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FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN

master in de revalidatiewetenschappen en de kinesitherapie

Masterproef

The effects of an 8-week robot-mediated upper limb training featuring I-TRAVLE in persons with Multiple Sclerosis

Promotor :
Prof. dr. Peter FEYS

Copromotor :
dr. Ilse LAMERS
dr. Anneleen MARIS

Wouter Dielkens , Sander Geurts

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

universiteit hasselt
KNOWLEDGE IN ACTION

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Furthermore, we would like to thank our parents for giving us the opportunity to study within this Master education of Rehabilitation science and Physiotherapy and also for believing in us. Also, we would like to thank our partners - Natasja and Evelien - for their personal support and encouragement. Last but not least, we wish to thank our colleague students and friends for all the enjoyable moments, tips and advice.

Lommel, June 2015 W.D.

Maasmechelen, June 2015 S.G.

Research framework

The presenting clinical trial is situated in a technology-supported rehabilitation context and fits in a neurological rehabilitation domain. It is part of the Interreg IV project 'I-TRAVLE', Individualised Technology-supported Robot-Assisted Virtual Learning Environments (IVA-VLANED-1.58). The master's thesis is led by the research team of Prof. dr. Peter Feys (promoter), dr. Anneleen Maris (co-promoter) and dr. Ilse Lamers (co-promoter) from the Rehabilitation Research centre (REVAL) of Hasselt University. They perform scientific research in assessment and rehabilitation strategies in neurological populations. This trial was conducted in the Rehabilitation and MS centre Overpelt (Ms. V. Truyens and Prof. dr. B. Van Wijmeersch, Belgium). Other project partners within this Interreg IV project are REVAL, Biomedical research institute of Hasselt University, Expertise centre of Digital Media (EDM) of Hasselt University (Prof. dr. K. Coninx) and Centre of Expertise in Rehabilitation and Audiology in Hoensbroek (dr. H. Seelen, The Netherlands).

This master thesis is directed to other researchers and clinicians who are interested in the effects of rehabilitation strategies for the upper limb (UL) function in persons with Multiple Sclerosis (pwMS). Multiple sclerosis (MS) is a progressive, inflammatory autoimmune disease which affects the white matter of the central nervous system (CNS) [1-3]. In an acute phase, it manifests itself by a relative axonal loss due to inflammatory demyelination and a limited re-myelination. This results in the formation of chronic sclerotic plaques [1, 3]. The estimates of prevalence and incidence in Europe are relatively higher in case of females compared to males with a ratio 3:1 [1, 4]. In Flanders (Belgium), the prevalence estimates of MS range from 80-90 cases per 100.000 [5]. Symptoms can vary among pwMS and are specifically related to the localisation of the inflammatory processes [1-3].

PwMS can develop a broad spectrum of disabilities influencing the performance of their activities of daily living (ADL) [2]. Although walking issues and balance problems are reported as most frequent disabilities, functional UL disabilities are also very common [2, 6]. Most studies in MS rehabilitation research are concerned with rehabilitation of lower limb function and gait [7], but few studies implement UL training in pwMS. We conducted a systematic review in our first master year to review the published effects of UL rehabilitation programs in pwMS. This review concluded that UL rehabilitation can lead to beneficial results on body function and structures level and on activity level of the International Classification of Functioning, Disability and Health (ICF) for improving UL function. It also highlighted UL robot therapy as an upcoming trend in UL rehabilitation. Included studies showed promising results but lacked the implementation of an individualised training program with a follow-up period, qualitative outcome measures and a large sample size.

Given the above, this clinical trial aims to identify the short- and long term effects of an 8-week individualised training regime featuring the I-TRAVLE system on UL function in pwMS. The research question was already available for both students Wouter Dielkens and Sander Geurts. The role of both students within this Interreg IV project I-TRAVLE (IVA-VLANED-1.58) was guiding participants during training sessions, fill in data from clinical outcome measurements in excel files, fulfil a statistical analyses

with Statistical Package for the Social Sciences (SPSS) and writing a scientific article according to the guidelines of the Journal of NeuroEngineering and Rehabilitation (JNER).

To provide adequate feedback, both students kept daily contact by mobile phone and e-mail. Communication with promoters has mostly taken place by mail and regular meetings. Both students always consulted each other before mailing promoters. The students Sander Geurts and Wouter Dielkens did not request approval for this study from the Ethics Committee.

Abstract

Background: Upper limb (UL) dysfunction in persons with Multiple Sclerosis (pwMS) may have substantial impact on the performance of activities of daily living and quality of life. Recent pilot studies showed potential benefits of robot-mediated therapy as a supplementary therapeutic approach to usual care in MS and other neurological chronic diseases. Therefore, this non-comparative proof of concept study aims to identify the short and long term effects of an 8-week individualised training regime featuring the I-TRAVLE system on UL function in pwMS.

Methods: Thirteen PwMS with UL dysfunction were included and participated in an I-TRAVLE intervention supplementary to the usual care. The intervention (40 sessions, 10 sessions per 2 weeks, 2 sessions of each 30 minutes of training per training day) consisted of basic motor function exercises and games with the Haptic Master in a virtual environment, displayed on a LCD-screen. Active range of motion (AROM) of shoulder anteflexion and abduction, Motricity Index, JAMAR, perceived fatigue and perceived strength, Wolf Motor Function test (WMFT), ABILHAND and Manual Ability Measure-36 were assessed before and after treatment, and after a follow-up of 12 weeks. Subgroups based on the inclusion criteria were performed to more detailed insights.

Results: After treatment, group analyses (N=13) showed statistically significant improvements in AROM shoulder (sustained) anteflexion, perceived fatigue, JAMAR and Wolf Motor Function Test (WMFT) time and functional measure scale. No outcome measures showed a significant deterioration after treatment. PwMS with moderate UL dysfunction (n=6/13) had the highest improvements ($p < 0.05$) on the body function and structures level and activity level outcome measures (active range of motion shoulder anteflexion, perceived fatigue, JAMAR and WMFT time) after the training program.

Conclusions: Additional I-TRAVLE training with the Haptic Master can induce beneficial effects on the UL function in pwMS. Most benefits can be gained in pwMS with moderate to severe UL dysfunction. The AROM (sustained) shoulder anteflexion and WMFT time were the most improved UL outcome measures after treatment.

1. Introduction

Multiple sclerosis (MS) is a progressive inflammatory autoimmune disease which affects the white matter of the central nervous system, predominantly in young adults [1-3]. Due to the disease, persons with MS (pwMS) may have a great variety of symptoms which are related to the specific localisation of the inflammatory processes [1-3]. Symptoms may include: muscle weakness, extreme fatigue, impaired speech, loss of balance, reduced cognitive function, vision problems and paralysis [1, 5].

Preceding symptoms can lead to several restrictions in the activities of daily living. Dysfunction in muscle power, gait and mobility were the most frequently reported disabilities on body function and structures level of the International Classification of Functioning, Disability and Health (ICF) model in PwMS. [8]. Restrictions in walking and activities of leisure time (hobbies, sports), were the most frequently reported on the levels of activities and participation of the ICF model [10].

Although lower limb dysfunction is reported most commonly [9], upper limb (UL) dysfunction is also very common in pwMS [2, 6, 8]. Kister I et al. (2013) reported that half of the participants were confronted with hand dysfunction during the first year diagnosed with MS (N=23931) [2]. Furthermore, it has been observed that after a disease duration of 10 years, almost 75% pwMS reported hand dysfunction [2, 8]. According to a descriptive study of Holper T et al. (2010), 70% of pwMS struggle with hand an arm use during their activities of daily living. Considering a high prevalence of UL dysfunction and its consequences on quality of life and loss of independence [1, 6, 10-12], it is necessary to acknowledge the importance of UL rehabilitation in pwMS.

Although there is a great need for rehabilitation studies investigating the effects of UL strategies in pwMS, limited research has been conducted. Spooren A et al. (2012) indicated the restorative potential of UL function in pwMS after motor training programs. Moreover, based on our own systematic literature review performed in our first master year, we reported that sensory education [13], Constraint Induced Movement Therapy (CIMT) [14], aquatic training [15] and traditional rehabilitation strategies such as Bobath, resistance and endurance training [16-18] may improve UL function in pwMS. We also found UL training with robotic modalities to be an upcoming trend in UL rehabilitation in a neurological population [19-22].

