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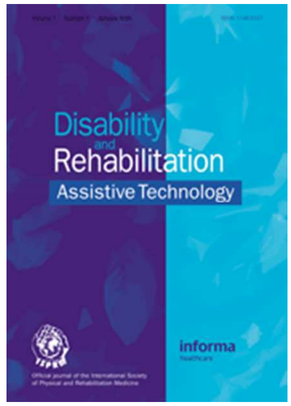

The impact of robot-mediated adaptive I-TRAVLE training on impaired upper limb function in chronic stroke and Multiple Sclerosis

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ABSTRACT

Purpose: The current study aimed to investigate proof-of-concept efficacy of an individualized, robot-mediated training regime for people with MS (pwMS) and stroke patients.

Method: 13 pwMS and 14 chronic stroke patients performed 36 (stroke) or 40 (pwMS) training sessions with the I-TRAVLE system. Evaluation of upper limb function was performed at baseline, after training and at 3 months follow-up. Clinical outcome measures consisted of active range of motion, Motricity Index, Jamar handgrip strength, perceived fatigue and strength, Wolf Motor Function Test (WFMT) and ABILHAND. Robot-generated outcome measures consisted of movement velocity, range of motion and actual covered compared to straight-line distance.

Results: ~~Upper limb function at baseline was more impaired in stroke patients than in pwMS.~~ In pwMS, significant improvements were found after training in active shoulder range of motion, handgrip strength, perceived strength and WMFT activities. No significant change in clinical outcome was found in stroke patients, except for perceived strength. Significant improvement in speed and movement duration was found after training in both groups. At follow-up, clinical outcome deteriorated in pwMS and was maintained in stroke patients.

Conclusions: Robot-mediated training resulted in improved movement coordination in both groups, as well as clinical improvement in pwMS. Absence of functional improvements in stroke patients may relate to severe upper limb dysfunction at baseline.

INTRODUCTION

People with a neurological disease such as stroke [1,2] or Multiple Sclerosis (MS) [3,4] may experience upper limb dysfunction. Unilateral motor deficit leads to chronic upper extremity impairment in 40% of stroke patients [5-7] while half the people with MS (pwMS) report to have unilateral or bilateral upper limb dysfunction, even in early stage of the disease [3,8-10]. Muscle weakness, spasticity, loss of coordination and sensory disorders of the upper limbs may occur in both pwMS and stroke patients [3,11]. An adequate upper limb function is crucial to independently perform activities of daily living (ADL) such as eating, self-care, typing, carrying and manipulating objects [12]. Consequently, upper limb dysfunction may have a major impact on patients' quality of life and their level of independence [9,13].

Reviews and practical guidelines [14-16] for upper limb rehabilitation in stroke have concluded that therapy should be applied as intense as possible and be available as out-patient training modality given the reduction of upper limb capacity after discharge from specialized centres [1,14]. Further improvement of upper function in stroke patients can be obtained by additional motor training and variability in training content [17-19]. Recently, more attention is directed towards robot-assisted training since it allows higher intensity, task-oriented and autonomous training. Evidence showed that robot-assisted therapy can improve arm-hand performance in chronic stroke patients and is increasingly considered to be as effective compared to conventional comparison treatment [20,21].

Rehabilitation research focusing on the upper limb function in MS is limited compared to research performed in other neurological diseases such as stroke [16]. Recent reviews concluded that different type of upper limb rehabilitation strategies can improve upper limb function in pwMS [22,23]. However, it is still not clear whether (robot-mediated) upper limb training is successful in pwMS to the same extent as stroke patients, due to progressive neurodegeneration and presence of motor fatigue potentially interfering with feasible training intensity [24,25]. As in stroke, new training technologies, focusing on robotic and/or sensor-based technology, are being developed to improve upper limb movement in pwMS and indications for improvement were found in previous studies [26-28]. However, previous studies mainly included pwMS with relatively mild disability and treatment options with regard to independent training for patients with marked to severe arm dysfunction are lacking.

To increase therapy compliance, games can be implemented in training approaches. A recent review of Taylor et al. (2014) in MS showed that serious games in a virtual learning environment have the advantage that patients can experience success during training, increasing motivation for intensive and long-term active motor training, and allow for independent training as well [29]. In our previous pilot RCT investigating the feasibility and effectiveness of 6 weeks of additional, robot-mediated, I-TRAVLE training for the upper limb in MS, no significant change on body functions and structures and activity level of the ICF could be demonstrated despite improved motor coordination [30]. However, assessment might not have been comprehensive enough, while a training intensity of 30 minutes daily might have been too long and exercise progression not sufficient enough. During the pilot RCT, an initial version of the I-TRAVLE system allowed patients to train upper limb function by means of basic motor function exercises and serious games but adapting training difficulty was not applied in a systematic way.

