each training group no statistical analyses were performed to investigate whether the response to task-oriented upper limb training differed for pwMS with varying upper limb disability levels. Visual inspection of the raw data (see figure 3 as an example) did not reveal clear differences in training response between pwMS with different upper limb disability levels. Another limitation of this study is that intensity of training in the control group was not registered as different rehabilitation strategies were used in the control group.

4. Conclusion

PwMS with different upper limb disability levels were able to perform a task-oriented upper limb training program at 50% or 100% of their individual maximum number of repetitions for 8 weeks at frequency of 5 days/week with a duration of one hour for each training session. Several significant improvements over time, but no clear intensity-dependent effects during

task-oriented training were found. However, the results on the BBT and SFI suggests a superiority of task-oriented training at a higher intensity. In addition this pilot study indicated the importance of individualizing task-oriented upper limb training in PwMS.

Acknowledgment

The authors thank the participants of this study, as well was the Rehabilitation and MS center Overpelt for the facilities. The authors gratefully acknowledge Dr. Iris Jakob of Tyromotion and Dr. ir. Willem Fontijn of Symbio Therapy for lending the devices and Dr. Francesca Solmi of CenStat- UHasselt for the statistical advice.

References

1. Lassmann H. The pathology of multiple sclerosis and its evolution. *Philosophical Transactions of the Royal Society of London B: Biological Sciences* 1999; 354: 1635-1640.

2. Kister I, Bacon TE, Chamot E, et al. Natural history of multiple sclerosis symptoms. *International journal of MS care* 2013; 15: 146-158. DOI: 10.7224/1537-2073.2012-053.

3. Bertoni R, Lamers I, Chen CC, et al. Unilateral and bilateral upper limb dysfunction at body functions, activity and participation levels in people with multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2015; 21: 1566-1574. 2015/02/11. DOI: 10.1177/1352458514567553.

4. Kierkegaard M, Einarsson U, Gottberg K, et al. The relationship between walking, manual dexterity, cognition and activity/participation in persons with multiple sclerosis. *Multiple Sclerosis Journal* 2012; 18: 639-646.

5. Lamers I, Maris A, Severijns D, et al. Upper Limb Rehabilitation in People With Multiple Sclerosis: A Systematic Review. *Neurorehabil Neural Repair* 2016; 30: 773-793. 2016/01/10. DOI: 10.1177/1545968315624785.

6. Pollock A, Farmer SE, Brady MC, et al. Interventions for improving upper limb function after stroke. *Cochrane Database Syst Rev* 2014; 11: Cd010820. 2014/11/12. DOI: 10.1002/14651858.CD010820.pub2.

7. Veerbeek JM, van Wegen E, van Peppen R, et al. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. *PloS one* 2014; 9: e87987. 2014/02/08. DOI: 10.1371/journal.pone.0087987.

8. Bonzano L, Tacchino A, Brichetto G, et al. Upper limb motor rehabilitation impacts white matter microstructure in multiple sclerosis. *Neuroimage* 2014; 90: 107-116. DOI: 10.1016/j.neuroimage.2013.12.025.

9. Page SJ, Schmid A and Harris JE. Optimizing terminology for stroke motor rehabilitation: recommendations from the American Congress of Rehabilitation Medicine Stroke Movement Interventions Subcommittee. *Archives of physical medicine and rehabilitation* 2012; 93: 1395-1399. 2012/03/27. DOI: 10.1016/j.apmr.2012.03.005.

10. Lohse KR, Lang CE and Boyd LA. Is more better? Using metadata to explore dose–response relationships in stroke rehabilitation. *Stroke; a journal of cerebral circulation* 2014; 45: 2053-2058.

11. Lang CE, Strube MJ, Bland MD, et al. Dose response of task-specific upper limb training in people at least 6 months poststroke: A phase II, single-blind, randomized, controlled trial. *Ann Neurol* 2016; 80: 342-354. DOI: 10.1002/ana.24734.