Technology has improved exponentially in the last decade, which could be useful in context of neurological rehabilitation. Several reviews concerning UL robot rehabilitation in stroke patients, conclude that robot therapy is a beneficial additional therapy and could also be equally effective as intensive conventional training when the right amount of training duration and intensity is provided [23-25]. In contrast to the large amount of robot therapy studies in people with stroke [23, 24, 26], limited research concerning robot therapy has been conducted in pwMS. A systematic search of the literature showed 4 clinical trials [19-22] that have assessed the effects of UL robot assisted rehabilitation in pwMS. Two different robot devices were used: the “Armeo Spring”, an exoskeleton electromechanical device [21] and the “Braccio Di Ferro”, an end-effector type of device [19, 20, 22]. All 4 studies used different intervention content such as reaching tasks [21, 22], reaching and manipulation [20] and comparison of error-reducing and error-enhancing force fields training [22]. A significant amelioration in

the Nine Hole Peg Test (NHPT) was noted after 8 treatment sessions [19, 20], while Gijbels D et al. (2011) reported a borderline significant therapy effect after 8 weeks of training. Additionally, in the study of Carpinella I et al. (2012), also a significant effect was found in Action Research Arm Test (ARAt) after treatment. In summary, insights of previous studies have indicated the potentially additional value of robot-mediated therapy as a supplementary therapeutic approach to usual care. In order to provide better scientific evidence, there is need for studies providing a larger sample size, individualised training programs which include quantitative and qualitative outcome measurements and an additional follow-up period. To our knowledge, personalised and autonomous training is needed and the inclusion of qualitative outcome measures that may contribute to see a global picture of UL function in pwMS should be included.

Therefore, we conducted a clinical trial in order to provide scientific insights on the following research question: “What are the short and long term effects of an 8-week robot-mediated UL training featuring I-TRAVLE in pwMS”? The advantage of the I-TRAVLE intervention with the haptic master (HM) “robotic device” in our clinical trial is, that it may act as a supplementary intensive therapy to usual care for improving UL function. Consequently, pwMS can train more autonomously and can gain more profits. The second advantage of the I-TRAVLE intervention might be, that it may increase therapy compliance e.g. (attractive games, potential of individual fine tuning for difficulty of exercises, interactive virtual learning environment with haptic feedback, autonomous therapy, potential home rehabilitation in the future and inter-motivation between pwMS while scoring their exercises). Furthermore, we suggest that even pwMS with moderate to severe UL dysfunction can work successfully with the virtual reality environment. We hypothesized that UL training with the I-TRAVLE intervention will enhance qualitative and quantitative outcome parameters related to UL function in pwMS. More specifically, ameliorations in UL outcome measurements related to the body function and structures level and activity level of the ICF model are expected. We also expect that pwMS with a severe UL dysfunction can make the most progression.

2. Methodology

2.1 Participants

Recruitment of all pwMS took place at the Rehabilitation and MS centre Overpelt (RMSC) (Belgium). Participants were redirected by the rehabilitation physician at RMSC Overpelt.

For inclusion, all participants had to meet following criteria: being at least 18 years old, clinical diagnosis of MS, time since last exacerbation more than 3 months ago, low to moderate proximal arm muscle strength based on: abduction item of the Motricity Index (MI) > 14 and $\leq$ 25, analogue to maximal active shoulder abduction to 90 degrees without application of resistance AND/OR low to moderate proximal arm Range of Motion (ROM): active shoulder anteflexion > 30 and < 120 degrees which can be maintained steady for maximal 10 seconds.

Participants were excluded in case any of the following criteria is present: severe cognitive impairments which may have an impact on the comprehension of the virtual tasks or severe spasticity (Modified Ashworth scale score for wrist and elbow flexors each > 3) or severe visual deficits which may have an impact on the execution of the tasks in a virtual environment or measurements or other diagnosis e.g. musculoskeletal disorders of the shoulder girdle which could limit the participants UL functioning or unable to understand the questionnaires and measurement instructions or no signed informed consent.

For more detailed subgroup analyses, all participants were divided, based on our inclusion criteria in this study (MI and AROM shoulder), in 3 subgroups: mild UL dysfunction group, moderate UL dysfunction group and severe UL dysfunction group. Participants of the mild UL dysfunction group scored 25 points on MI shoulder abduction and at least 120 degrees of AROM shoulder anteflexion that was not sustained. The participants of the moderate UL dysfunction group also scored 25 points on MI shoulder abduction, but reached AROM shoulder anteflexion between 100 and 120 degrees. The severe UL dysfunction group scored less than 25 points on MI shoulder abduction and less than 100 degrees in AROM shoulder anteflexion.

2.2 Procedure

2.2.1 Design

A non-comparative proof of concept study design was used, with an 8 week training period and 12 weeks of follow-up. To determine baseline stability of clinical UL function, baseline measurements were conducted 3 times (T_{-2}, T_{-1} and T_0), interspaced by 1 week. Figure 1 shows the flowchart of the study design including baseline (T_0), after treatment (T_1) and follow-up (T_2) measurements. Figure 2 shows the flowchart of the intervention study.

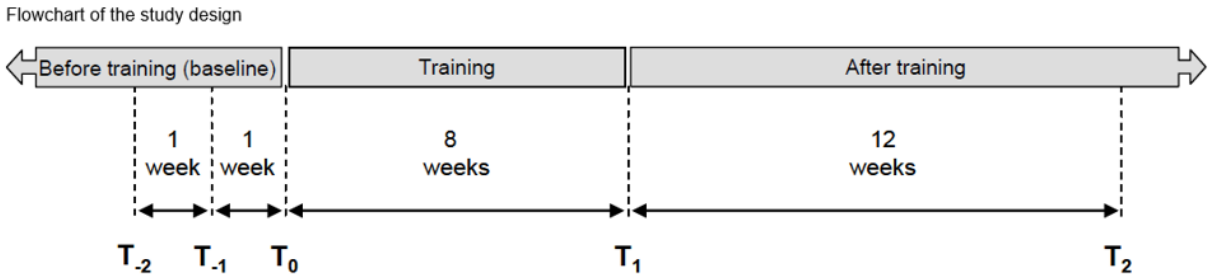

Figure 1. Flowchart of the study design

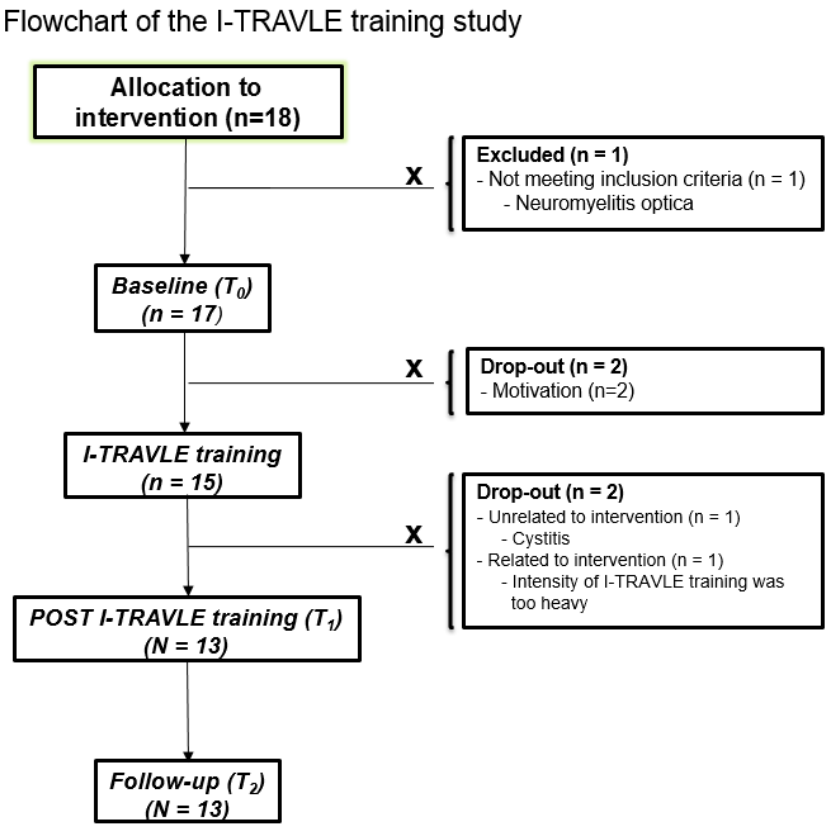

Figure 2. Flowchart of the I-TRAVLE training study

2.2.2 Training

The supervised intervention includes unilateral UL training of which exercises were individualized. Each participant performed 40 training sessions (20 hours) during 8 consecutive weeks at the RMSC Overpelt. Participants performed 5 hours of training (10 training sessions) per 2 weeks. To avoid fatigue and overload from exercising, training days were composed of 2 training sessions of each 30 minutes, interspaced by a small break of at least 30 minutes. The first 30 minutes of training were supervised by a therapist, the second 30 minutes of training participants trained autonomously.

In the first 4 weeks of training, training was focussed on UL endurance. Therefore resistance of the Haptic Master (HM) has been set low, so participants could generate a large number of repetitions. Emphasis on improving strength started from the fifth week and finished at the last training session in week 8.