To improve the constant provision of an optimal training load, we developed a software architecture that made adaptations to the continuously changing and possibly improving capabilities of the subjects using it, including training intensity and difficulties of the tasks [31]. Therefore, system adaptivity was integrated in the upgraded version of the I-TRAVLE system that was used for the present intervention study. An individualized, autonomous and intensive training regime was applied, featuring the updated I-TRAVLE system. The general aim of the current trial was to obtain proof of concept evidence on the efficacy of additional and individualized, adaptive robot-mediated I-TRAVLE training to improve upper limb function and skill performance in pwMS and chronic stroke patients with low to moderate proximal muscle strength or limited active range of motion of the arm.

METHODS

Participants

PwMS and chronic stroke patients were recruited in the Rehabilitation & MS Centre in Overpelt (Belgium) and the Adelante Centre of Expertise in Rehabilitation and Audiology in Hoensbroek (the Netherlands), based on historical data files. Inclusion criteria were: 18 years of age or older, diagnosed with MS or stroke, >3 months relapse-free or >6 months post-stroke and a fair cognitive level to understand the serious games. A minimum score of 14 and maximum 25 (out of 33) on the shoulder/arm item of the Motricity Index (MI) was required, or a minimum active shoulder anteflexion of 30 degrees and maximum active range of motion of 120 degrees shoulder joint anteflexion which can actively be maintained for 10 seconds. Subjects with severe spasticity of the arm, tremor, severe visual impairment, neglect, apraxia and/ or aphasia were excluded. Ethical approval was obtained from the Medical Ethical Committee of the University Hospitals Leuven (B), the Medical Ethical Committee of Hasselt University (B), the ethical committee of the Rehabilitation and MS centre of Overpelt (B) and the Medical Ethical Committee of academic hospital/ University Maastricht (NL). Written informed consent was obtained from all included patients. The trial has been registered in the Clinical Trials GOV register (code: NCT01918748).

Experimental design and procedure

In this prospective cohort study, pwMS attended 5 training sessions per 2 weeks, alternating 3 and 2 training sessions every other week, during 8 consecutive weeks whereas chronic stroke patients attended 3 training sessions per week during 6 consecutive weeks. Belgian subjects were either hospitalized at the rehabilitation centre or visiting the centre ≥three times per week on an ambulant basis for study purpose. Dutch subjects visited the hospital 3 times per week to attend the robot-mediated I-TRAVLE training sessions. Each training session consisted of 2 times 30 minutes I-TRAVLE robot-mediated training, interspaced by at least half an hour to avoid fatigue and overuse of the affected arm. The first 30 minutes of each session, training was supervised and the second 30 minutes training occurred autonomous. Subsequently, pwMS completed 20 hours of I-TRAVLE robot-mediated training and chronic stroke patients 18 hours. The difference in training intensity was determined based on previous research within both populations. Six weeks of training is commonly applied and effective in stroke patients [32] whereas 8 weeks of training is often applied in MS [26-28,30]. In pwMS with overall high disability, a more extensive but more time-spread training program was required taking into account the occurrence of activity-related motor fatigue and higher risk for training overload [24].

In chronic stroke patients and unilateral affected pwMS, the impaired arm was trained. In pwMS with bilateral arm dysfunction, the most affected arm according to the MI, was chosen. If both arms were equally affected, the preferred arm was trained. Training focused on motor control, strength, endurance and coordination of the arm.

Eligible participants were contacted by an occupational therapist of the rehabilitation centres in Belgium and the Netherlands and were informed about the I-TRAVLE intervention study. If interested, they received an information letter about the aim and the content of the study, as well as an informed consent form (and 'declaration of willingness' form for the Dutch participants).

Evaluation of upper limb function occurred at baseline (T_0), once after I-TRAVLE training (T_1) and at three months of follow-up (T_2). Each time prior to testing, participants were questioned on the occurrence of any serious event over the previous two weeks (like flu, falls etc.) that might potentially influence the results. Clinical outcome measures were administered in the same order for subsequent measures in each patient but order varied between patients to avoid bias related to potential fatigue. The same therapists (L.K., M.L. and S.S.) executed both the testing and the training. To optimize inter-rater reliability between testers in different centres, a familiarization session with regard to the selected outcome measures was organized before the start of the study while a detailed instruction manual was available.