12. Birkenmeier RL, Prager EM and Lang CE. Translating animal doses of task-specific training to people with chronic stroke in 1-hour therapy sessions: a proof-of-concept study. *Neurorehabilitation and neural repair* 2010; 24: 620-635. 2010/04/29. DOI: 10.1177/1545968310361957.

13. Waddell KJ, Birkenmeier RL, Moore JL, et al. Feasibility of high-repetition, task-specific training for individuals with upper-extremity paresis. *The American journal of occupational therapy : official publication of the American Occupational Therapy Association* 2014; 68: 444-453. 2014/07/10. DOI: 10.5014/ajot.2014.011619.

14. Severijns D, Octavia JR, Kerkhofs L, et al. Investigation of Fatigability during Repetitive Robot-Mediated Arm Training in People with Multiple Sclerosis. *PloS one* 2015; 10: e0133729. DOI: 10.1371/journal.pone.0133729.

15. Fernandez-Munoz JJ, Moron-Verdasco A, Cigaran-Mendez M, et al. Disability, quality of life, personality, cognitive and psychological variables associated with fatigue in patients with multiple sclerosis. *Acta neurologica Scandinavica* 2015; 132: 118-124. 2015/02/04. DOI: 10.1111/ane.12370.

16. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Annals of neurology* 2001; 50: 121-127. 2001/07/18.

17. Tetteroo D, Timmermans AA, Seelen HA, et al. TagTrainer: supporting exercise variability and tailoring in technology supported upper limb training. *Journal of neuroengineering and rehabilitation* 2014; 11: 1.

18. Hochstenbach-Waelen A, Timmermans A, Seelen H, et al. Tag-exercise creator: towards end-user development for tangible interaction in rehabilitation training. In: *Proceedings of the 4th ACM SIGCHI symposium on Engineering interactive computing systems* 2012, pp.293-298. ACM.

19. Tetteroo D, Seelen H, Timmermans A, et al. Rehabilitation Therapists as Software Creators?: Introducing End-User Development in a Healthcare Setting. *International Journal of Sociotechnology and Knowledge Development (IJSKD)* 2014; 6: 36-50.

20. Feys P, Coninx K, Kerkhofs L, et al. Robot-supported upper limb training in a virtual learning environment : a pilot randomized controlled trial in persons with MS. *Journal of neuroengineering and rehabilitation* 2015; 12: 60. 2015/07/24. DOI: 10.1186/s12984-015-0043-3.

21. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444-1452.

22. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971; 9: 97-113.

23. Hooper J, Taylor R, Pentland B, et al. Rater reliability of Fahn's tremor rating scale in patients with multiple sclerosis. *ArchPhysMedRehabil* 1998; 79: 1076-1079. DOI: S0003-9993(98)90174-5 [pii].

24. Bohannon RW and Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *PhysTher* 1987; 67: 206-207.

25. Kos D, Kerckhofs E, Carrea I, et al. Evaluation of the Modified Fatigue Impact Scale in four different European countries. *MultScler* 2005; 11: 76-80.

26. Drake A, Weinstock-Guttman B, Morrow S, et al. Psychometrics and normative data for the Multiple Sclerosis Functional Composite: replacing the PASAT with the Symbol Digit Modalities Test. *Multiple Sclerosis* 2009.

27. Feys P, Lamers I, Francis G, et al. The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. *Multiple Sclerosis Journal* 2017; 23: 711-720.

28. Platz T, Pinkowski C, van Wijck F, et al. Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer Test, Action Research Arm Test and Box and Block Test: a multicentre study. *Clinical Rehabilitation* 2005; 19: 404-411. DOI: 10.1191/0269215505cr832oa.

29. Feys P, Duportail M, Kos D, et al. Validity of the TEMPA for the measurement of upper limb function in multiple sclerosis. *Clinical rehabilitation* 2002; 16: 166-173. 2002/03/26.

30. Chen CC and Bode RK. Psychometric validation of the Manual Ability Measure-36 (MAM-36) in patients with neurologic and musculoskeletal disorders. *Archives of physical medicine and rehabilitation* 2010; 91: 414-420.