2.2.3 Experimental system

This study is part of the Interreg IV 'I-TRAVLE' project (IVA-VLANED-1.58). In this study, participants trained the UL in a virtual setting with the use of the HM. It is a robotic device that provides feedback that can either facilitate or challenge the participant to perform the UL tasks in the virtual environment (figure 3). Feedback is given in different forms, such as auditory or visual feedback, but also by haptic feedback. Haptic feedback can be given as a sensation of being pulled to the ideal movement trajectory when a participant deviates from reaching the target. The system also gives haptic feedback in order to better perceive the virtual environment (such as blocking movements when hitting a wall in the virtual reality). The HM consists out of a movable tube with the hand attached to an Activities of Daily Living (ADL) gimbal. The base of the HM is fixed to the ground and the virtual environment is displayed on a LCD screen, approximately two meters in front of the participant (figure 3).

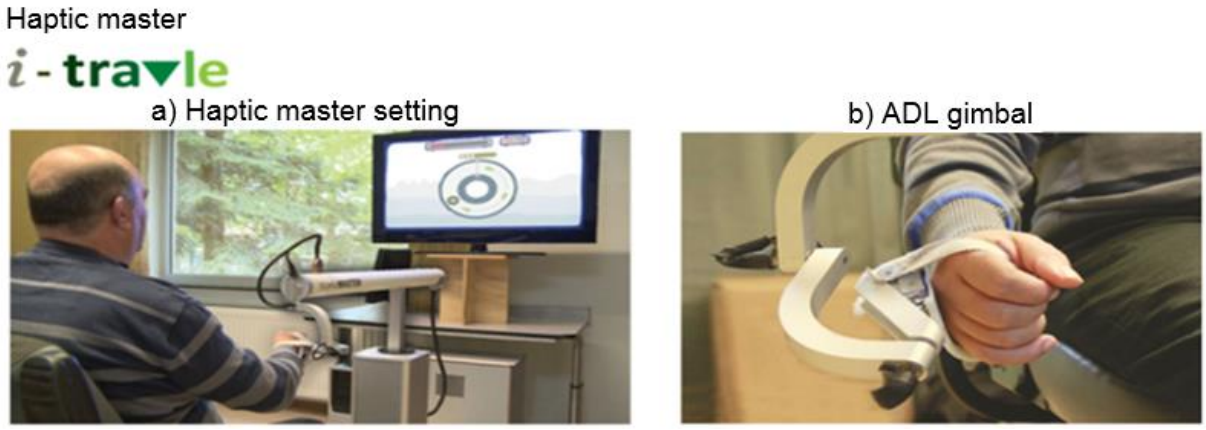

Figure 3. Setup of the haptic master

A correct positioning and posture of the participant was individually controlled by the guiding therapist. The participant should sit comfortable in front of the LCD screen and the HM. The participants should be able to move the tube of the HM forward as far as possible with the target UL. It is also important that the back of the participant remains in contact with the support of the chair. In wheelchair bounded

patients, the (wheel)chair must have a back support and the UL should be free for executing the tasks efficiently. The hand is fastened by a small band to the ADL gimbal. Fixation is merely to provide more support. From this position, the participant has the opportunity to move his hand in three dimensional movements. The ADL gimbal position is displayed on the LCD screen as an avatar during the exercises and games.

Training exercises consist out of goal-directed motor exercises without hand manipulation. Figure 4 presents 2 categories of exercises: a) basic motor function exercises in different directions e.g. reaching, transporting, lifting, pushing, pulling, turning (pro- and supination). The participant must be able to stabilize for a few seconds before going to the next target. In the 'pull' and 'push' exercises, a certain amount of force is needed to pull an object back or to push it forward. The number of repetitions and selection of exercises is set by the guiding therapist. Figure 4 (a) gives an example of a transporting exercise where the participants need to transport the green disc to the 'C-shape' target. b) several games which are a combination of basic motor function exercises, with a maximum play time of 120 seconds (e.g. penguin). Prior to these games, all basis motor function exercises from the first category should be completed. Figure 4 (b) shows 'the penguin game' were participants need to give the penguins the right colours by transporting the penguin to the colour boxes (below and above) and holding it stable for a few seconds to obtain the colour.

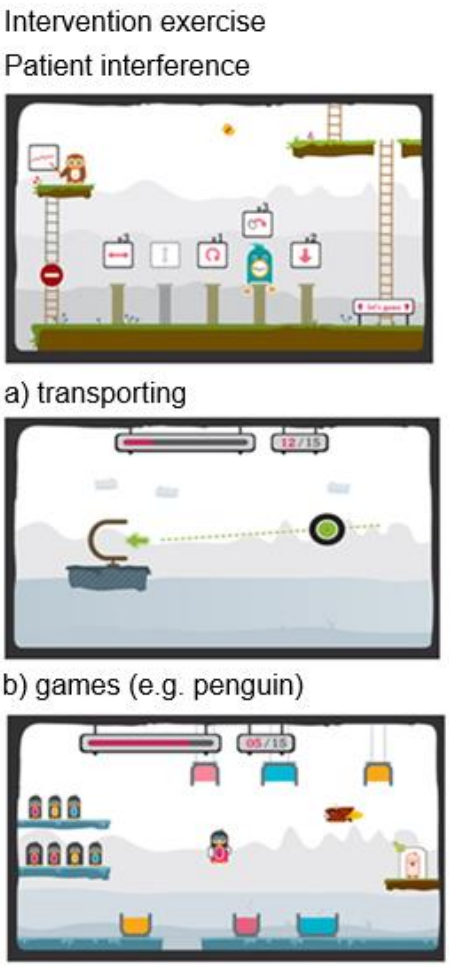

Figure 4. Overview of exercises and games with the HM software

Before training, the participant has to create a personal workspace by determining a three dimensional box with the HM. This workspace contains the maximum distance a participant actively can reach in 3 different directions (front-back, up-down, left-right) without compensation strategies (such as trunk movements). The determination of the personal workspace is performed prior to the training session and can change individually during the training period due to improvement of the AROM. Therefore, the workspace is measured every 2 weeks of training. By means of adaptively, the difficulty level will be automatically changed by the computer system based on the scores of the last 2 training sessions. The difficulty level of exercise could also be manually set by the guiding therapist in case of a practical or personal problem with the participant. The difficulty level of each exercise consists out of a spatial component (such as workspace), feedback (visual, auditory and haptic) and training volume (number of repetitions). It is possible to adjust the number of exercises a participant has to perform in a close (easy) or broad (hard) workspace. Visual feedback (avatar, colours, help line trajectory) will not always be present. Auditory feedback can also be given by the computer. The haptic effects can be changed by giving more or less attractive power or resistance towards reaching the goal to make the exercises more difficult or easier. The weight of an object that needs to be lifted in an exercise can also be changed by the therapist.

2.3 Outcome measurements

2.3.1 **Descriptive** outcome measurements

The following characteristics were addressed: age, gender, MS type (Secondary Progressive MS, Primary Progressive MS, Relapse Remitting MS and Relapse Progressive MS), EDSS, disease duration (DD), hand dominance, most impaired UL, trained UL and use for a wheelchair.

The Neurological Fatigue Index (NFI) and the Symbol Digit Modality Test (SDMT) were measured to determine fatigue and cognitive status.

2.3.2 Clinical outcome measurements

The AROM of shoulder anteflexion and abduction, perceived fatigue and strength, MI and JAMAR handgrip strength are related to the body function and structures level of the ICF model. Wolf Motor Function Test (WMFT) time and Functional Measure Scale (FMS), ABILHAND and MAM-36 are related to the activity level of the ICF model. A different order of testing was performed between pwMS and the same order within one pwMS.

2.3.3 Body function and structures level of the ICF model

The AROM was used for evaluating active anteflexion and abduction of the shoulder by use of a digital mini protractor. The ability to actively hold the shoulder in anteflexion or abduction for 10 seconds was also measured with a digital mini protractor.

The perceived strength and fatigue rated by the participant themselves were addressed using a Visual Analogue Scale (VAS). The following two questions will be asked: “How strong do you feel regarding your UL muscles at this moment?” and “How fatigued does your UL feel at this present moment?”. The participant has to make a mark on the line (0-10 cm) that represents its most accurate answer [27]. When measuring perceived fatigue, a score of zero represents ‘feeling no fatigue’ and a score of 10 represents ‘feeling most fatigued’. When measuring perceived strength, a score of zero represents ‘feeling very weak’ while a score of 10 represents ‘feeling very strong’.

The MI was used as an outcome measurement to assess UL strength. The UL items contain: pinch grip, elbow flexion and shoulder abduction. UL strength is rated by a 6-point ordinal scale between 0-33. A total maximum score of 100 points can be reached which indicates no UL weakness [28].

The JAMAR evaluates maximum handgrip strength (kg) by the use of the JAMAR hand-held dynamometer [29].

2.3.4 Activity level of the ICF model

2.3.4.1 Capacity

The WMFT is a capacity outcome measurement. It consists of 15 timed tasks and additional 2 strength items, which are progressively ordered to more complex tasks. The 2 strength items consist of lifting the weighted UL and a grip strength task measured with a hand dynamometer. Quality of movement will be rated using a 6-point functional ability scale by skilled observers (0 = does not attempt and 5 = normal movement), strength and performance time will be recorded by test administrators. The time limit for each individual time-item is fixed on 120 seconds [30, 31].