Robot-mediated intervention

The Haptic Master (HM) served as a hardware interface (MOOG, the Netherlands) for the I-TRAVLE training (Figure 1). By means of a ~~n ADL~~ gimbal (MOOG, the Netherlands) to fixate the hand and offer support throughout movements of the upper limb during games based on ADL, the HM can be controlled and the patient can move in the virtual learning environment by means of an avatar that is shown on the screen. I-TRAVLE is the acronym for Individualized, Technology-supported and Robot-Assisted Virtual Learning Environments (Interreg IV "I-TRAVLE" IVA VLANED 1.58; see www.i-travle.eu). To improve execution of functional movements of the arm and hand in ADL, specific skill components underlying these movements are trained [33]. A selection of basic motor function exercises as well as serious games, all inspired by the ADL items of the Motor Activity Log, have been implemented in the I-TRAVLE system [34]. Basic motor function exercises are skill components of arm movement that can be trained separately, such as reaching, lifting, transporting, rubbing, pushing and pulling (Figure 2). In the serious games, several skill components are combined. For instance, figure 3 presents the 'chicken and eggs'-game, which purpose is to collect as many eggs as possible and push or pull the foxes away. This specific game requires lifting, transporting, pushing and pulling of the arm.

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Through the therapist interface, the therapist can determine settings and values of parameters to personalize the exercises according to the capabilities of the patients, thus allowing to train on suitable levels of difficulty and with appropriate haptic support. The therapist interface provides the therapists and researchers a view on the logged data of the subject's training to monitor progress, whereas the patients get feedback on their performance in their user interfaces. The patient interface allows autonomous training, without supervision of a therapist, by providing access to exercises that are unlocked by the therapist. By determining the level of difficulty (which is based on a combination of components such as required movement amplitude, the extent of visual, auditory and haptic feedback (support *versus* resistance), number of distractors and training volume), training can be adapted to a subject's individual capacity and needs. The Haptic Master can provide gravity compensation at the hand, by means of an active positioning procedure {Bastiaens, 2011 #1830}, and also provide assistive/ resistive forces toward the target. Furthermore, the current I-TRAVLE system applies a semi-automatic approach of adaptivity which means that the system suggests the level of difficulty, based on changes in movement performance parameters detected by the system during the previous 2 training sessions, but the suggestions can be confirmed or refused by a human user [24,31].

At the beginning of each training session, the individual workspace of the subject in the virtual learning environment is defined. Subsequently, all basic motor function exercises and serious games are scaled to this three-dimensional workspace. A standardized starting position of the body is required, i.e. being seated upright in a chair or wheelchair with back-support, 45° of elbow flexion at 0° shoulder anteflexion, whereas the hand is held at a height of approximately 50% between shoulder and knee position [35].

Descriptive and clinical outcome measures

At baseline, the Neurological Fatigue Index for pwMS (NFI-MS) and stroke patients (NFI-stroke) was administered to document fatigue, the Modified Ashworth Scale (MAS) was used to assess patient's level of spasticity and the Symbol Digit Modalities Test (SDMT) to assess cognitive function. Clinical outcome measures at different ICF levels were selected. On body functions and structures level, the Motricity Index (MI) [36], active maximum and 10" sustained shoulder range of motion (ROM) by means of the mini digital protractor inclinometer and Jamar handgrip strength [37] were performed. The Wolf Motor Function Test (WFMT) [38] was used as a capacity measure on activity level and perceived everyday performance of the impaired arm was measured by the ABILHAND [39]. Perceived fatigue and strength were assessed by means of a Visual Analogue Scale (VAS) at baseline, after training and at follow-up.

Robot-generated outcome measures

After the first and last week of training, subjects performed an evaluation module, implemented in the I-TRAVLE system. Active range of arm movement was determined in six directions i.e. forward, backward, upward, downward, lateral and medial. For the skill components transporting (lateral and medial directions), reaching (forward and backward directions) and lifting (upward and downward directions), movement velocity and hand path ratio were measured. The system automatically stores movement duration, shortest distance between two targets and real distance covered, allowing to determine the above mentioned parameters. Movement velocity (m/s) is the actual covered distance divided by movement duration. Movement quality in terms of hand path ratio (HPR) is the actual covered distance divided by the straight-line distance between the starting point and target. Performance of three skill components was repeated 3 times and subsequently mean values were used for statistical analysis.