31. Rasova K, Martinkova P, Vyskotova J, et al. Assessment set for evaluation of clinical outcomes in multiple sclerosis: psychometric properties. *Patient Relat Outcome Meas* 2012; 3: 59-70. DOI: 10.2147/PROM.S32241.

32. Allen D and Barnett F. Reliability and validity of an electronic dynamometer for measuring grip strength. *International Journal of Therapy and Rehabilitation* 2011; 18: 258.

33. Surakka J, Romberg A, Ruutiainen J, et al. Assessment of muscle strength and motor fatigue with a knee dynamometer in subjects with multiple sclerosis: a new fatigue index. *Clinical rehabilitation* 2004; 18: 652-659.

34. Bell-Krotoski J and Tomancik E. The repeatability of testing with Semmes-Weinstein monofilaments. *JHand SurgAm* 1987; 12: 155-161.

35. Jerosch-Herold C. Assessment of sensibility after nerve injury and repair: a systematic review of evidence for validity, reliability and responsiveness of tests. *J Hand Surg Br* 2005; 30: 252-264. DOI: 10.1016/j.jhsb.2004.12.006.

36. Cuypers K, Leenus DJ, van den Berg FE, et al. Long-term TENS treatment decreases cortical motor representation in multiple sclerosis. *Neuroscience* 2013; 250: 1-7. DOI: 10.1016/j.neuroscience.2013.06.046.

37. Pestronk A, Florence J, Levine T, et al. Sensory exam with a quantitative tuning fork Rapid, sensitive and predictive of SNAP amplitude. *Neurology* 2004; 62: 461-464.

Supplementary material

Table 1. List of training tasks based on the ABILHAND and Manual Ability Measure-36 questionnaires.

Eating a slice of bread	Opening a carton (milk, cereals)
Drinking a glass of water	Pouring liquid from a bottle in a glass
Picking-up a half-full can	Opening a bottle with a child-proof top
Using a spoon or fork	Opening an envelope
Spreading butter/jam on a slice of bread	Peeling fruits or vegetables
Cutting meat with a fork and a knife	Handling money
Squeezing toothpaste on a toothbrush	Taking things out of a wallet
Brushing teeth	Writing sentences
Brushing, combing or drying your hair	Turning pages
Washing your hands	Shuffling cards
Wringing a towel	Using a screwdriver
Zipping pants	Hammering a nail
Zipping a jacket	Folding clothes
Buttoning clothes	Opening a CD/DVD
Fastening a snap (jacket, bag)	Peeling onions
Cutting nails	Sharpening a pencil
Tying shoes	Taking the cap off a bottle
Using a remote control	Filing one’s nails
Dialing a telephone number	Tearing open a pack of chips
Turning a door knob	Unwrapping a chocolate bar
Turning a key in a keyhole	Threading a needle
Loading and carrying a shopping bag	Wrapping up gifts
Opening a jar (jam, mayonnaise)	Shelling hazel nuts

Table 2. Standardized rules for up- an downgrading of difficulty levels of the tasks and when to select a new task.

Principles of progression (up or down grading of a task)

- Changes in the antigravity support (provided in this study by the DIEGO, Tyromotion).
- Changes in the workspace (placement of the targets and objects relative to the person).
- Changes in the object characteristics (weight, size, material, etc).
- Changes in patient positioning (sitting, standing).
- Increase or decrease load/resistance (0.5 or 1.0 kg at the distal forearm).
- Variability within the task (alternate different object characteristics in subsequent repetitions).
- Part practice: divide a task in different skill components or combine these parts to perform the whole task.

Rules for progression (up or down grading of a task) or selection of a new task

Upgrading

- The participant reaches his/her individual maximum number of repetitions of a training task without abnormal compensations and adverse effects (pain, fatigue, etc.) in 2 consecutive training sessions.

Downgrading

- The participant is not able to perform his/her individual maximum number of repetitions of a training task without abnormal compensations or adverse effects (pain, fatigue, etc.) in 2 consecutive training sessions.

Selection of a new task

- The participant is able to perform the task at the highest difficulty level at their maximum number of repetitions without abnormal compensations and adverse effects in 2 consecutive training sessions.
- The participant is not able to make any progression for 4 weeks.