2.3.4.2 Perceived performance

The ABILHAND questionnaire is a qualitative outcome measurement which evaluates “difficulty in ADL tasks” and perceived performance of 23 bimanual ADL tasks [32-34]. It uses a 3-level ordinal rating scale: impossible (0), difficult (1), and easy (2) to perform. Activities which are not performed in the last three months are not scored. The scores are converted based on a Rasch Analyses [35].

The MAM-36 is a qualitative outcome measurement which evaluates perceived performance. It consists out of 36 bimanual and manual tasks which are scored categorical: the task is not applicable (0), the task is impossible (1), the task is very difficult (2), the task is little difficult (3), the task is easy (4) [36]. A MAM-36 conversion table is used to convert the total score to a score from 1-100. The higher a participants scores, the better this person can perform in activities of daily life.

2.4 Statistical analyses

Due to the small sample size and skewed distribution of the data, which was checked with the Shapiro-Wilk test, non-parametric statistics analyses were performed. In order to determine the stability of our 3 baseline measures (T_{-2}, T_{-1} and T_0), we calculated the intraclass correlation coefficient (ICC) and the standard error of mean (SEM). ICC's value reach from zero to 1 of which a higher ICC represents a better correlation. Cut-off value has been set on 0.75 and represents a good ICC. Values above 0.90 are considered as an excellent ICC. To investigate the changes between baseline (T_0), after training (T_1) and at follow-up (T_2), the Wilcoxon Signed Rank test was used. We investigated changes between baseline outcome measures (T_0) and outcome measures taken immediately after treatment (T_1). Data of follow-up (T_2) was statistically compared with outcome measures taken immediately after treatment in order to investigate for changes after treatment. Subgroup analyses were performed using the same statistics. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS). The level of statistical significance was set at $p < 0.05$.

2.5 Medical ethics

This clinical study is registered through the ClinicalTrials.gov, registry of „Clinical trials" (NCT01918748). It is certified (code: S55614) by the Ethics Committee on 2nd August 2013 (Belgium).

3. Results

3.1 Participants (descriptive characteristics)

Thirteen pwMS, of which 4 men and 9 women, were included in this clinical trial. Table 1 describes the characteristics of the included pwMS who all completed the 8-week intervention and follow-up period. The median disease duration was 17.00 years (5.5-28.5) and varied from 3 to 31 years. The following types of MS were administered: SPMS (n=6/13), RRMS (n=3/13), PPMS (n=2/13) and RPMS (n=2/13). The EDSS values of the participants ranged from 2.5 to 8 with a median value of 6.50 (6.5-8.5). Nine out of 13 participants were wheelchair-bound and had an EDSS score of at least 6. The dominant UL was trained in 7 out of 13 participants. The NFI shows a median score of 50 points. Taken in account that the highest possible score is 69 points, this group shows to be frequently fatigued.

Table 1. Patient characteristics (N=13)

Participant	Age (y)	Gender (♂/♀)	MS type (SP/PP/RR/RP)	EDSS	DD (y)	NFI	Hand dominance	Most impaired UL	UL trained (D/ND)	Wheelchair
P_1	38	♀	SP	3.5	3	38	Right	Left	Left	/
P_2	66	♂	PP	7.5	17	15	Left	Left	Left	Electric
P_3	22	♀	RP	6.5	4	58	Right	Left	Left	Scooter
P_4	38	♂	RP	7	9	58	Right	Left	Left	Manual
P_5	52	♀	SP	7	28	43	Right	Right	Left	Manual
P_6	49	♀	RR	6.5	27	31	Right	Left	Left	Manual
P_7	55	♀	RR	2.5	4	54	Right	Left	Right	/
P_8	39	♀	SP	7.5	21	60	Right	Right	Right	Electric
P_9	57	♂	SP	8	30	59	Right	Left	Right	Manual
P_{10}	54	♀	SP	7.5	17	49	Left	Left	Left	Manual
P_{11}	61	♀	SP	5	6	50	Right	Right	Right	/
P_{12}	63	♂	PP	6	7	44	Right	Left	Left	Scooter
P_{13}	63	♀	RR	3	31	60	Right	Right	Right	/
Median (Q1 - Q3)	54.00 (42-66)	4/9	6/2/3/2	6.50 (5-8)	17.00 (5.5-28.5)	50.00 (41-59)	2L/11R	9L/4R	8L/5R	9/13

Used abbreviations: MS = Multiple Sclerosis; SP = Secondary Progressive; PP = Primary Progressive; RR = Relapse Remitting; RP = Relapse Progressive; EDSS = Expanded Disability Status Scale; DD = Disease Duration; NFI = Neurological Fatigue Index; UL = Upper Limb; D = Dominant; ND = Non Dominant

3.2 Intraclass correlation coefficient and standard error of the mean

ICC and SEM of included outcome measures can be found in table 2. Baseline stability (ICC > 0.75; $p < 0.05$) has been achieved for 10 clinical outcome measures (AROM and sustained shoulder anteflexion and abduction, MI, JAMAR, WMFT time and FMS, ABILHAND and MAM-36). Only the perceived fatigue and strength showed an ICC lower than the cut off value (ICC <0.75). Consequently, the median scores of the 3 baseline measures (T_{-2}, T_{-1} and T_0) of all outcome measures of each participant have been used for statistical analyses and represent the baseline value (T_0).

Table 2. Intraclass correlation coefficient and standard error of the mean of clinical outcome measures (N = 13)

ICF-level	Outcome measures		ICC	Lower bound	Upper bound	p-value	SEM
FUNCTION	AROM	**AROM Shoulder anteflexion**	0.97	0.92	0.99	**p < 0.001**	7.44
		AROM Shoulder anteflexion 10"	0.97	0.88	0.99	**p < 0.001**	11.83
		AROM Shoulder abduction	0.92	0.76	0.98	**p < 0.001**	24.83
		AROM Shoulder abduction 10"	0.96	0.88	0.99	**p < 0.001**	15.83
	VAS	**Perceived fatigue**	0.22	- 1.19	0.75	ns	2.85
		Perceived strength	- 0.04	- 1.91	0.67	ns	2.01
	Strength	**MI**	0.89	0.72	0.97	**p < 0.001**	9.01
		JAMAR	0.77	0.40	0.93	**p < 0.05**	5.74
ACTIVITY	Capacity	**WMFT time**	0.82	0.53	0.94	**p < 0.001**	30.74
		WMFT FMS	0.88	0.69	0.96	**p < 0.001**	0.63
	Perceived performance	**ABILHAND**	0.97	0.93	0.99	**p < 0.001**	0.64
		MAM-36	0.96	0.89	0.99	**p < 0.001**	4.67

Used abbreviations: ICF = International Classfication of Functioning disability and health; ICC = Intraclass Correlation Coefficient; SEM = Standard Error of the Mean; AROM = Active Range of Motion; MI = Motricity Index; WMFT = Wolf Motor Function Test; FMS = Functional Measure Scale; MAM-36 = Manual Ability Measure; ns = not significant

3.3 Group analyses

Table 3 shows the results of all outcome measures at group level (N=13). A statistically significant amelioration was found after treatment (T_1) in 6 outcome measures (AROM shoulder anteflexion and AROM sustained shoulder anteflexion, perceived strength, JAMAR, WMFT time and FMS). After treatment, 7 out of 13 participants improved in (sustained) AROM anteflexion. Furthermore, 10 out of 13 participants experienced less fatigue. Five participants showed improvement in the MI. In addition, 5 participants improved in the MAM-36 after treatment. The JAMAR handgrip strength was the only outcome measure that showed a statistically significant improvement after treatment and a statistically significant deterioration at follow up (T_1-T_2).