Statistical analysis

Because of the small sample sizes and skewed distribution of data, non-parametric statistics were used for the analyses. Median values and interquartile range between percentile 25 and 75 were calculated. The Mann-Whitney U test and Chi² were used to compare patient groups at baseline. Within group comparisons over time were conducted using the Friedman test and Wilcoxon signed rank test for clinical (pre, post, follow-up) and robot-generated (pre, post) outcome measures. As to multiple comparison conditions, a Bonferroni approach was applied to correct for spurious false positive findings. For the robot-generated outcome measures, data were missing of 2 pwMS, so data of 11 pwMS were used for this analysis. The statistical SAS® for Windows package (SAS institute, Cary, NC, USA) was used for all analyses. Statistical significance was set at $p<.05$.

RESULTS

Participants

Thirteen pwMS (age, range 22-66) and 14 chronic stroke patients (age, range 38-74) completed the training (Figure 4). Participants' demographic characteristics are presented in table 1. In most pwMS (10/13), the most impaired arm was used for training. No adverse effects related to upper limb function were reported during training.

PwMS experienced significantly more and severe physical and general fatigue ($p<.001$) at baseline compared to chronic stroke patients, based on the NFI and VAS of perceived fatigue. Furthermore, median score on the SDMT was lower in stroke patients compared to pwMS (Table 1).

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Group comparison

At baseline, both groups differed significantly on active maximum and sustained shoulder anteflexion ROM, the total score of the MI, and the functional ability and time needed to perform activities of the WMFT (p <0.05). Both patient groups presented moderate to severe upper limb dysfunction at baseline but chronic stroke patients had worse upper limb function compared to pwMS (Table 2). Perceived performance of upper limb function did not differ between groups.

Clinical outcome measures

In pwMS, significant improvement was found in active maximum and sustained shoulder anteflexion ROM, handgrip strength and perceived strength at body functions and structures level (Table 2). Furthermore, functional ability and time needed to perform activities of the WMFT improved significantly after training. No change in perceived performance measures was found. At 3 months of follow-up, most outcome measures deteriorated to baseline level, except for perceived strength and fatigue and the WMFT scores.

*** insert Table 2 about here ***

In chronic stroke patients, an increase in handgrip strength, MI scores and perceived strength was found after training and maintained at follow-up (Table 2). Time needed to perform the activities of the WMFT test decreased over time, indicating faster movement performance. However, these changes were not statistically significant, except for perceived arm strength.

Robot-generated outcome measures

PwMS showed a significant improvement in movement velocity during transporting, while movement velocity improved significantly for all movement directions in chronic stroke patients (Table 3). Furthermore, stroke patients were able to move the affected arm forward, upward and sideward significantly faster after training.

*** insert Table 3 about here ***

DISCUSSION

The objective of this proof of concept study was to investigate the effect of an additional, individualized and robot-mediated training regime featuring the I-TRAVLE system on upper limb function in pwMS and chronic stroke patients. Improvement of upper limb function by means of both objective and subjective outcome measures could be demonstrated, however, clinical training effects were only significant in pwMS.

People with MS

In MS, significant clinical changes were found on body functions and structures level as well as activity level of the ICF model. Significant improvement of aROM of the shoulder was found which could be expected since I-TRAVLE training requires a large number of repetitions of anteflexion movements. Most pwMS (10/13) were able to lift the arm higher and stabilize this position for a longer time after training, allowing arm movements in daily life such as cleaning the windows or placing a cup on a shelf. Jamar handgrip strength and perceived strength improved significantly as well. Evidence indicates handgrip strength can be an important predictor for perceived performance of ADL [4,40]. It is conceivable that subjects unconsciously squeeze th~~d~~e gimbal which supports the hand during all basic motor function exercises and serious games, thereby training handgrip as well. PwMS in our study also improved on activity level with better performance on the WMFT, similar to Mark et al (2008) who reported on effects of constraint induced movement therapy (CIMT) [41]. It is difficult to directly compare our results to previous studies on robot-mediated upper limb rehabilitation in MS given that other outcome measures have been used. Gijbels et al (2011) did not find improvement in handgrip and the MI but demonstrated significant changes on the Nine Hole Peg Test (NHPT) and TEMPA (Test d'Evaluation de la performance des Membres Supérieurs des Personnes Agées) after 8 weeks of upper limb training with the Armeo Spring exoskeleton [28]. In three more studies using a two-dimensional end-effector robot, the NHPT [42] or Action Research Arm test (ARAT) [43,44] which assess fine motor function and dexterity was used, revealing a positive impact of robot training [26,27,45].