Table 3. Results of the clinical outcome measures at group level (N=13)

			Before treatment (T_0)		After treatment (T_1)		Follow-up (T_2)		p-value T_1-T_0	p-value T_2-T_1
ICF-level		**Outcome measures**	**median**	**Q1 - Q3**	**median**	**Q1 - Q3**	**median**	**Q1 - Q3**		
FUNCTION	AROM	**AROM Shoulder anteflexion (°)**	110.00	97.00 - 132.00	137.00	112.00 - 144.00	117.00	87.20 - 144.00	**p < 0.05**	ns
		AROM Shoulder anteflexion 10" (°)	102.00	92.00 - 120.00	129.00	100.00 - 138.00	105.00	81.90 - 137.00	**p < 0.05**	ns
		AROM Shoulder abduction (°)	106.00	76.00 - 118.00	108.00	77.00 - 128.00	85.40	63.90 - 133.00	ns	ns
		AROM Shoulder abduction 10" (°)	102.00	62.00 - 108.00	88.00	74.00 - 125.00	84.60	52.00 - 128.00	ns	ns
	VAS	**Perceived fatigue (VAS)**	3.60	1.80 - 5.10	1.70	0.70 - 5.60	0.80	0.30 - 3.70	ns	ns
		Perceived strength (VAS)	3.90	3.00 - 4.60	7.40	5.10 - 8.60	7.50	3.80 - 8.30	**p < 0.05**	ns
	Strength	**MI**	76.00	70.00 - 83.00	76.00	72.00 - 84.00	76.00	66.00 - 100.00	ns	ns
		JAMAR (kg)	13.22	9.12 - 16.18	14.82	11.24 - 20.20	13.55	11.55 - 18.60	**p < 0.05**	**p < 0.05**
ACTIVITY	Capacity	**WMFT time (s)**	2.43	1.53 - 4.81	1.56	1.00 - 1.73	1.36	1.02 - 1.95	**p < 0.05**	ns
		WMFT FMS	4.00	3.38 - 5.00	5.00	4.50 - 5.00	5.00	4.50 - 5.00	**p < 0.05**	ns
	Perceived performance	**ABILHAND**	0.53	-1.28 - 1.82	0.92	-0.60 - 1.82	0.14	-1.15 - 1.33	ns	ns
		MAM-36	54.50	40.00 - 64.00	54.50	46.00 - 63.00	54.50	40.50 - 62.00	ns	ns

Used abbreviations: ICF = International Classification of Functioning disability and health; Q1 = Quartile 1; Q3 = Quartile 3; AROM = Active Range of Motion; VAS = Visual Analogue Scale; MI = Motricity Index; kg = kilogram; s = seconds; WMFT = Wolf Motor Function Test; FMS = Functional Measure Scale; MAM-36 = Manual Ability Measure, ns = not significant

3.4 Subgroup analyses

The mild UL dysfunction group (n=3/13) had a median AROM shoulder anteflexion of 151.00 degrees and median MI of 92.00; the moderate UL dysfunction group (n=6/13) had a median AROM shoulder anteflexion of 115.00 degrees and median MI of 76.00 and the severe UL dysfunction group (n=4/13) had a median AROM shoulder anteflexion of 70.50 degrees and median MI of 63.00. Illustrative figures were made from the important UL outcome measures. More detailed data of the 3 different subgroups can be found in the tables presented in appendix 1.

After treatment, a statistically significant amelioration was found in the moderate UL dysfunction group in the AROM sustained shoulder flexion (figure 5). A trend to significance was found in the severe UL dysfunction group in the AROM sustained shoulder flexion. The moderate UL dysfunction group also felt less fatigued which resulted in a statistically significant effect (figure 6). Three out of 4 participants of the severe UL dysfunction group also showed less fatigue, however not significant. The mild UL dysfunction group showed a tendency of increased fatigue after treatment (T_1). All subgroups showed a clinical important amelioration tendency of the perceived strength after treatment, but these were not statistically significant (figure 7). Figure 8 shows that participants from all subgroups were faster in executing the tasks in the WMFT after treatment. Especially in the moderate UL dysfunction group which was found statistically significant. Furthermore all subgroups reached a plateau phase in the follow-up period.

The moderate UL dysfunction group is the only subgroup that showed statistically significant improvements after treatment in AROM shoulder anteflexion, perceived fatigue and WMFT time.

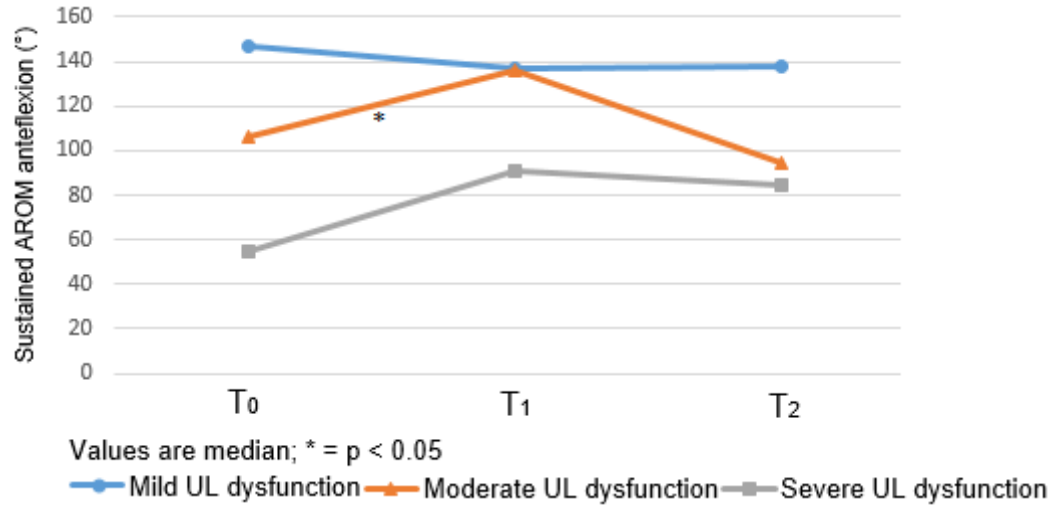

Figure 5. Sustained AROM anteflexion before, immediately and 12 weeks after the intervention for subgroups with mild, moderate and severe UL dysfunction

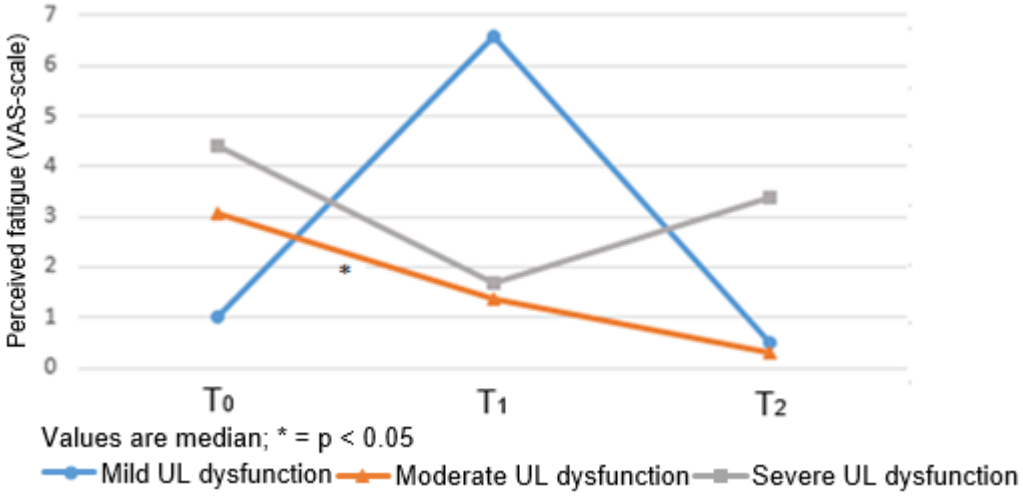

Figure 6. Perceived fatigue before, immediately and 12 weeks after the intervention for subgroups with mild, moderate and severe UL dysfunction

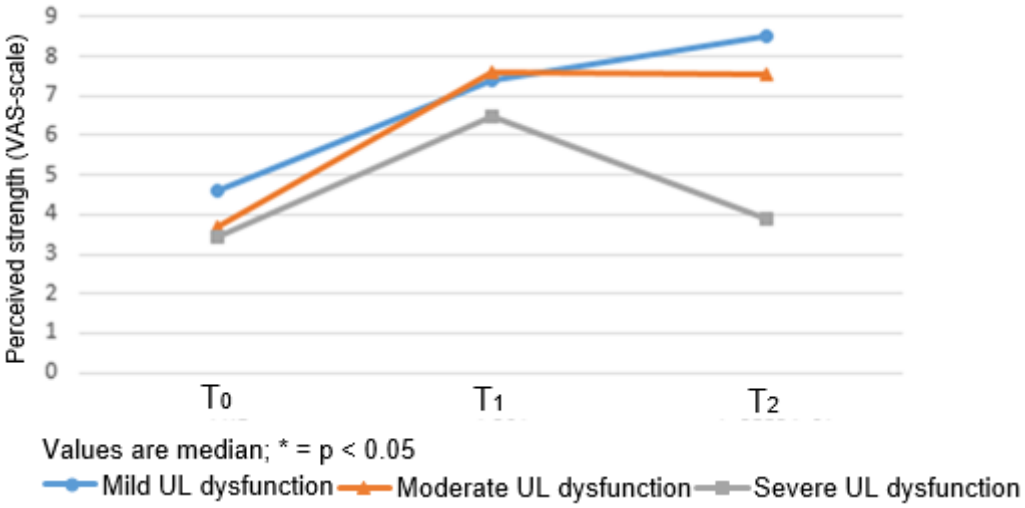

Figure 7. Perceived strength before, immediately and 12 weeks after the intervention for subgroups with mild, moderate and severe UL dysfunction

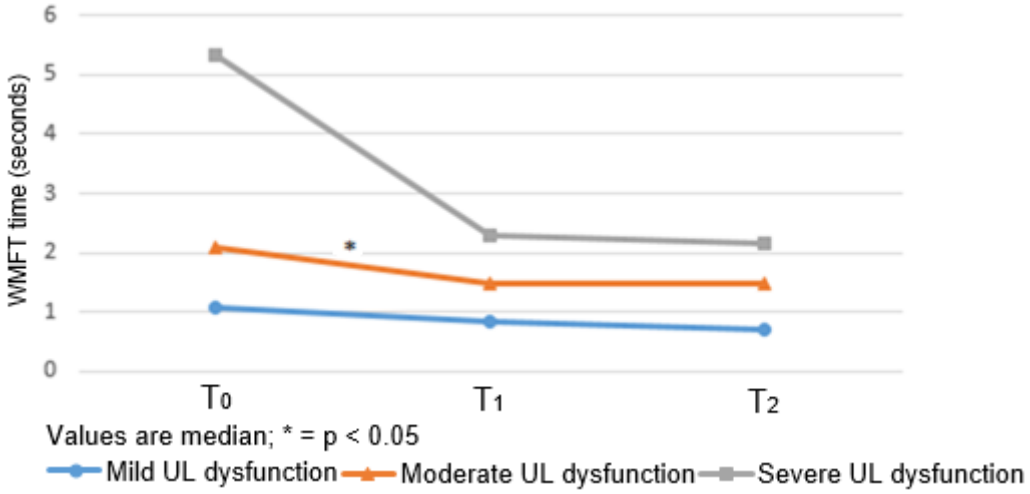

Figure 8. WMFT time before, immediately and 12 weeks after the intervention for subgroups with mild, moderate and severe UL dysfunction

4. Discussion

The main objective of this non-comparative proof of concept study was to investigate the short and long term effects of an 8-week individualised training regime featuring the I-TRAVLE system on UL function in pwMS. The findings of the study confirm our hypothesis that an 8-week additional and robot-mediated training within the I-TRAVLE improves both qualitative and quantitative outcome measures of UL function.

Group analyses showed that the pwMS improved significantly on body function and structures level and as well as on the activity level of the ICF model. On body function and structures level the participants improved significantly on AROM shoulder anteflexion as expected since the training requires a large number of repetitions of anteflexion movements. Similar results were found for active amplitude of sustained shoulder anteflexion. PwMS reported that after training, they could lift higher and stabilize their trained UL longer for a certain period. Remarkably, we did not find this results for AROM shoulder abduction. This could be due to compensation methods that the participants could have used such as trunk movements or using scapular elevation. Subgroup analyses shows that mostly participants with moderate to severe UL dysfunction improved in AROM shoulder anteflexion. It is possible that participants with a mild UL dysfunction have reached a ceiling effect in training with the HM. Noteworthy, we found no other intervention study with pwMS that used the AROM as an outcome measure. Because of the importance of capability of lifting and stabilizing the UL in home activities, we included the (sustained) AROM of the shoulder as an outcome measure.

The VAS for perceived fatigue and strength did not reach baseline stability and are therefore needed to be evaluated with caution. Although 10 out of 13 participants felt less fatigue in their UL after training, a significant effect was not reached in perceived fatigue. This could be due to experienced fluctuations in fatigue feelings, perhaps due to uncontrolled preceding daily life activities, which was also indicated by the low ICC. Another intervention study [14], that investigated the effects of CIMT in pwMS, also used perceived fatigue as one of the outcome measures. They included only 5 participants of which 4 felt mostly no fatigue, which was not the case in our group of participants. Nonetheless the small group, they also found statistically significant improvements in fatigue feelings after training.

In contrast to perceived fatigue, a statistically significant improvement was reached in the perceived strength after treatment, also measured with a 0-10 cm VAS-scale. Perceived strength improvement was comparable in every subgroup. Thus measured by qualitative outcome measures, most participants felt stronger in their trained arm after the training period. Quantitative outcome measures concerning handgrip strength measured by JAMAR also showed statistically significant improvements after training This findings is to some extent surprising, given that participants did not specifically train handgrip strength during the I-TRAVLE intervention. There were still 9 participants that improved on the JAMAR. This could result of a continuous increased applied handgrip strength at the ADL gimbal during training or a fluctuating increase in handgrip strength when exercises became more difficult. In contrast, overall UL strength measured by the total score of MI did only show improvements in 4 participants of which 3 with a severe UL dysfunction. It could be possible that the subjective feeling of being strong in the arms,

was felt mostly in the ability to hold something more firmly or to stabilize the UL. A similar intervention study used the Armeo Spring as a robotic training modality and found similar negative results in the MI, but found no statistically significant effect in the JAMAR handgrip strength in contrast to our study [21].

At activity level of the ICF model, we found different results according to the UL outcome measures. The participants improved statistically significant in the WMFT time after treatment. Individual improvements after treatment were noticed in participants from each subgroup. The high SEM value was caused by 2 participants who had a median score of 120 seconds (outliers) and therefore the SEM value increased greatly. The FMS values of the WMFT correspond to the WMFT time values and resulted that the participants also reached statistically significant improvements after treatment. From our review of UL intervention studies in pwMS, we found one study [14] that also included the WMFT time as outcome measure. Participants of this study [14] improved in the WMFT time after treatment, but in contrast to our study, without statistically significant effect. Besides the WMFT, which is a capacity measure also the ABILHAND and MAM-36 (perceived performance) were used. The rash data of the ABILHAND shows that 7 participants improved after treatment. Reaching statistically significant improvements in ABILHAND is difficult because it only provides 3 possible answers for each item in the questionnaire (impossible to perform, difficult to perform or easy to perform). The ABILHAND also includes many hand manipulative tasks which were not trained during this I-TRAVLE intervention. Still we included the ABILHAND as an outcome measure in our study, because we expected participants would also not deteriorate in fine motor skills. Therefore it could still have been possible to find positive results in ABILHAND rasch scores. There were few participants that improved in MAM-36 after treatment. We found no other intervention studies with pwMS that used the ABILHAND or the MAM-36 as outcome measures The study of Mark VW et al. (2008) used the Motor Activity Log (MAL), which is a similar outcome measure measuring perceived use of the UL in daily life and found statistically significant improvements after treatment and after a follow-up of 4 weeks.

Other studies that looked into the effects of robotic training in pwMS also report significant improvements after training [19-22]. Two studies by Carpinella I et al. (2009;2012) investigated the effects of training with the ‘Braccio di Ferro’ and found positive results measured by the NHPT and the ARAt [20]. The positive results in the NHPT could have been achieved because of a large number of repetitions of horizontal movements with the assistance of the Braccio di Ferro which leads to a smaller workspace that corresponds with the workspace of a NHPT. The Braccio di Ferro differs from the Haptic Master because it does not provide haptic feedback and only horizontal movements can be trained in 2 dimensions (forward-backward, left-right). Improvements in the ARAt were probably found because also hand manipulation tasks were trained in the second study of Carpinella I et al. (2012). The training methods were comparable, except that their participants only trained 8 sessions of 30-45 minutes. One other study [22] also used the Braccio di Ferro and also found significant improvements in NHPT after a training period of 8 weeks. Gijbels D et al. (2011) used the Armeo Spring as robotic modality during an intervention study with 24 training sessions of 30 minutes. The Armeo Spring is an exoskeleton used for UL training and can also be used in a virtual reality environment. They found statistically significant improvements after treatment measured by ARAt and TEMPA. After a follow-up period of 8 weeks, they

found statistically significant improvements in the NHPT and the TEMPA scale compared to the baseline measures.

In this study we used 12 outcome measures to search for the possible effects on body function and structures level and activity level (ICF). Other studies [19-22] mainly used the ARAt and the NHPT. We did not use these outcome measures because we did not trained fine motor skills. As mainly gross goal-directed arm movements with a high number of repetition were trained in our program it was more logical to include outcome measures which evaluates gross arm movements. Therefore, we expected that the participants would improve their AROM of the shoulder. However the importance of the AROM of the shoulder in UL training, none of previous UL intervention studies that we found in our review, included this as an outcome measure[13-22, 37, 38]. In addition, we wanted to explore if when significant improvements on body function and structures level, also lead to improvements in performing activities in their daily life. For this reason, we included the ABILHAND and the MAM-36. We found these lacking in previous intervention studies concerning UL training in pwMS [13, 15, 17-19, 22]. Because of the large amount of outcome measures, it is possible that participants got more tired during the tests and therefore were not able to reach their best score. In order to avoid this, we used the same testing order within one person and a random order between persons. In that way, it could still be possible that the participants did not reach their best scores during some tests, but this would normally also be the case in the testing period after treatment and at follow-up. In order to definitively prevent the tiring of participants, testing time would had to be done on multiple testing days.

From a critical point of view, the results of this non-comparative proof of concept study need to be taken cautiously because of following limitations. Firstly, our study design included no comparison with a control group (no treatment or usual care), which means that we are not able to determine the added value of robot-mediated training in comparison with usual care or other treatment modalities in pwMS. Moreover, we cannot conclude that we have a significant treatment effect of the robot-mediated training as pwMS also received conventional therapy. For future trials, it could be advised to use the data of the non-trained arm of the participants as a control. Even so, if because of training, participants were able to perform more bimanual tasks during their daily life, it could be possible that the non-trained also improved. Therefore, a control group that did not receive training with the HM would have been better to investigate a treatment effect. Secondly, we only included 13 pwMS in this intervention study. Thirdly, there was no blinding of the therapists which guided or tested the pwMS. Fourthly, we did not use the data about the individual training intensity of each pwMS [39]. This would have given us more insights in why some participants improved and others did not. Fifthly, participants were tested by multiple therapists, which means that not every participant was evaluated by the same therapist. Consequently, the outcome measures could have been influenced by inter-rater and intra-rater flexibility. To counter this, we could have included a familiarization period before start of the study. Furthermore, performance bias and visualising the scores of the different games could (de)motivated the pwMS to training. At last, embedding outcome measures related to the participation level of the ICF model e.g. subjective MAL, would have made a better global picture of the UL function in pwMS.

The study design shows multiple positive aspects which we found to be lacking in previous studies [20, 19, 21, 22]. Firstly, participants in our study trained more hours and sessions compared to participants from other robot mediated studies [20, 19, 21, 22]. Secondly, training was based on an individualised approach for each participant. The adaptively capacity of the HM made sure that training sessions were adapted to each individual abilities, but still remained a challenge for the participants in order to make progress in UL function. Thirdly, we find it a great advantage that pwMS were able to train autonomously. This could also be useful in rehabilitation centres so participants can train more hours. Fourthly, all participants achieved the same duration of wash-out period between training sessions. This means that fatigue and overuse following exercising was partially limited. Fifthly, this study included a lot of outcome measures and consists out of qualitative and quantitative outcome measures. Sixthly, achieved SEM data from the stability characteristics of the included outcome measures gave information whether a statistically significant difference is still clinical relevant for clinicians. Lastly, a follow up period of 12 weeks was used in order to investigate for the long term effects of this intervention.

We recommend further studies with larger sample sizes and a control group which is provided with usual care or no treatment. We recommend that training intensity should be monitored in order to make more detailed analyses. Furthermore, it could add great value to address qualitative and quantitative UL outcome measures which are related to the ICF model. At last, it could also be interesting to study changes in outcome measures of participation of the ICF model.

5. Conclusion

This non-comparative proof of concept study shows that robot-mediated UL training after 8-week I-TRAVLE intervention resulted in improvements on UL function at body and structures level and at activity level of the ICF model and no deteriorations were found. These improvements were mostly present in pwMS with moderate upper limb dysfunction. The AROM (sustained) shoulder anteflexion and WMFT time were UL outcome measures that improved the most after treatment. We can conclude that robot-mediated UL training may have beneficial effects on UL function in pwMS. Further research must be encouraged to apply a larger sample of pwMS, a detailed overview of training intensity and a control group.

6. Reference list

1. Compston A, Coles A. Multiple sclerosis. Lancet. 2002;359(9313):1221-31. doi:10.1016/S0140-6736(02)08220-X.
2. Kister I, Bacon TE, Chamot E, Salter AR, Cutter GR, Kalina JT et al. Natural history of multiple sclerosis symptoms. International journal of MS care. 2013;15(3):146-58. doi:10.7224/1537-2073.2012-053.
3. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. The New England journal of medicine. 2000;343(13):938-52. doi:10.1056/NEJM200009283431307.
4. Kingwell E, Marriott JJ, Jette N, Pringsheim T, Makhani N, Morrow SA et al. Incidence and prevalence of multiple sclerosis in Europe: a systematic review. BMC neurology. 2013;13:128. doi:10.1186/1471-2377-13-128.
5. van Ooteghem P, D'Hooghe MB, Vlietinck R, Carton H. Prevalence of multiple sclerosis in Flanders, Belgium. Neuroepidemiology. 1994;13(5):220-5.
6. Johansson S, Ytterberg C, Claesson IM, Lindberg J, Hillert J, Andersson M et al. High concurrent presence of disability in multiple sclerosis. Associations with perceived health. Journal of neurology. 2007;254(6):767-73. doi:10.1007/s00415-006-0431-5.
7. Dalgas U, Stenager E, Jakobsen J, Petersen T, Hansen HJ, Knudsen C et al. Resistance training improves muscle strength and functional capacity in multiple sclerosis. Neurology. 2009;73(18):1478-84. doi:10.1212/WNL.0b013e3181bf98b4.
8. Holper L, Coenen M, Weise A, Stucki G, Cieza A, Kesselring J. Characterization of functioning in multiple sclerosis using the ICF. Journal of neurology. 2010;257(1):103-13. doi:10.1007/s00415-009-5282-4.
9. Latimer-Cheung AE, Pilutti LA, Hicks AL, Martin Ginis KA, Fenuta AM, MacKibbon KA et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. Archives of physical medicine and rehabilitation. 2013;94(9):1800-28.e3. doi:10.1016/j.apmr.2013.04.020.
10. Motl RW, McAuley E. Symptom cluster as a predictor of physical activity in multiple sclerosis: preliminary evidence. Journal of pain and symptom management. 2009;38(2):270-80. doi:10.1016/j.jpainsymman.2008.08.004.
11. Ben Ari Shevil E, Johansson S, Ytterberg C, Bergstrom J, von Koch L. How are cognitive impairment, fatigue and signs of depression related to participation in daily life among persons with multiple sclerosis? Disability and rehabilitation. 2014;36(23):2012-8. doi:10.3109/09638288.2014.887797.
12. Benito-Leon J, Morales JM, Rivera-Navarro J, Mitchell A. A review about the impact of multiple sclerosis on health-related quality of life. Disability and rehabilitation. 2003;25(23):1291-303. doi:10.1080/0963828031000160859l.
13. Kalron A, Greenberg-Abrahami M, Gelav S, Achiron A. Effects of a new sensory re-education training tool on hand sensibility and manual dexterity in people with multiple sclerosis. NeuroRehabilitation. 2013;32(4):943-8. doi:10.3233/NRE-130917.
14. Mark VW, Taub E, Uswatte G, Bashir K, Cutter GR, Bryson CC et al. Constraint-induced movement therapy for the lower extremities in multiple sclerosis: case series with 4-year follow-up. Archives of physical medicine and rehabilitation. 2013;94(4):753-60. doi:10.1016/j.apmr.2012.09.032.
15. Bayraktar D, Guclu-Gunduz A, Yazici G, Lambeck J, Batur-Caglayan HZ, Irkec C et al. Effects of Ai-Chi on balance, functional mobility, strength and fatigue in patients with multiple sclerosis: a pilot study. NeuroRehabilitation. 2013;33(3):431-7. doi:10.3233/NRE-130974.
16. Romberg A, Virtanen A, Ruutiainen J, Aunola S, Karppi SL, Vaara M et al. Effects of a 6-month exercise program on patients with multiple sclerosis: a randomized study. Neurology. 2004;63(11):2034-8.
17. Keser I, Meric A, Kirdi N, Kurne A, Karabudak R. Comparing routine neurorehabilitation programme with callisthenic exercises in multiple sclerosis. NeuroRehabilitation. 2011;29(1):91-8. doi:10.3233/NRE-2011-0682.

18. Taylor NF, Dodd KJ, Prasad D, Denisenko S. Progressive resistance exercise for people with multiple sclerosis. Disability and rehabilitation. 2006;28(18):1119-26. doi:10.1080/09638280500531834.
19. Carpinella I, Cattaneo D, Abuarqub S, Ferrarin M. Robot-based rehabilitation of the upper limbs in multiple sclerosis: feasibility and preliminary results. Journal of rehabilitation medicine. 2009;41(12):966-70. doi:10.2340/16501977-0401.
20. Carpinella I, Cattaneo D, Bertoni R, Ferrarin M. Robot training of upper limb in multiple sclerosis: comparing protocols with or without manipulative task components. IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society. 2012;20(3):351-60. doi:10.1109/TNSRE.2012.2187462.
21. Gijbels D, Lamers I, Kerkhofs L, Alders G, Knippenberg E, Feys P. The Armeo Spring as training tool to improve upper limb functionality in multiple sclerosis: a pilot study. Journal of neuroengineering and rehabilitation. 2011;8:5. doi:10.1186/1743-0003-8-5.
22. Vergaro E, Squeri V, Brichetto G, Casadio M, Morasso P, Solaro C et al. Adaptive robot training for the treatment of incoordination in Multiple Sclerosis. Journal of neuroengineering and rehabilitation. 2010;7:37. doi:10.1186/1743-0003-7-37.
23. Norouzi-Gheidari N, Archambault PS, Fung J. Effects of robot-assisted therapy on stroke rehabilitation in upper limbs: systematic review and meta-analysis of the literature. Journal of rehabilitation research and development. 2012;49(4):479-96.
24. Hochstenbach-Waelen A, Seelen HA. Embracing change: practical and theoretical considerations for successful implementation of technology assisting upper limb training in stroke. Journal of neuroengineering and rehabilitation. 2012;9:52. doi:10.1186/1743-0003-9-52.
25. Lo AC, Guarino PD, Richards LG, Haselkorn JK, Wittenberg GF, Federman DG et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. The New England journal of medicine. 2010;362(19):1772-83. doi:10.1056/NEJMoa0911341.
26. Peter O, Fazekas G, Zsiga K, Denes Z. Robot-mediated upper limb physiotherapy: review and recommendations for future clinical trials. International journal of rehabilitation research Internationale Zeitschrift fur Rehabilitationsforschung Revue internationale de recherches de readaptation. 2011;34(3):196-202. doi:10.1097/MRR.0b013e328346e8ad.
27. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Archives of neurology. 1989;46(10):1121-3.
28. Lamers I, Timmermans AA, Kerkhofs L, Severijns D, Van Wijmeersch B, Feys P. Self-reported use of the upper limbs related to clinical tests in persons with multiple sclerosis. Disability and rehabilitation. 2013;35(23):2016-20. doi:10.3109/09638288.2013.771703.
29. Trampisch US, Franke J, Jedamzik N, Hinrichs T, Platen P. Optimal Jamar dynamometer handle position to assess maximal isometric hand grip strength in epidemiological studies. The Journal of hand surgery. 2012;37(11):2368-73. doi:10.1016/j.jhsa.2012.08.014.
30. Morris DM, Uswatte G, Crago JE, Cook EW, 3rd, Taub E. The reliability of the wolf motor function test for assessing upper extremity function after stroke. Archives of physical medicine and rehabilitation. 2001;82(6):750-5. doi:10.1053/apmr.2001.23183.
31. Wolf SL, Catlin PA, Ellis M, Archer AL, Morgan B, Piacentino A. Assessing Wolf motor function test as outcome measure for research in patients after stroke. Stroke; a journal of cerebral circulation. 2001;32(7):1635-9.
32. Barrett LE, Cano SJ, Zajicek JP, Hobart JC. Can the ABILHAND handle manual ability in MS? Multiple sclerosis. 2013;19(6):806-15. doi:10.1177/1352458512462919.
33. Penta M, Tesio L, Arnould C, Zancan A, Thonnard JL. The ABILHAND questionnaire as a measure of manual ability in chronic stroke patients: Rasch-based validation and relationship to upper limb impairment. Stroke; a journal of cerebral circulation. 2001;32(7):1627-34.
34. Penta M, Thonnard JL, Tesio L. ABILHAND: a Rasch-built measure of manual ability. Archives of physical medicine and rehabilitation. 1998;79(9):1038-42.

35. Wang TN, Lin KC, Wu CY, Chung CY, Pei YC, Teng YK. Validity, responsiveness, and clinically important difference of the ABILHAND questionnaire in patients with stroke. Archives of physical medicine and rehabilitation. 2011;92(7):1086-91. doi:10.1016/j.apmr.2011.01.020.
36. Chen CC, 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(3):414-20. doi:10.1016/j.apmr.2009.11.012.
37. Hermens H, Huijgen B, Giacomozzi C, Ilsbroukx S, Macellari V, Prats E et al. Clinical assessment of the HELLODOC tele-rehabilitation service. Annali dell'Istituto superiore di sanita. 2008;44(2):154-63.
38. Huijgen BC, Vollenbroek-Hutten MM, Zampolini M, Opisso E, Bernabeu M, Van Nieuwenhoven J et al. Feasibility of a home-based telerehabilitation system compared to usual care: arm/hand function in patients with stroke, traumatic brain injury and multiple sclerosis. Journal of telemedicine and telecare. 2008;14(5):249-56. doi:10.1258/jtt.2008.080104.
39. Kwakkel G, Kollen BJ, Krebs HI. Effects of robot-assisted therapy on upper limb recovery after stroke: a systematic review. Neurorehabilitation and neural repair. 2008;22(2):111-21. doi:10.1177/1545968307305457.

7. Annex

7.1 Appendix 1. Tables of included outcome measures for the 3 different subgroups before and after the intervention and at follow-up

Table 4a. Results of the outcome measures of the mild upper limb dysfunction group (n=3/13)

ICF-level	Outcome measures		Before treatment (T_0)	After treatment (T_1)	Follow-up (T_2)	p-value T_1-T_0	p-value T_2-T_1
FUNCTION	AROM	**AROM Shoulder anteflexion (°)**	151.00	139.00	144.00	ns	ns
		AROM Shoulder anteflexion 10" (°)	147.00	137.00	138.00	ns	ns
		AROM Shoulder abduction (°)	141.00	128.00	133.00	ns	ns
		AROM Shoulder abduction 10" (°)	133.00	128.00	132.00	ns	ns
	VAS	**Perceived fatigue (VAS)**	1.00	6.60	0.50	ns	ns
		Perceived strength (VAS)	4.60	7.40	8.50	ns	ns
	Strength	**MI**	92.00	84.00	100.00	ns	ns
		JAMAR (kg)	18.83	18.55	20.90	ns	ns
ACTIVITY	Capacity	**WMFT time (s)**	1.08	0.82	0.71	ns	ns
		WMFT FMS	5.00	5.00	5.00	ns	ns
	Perceived performance	**ABILHAND**	1.06	1.20	0.39	ns	ns
		MAM	64.00	63.00	61.50	ns	ns

Used abbreviations: ICF = International Classification of Functioning, disability and health; AROM = Active Range of Motion; VAS = Visual Analogue Scale; MI = Motricity Index; kg = kilogram; s = seconds; WMFT = Wolf Motor Function Test; FMS = Functional Measure Scale; MAM-36 = Manual Ability Measure; ns = not significant

Table 4b. Results of the outcome measures of the moderate upper limb dysfunction group (n=6/13)

ICF-level	Outcome measures		Before treatment (T_0)	After treament (T_1)	Follow-up (T_2)	p-value T_1-T_0	p-value T_2-T_1
FUNCTION	AROM	**AROM Shoulder anteflexion (°)**	115.00	141.00	97.60	**p < 0.05**	ns
		AROM Shoulder anteflexion 10" (°)	106.00	136.00	94.50	**p < 0.05**	ns p = (0.05-0.1)
		AROM Shoulder abduction (°)	105.00	111.00	78.20	ns	ns
		AROM Shoulder abduction 10" (°)	103.00	94.00	76.30	ns	ns
	VAS	**Perceived fatigue (VAS)**	3.05	1.35	0.30	**p < 0.05**	ns
		Perceived strength (VAS)	3.70	7.60	7.55	ns	ns
	Strength	**MI**	76.00	76.00	80.50	ns	ns
		JAMAR (kg)	13.22	16.72	14.80	**p < 0.05**	ns p = (0.05-0.1)
ACTIVITY	Capacity	**WMFT time (s)**	2.09	1.49	1.48	**p < 0.05**	ns
		WMFT FMS	4.50	5.00	5.00	ns	ns
	Perceived performance	**ABILHAND**	-0.12	0.82	0.14	ns	ns
		MAM	51.50	50.50	46.75	ns	ns

Used abbreviations: ICF = International Classification of Functioning, disability and health; AROM = Active Range of Motion; VAS = Visual Analogue Scale; MI = Motricity Index; kg = kilogram; s = seconds; WMFT = Wolf Motor Function Test; FMS = Functional Measure Scale; MAM-36 = Manual Ability Measure; ns = not significant

Table 4c. Results of the outcome measures of the severe upper limb dysfunction group (n=4/13)

ICF-level	Outcome measures		Before treatment (T_0)	After treatment (T_1)	Follow-up (T_2)	p-value T_1-T_0	p-value T_2-T_1
FUNCTION	AROM	**AROM Shoulder anteflexion (°)**	70.50	98.00	106.00	ns p = (0.05-0.1)	ns
		AROM Shoulder anteflexion 10" (°)	55.00	91.00	84.80	ns p = (0.05-0.1)	ns
		AROM Shoulder abduction (°)	64.00	76.50	67.10	ns	ns
		AROM Shoulder abduction 10" (°)	50.00	67.00	59.45	ns	ns
	VAS	**Perceived fatigue (VAS)**	4.40	1.70	3.40	ns	ns
		Perceived strength (VAS)	3.45	6.50	3.90	ns	ns
	Strength	**MI**	63.00	73.50	71.00	ns	ns
		JAMAR (kg)	7.35	10.20	9.60	ns	ns
ACTIVITY	Capacity	**WMFT time (s)**	5.35	2.29	2.14	ns	ns
		WMFT FMS	3.38	4.00	4.50	ns p = (0.05-0.1)	ns
	Perceived performance	**ABILHAND**	-0.96	-0.75	-0.83	ns	ns
		MAM	47.25	48.75	47.00	ns	ns

Used abbreviations: ICF = International Classification of Functioning of disability and health; AROM = Active Range of Motion; VAS = Visual Analogue Scale; MI = Motricity Index; kg = kilogram; s = seconds; WMFT = Wolf Motor Function Test; FMS = Functional Measure Scale; MAM-36 = Manual Ability Measure; ns = not signicant

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