This is one of the few studies in MS on robot-mediated training that included a measure on perceived upper limb performance of daily life activities. Unfortunately, no improvements over time were found in pwMS despite our objective test results as well as the spontaneous verbal reports by patients on improved daily life activities as improved upper limb stability during cooking. This might be explained by the main focus of the robot-mediated I-TRAVLE training on proximal upper limb function without practicing hand/manipulative movements or bilateral upper limb function during training. In contrast, the items of the self-reported ABILHAND questionnaire most often require hand capacity during (complex) bilateral tasks. Future technological developments should include training of hand function. In support of treatment potential in MS, it has been recently shown that improved hand function is achievable, and perceived by pwMS after task-oriented training programmes [46]. Improvements are mirrored by emerging evidence in pwMS of brain plasticity and preservation [46,47].

Unfortunately, 12 weeks of follow-up after I-TRAVLE training showed that benefits were not retained. This is in support of Gijbels et al (2011) who included a follow-up period of 2 months and reported a decrease on activity measures as well [28]. Both studies indicate that weekly continued training is essential. An independent exercise programme in a home environment or tele-rehabilitation would be useful to continue training and maintain functionality [48].

Chronic stroke patients

No significant improvement on clinical outcome measures was found in chronic stroke patients although raw data suggested they improved on maximal anteflexion, MI and handgrip strength, felt subjectively stronger in the arm and needed less time to perform the activities of the WMFT. Furthermore, chronic stroke patients reported, non-significantly, improved perceived performance after training as measured with the ABILHAND questionnaire. The lack of significant clinical training effects was surprising given the above-mentioned significant effects in pwMS and those documented in previous trials on robot-mediated training in stroke. Different factors may apply. Upper limb function at baseline was impaired in both MS and stroke patients, but clearly worse in chronic stroke patients. It may be more difficult to reach functional improvements in chronic stroke patients with severe arm dysfunction. Effects of robot-mediated training can depend on recovery stage. Results on the effects of training in the chronic phase after stroke are inconsistent [20,49-52]. Mehrholtz et al. (2012) included electromechanical training besides robot-assisted training and reviewed 19 trials of which 7 included chronic stroke patients [53]. Except for upper limb strength, both upper limb function and ADL improved in acute and sub-acute stroke patients but not in most patients in the chronic phase after stroke. One could also hypothesize that training volume was inadequate to reach impact. Perhaps, 6 weeks of training is not long enough after all. In the multi-centre RCT of Lo et al (2010), no significant improvement in long-term upper limb function in chronic stroke patients with moderate to severe upper limb dysfunction was found after 12 weeks of robot-assisted therapy but after 36 weeks, the Fugl-Meyer score and time of the WMFT significantly improved compared to usual care [54]. Unfortunately, we have not counted the number of repetitions during training. Compared to pwMS, chronic stroke patients had lower scores on the SDMT, a test for information processing speed, potentially associated less movement performance during the unsupervised 30 minutes of training.

In contrast with the lack of improvement on the clinical measures, significant improvement on robot-generated parameters was found in chronic stroke patients. Velocity and duration of arm movements during transporting, reaching and lifting improved in stroke patients. Most robotic and sensor-based systems for arm and hand function practice movements in single joints and along single movement planes, reducing motor impairment but failing to improve performance of ADL [55,56]. Training effects seem context and task-specific, and transfer to other functional activities cannot be assumed [50]. The I-TRAVLE system and HM allow patients to train 3-dimensional movements, aiming to improve ADL.

Methodological considerations

Compared to most other robot-mediated training programmes, I-TRAVLE is particularly developed based on the principles of motor learning and the system is adaptive to a subject's individual capacity and training progression. The I-TRAVLE system allows patient-tailored rehabilitation and training of proximal skill components of upper limb function which are needed for ADL. Using the HM robot, haptic feedback can be provided to either support or challenge the participants. Furthermore, a more intensive and adaptive training protocol was applied since training sessions consisted of twice 30 minutes of training instead of 1 hour continuously, taking into account the risk of motor fatigue and training overload. An individualized and autonomous approach was applied to constantly challenge participants to perform better and make progress. However, based on the results in chronic stroke patients, training intensity or duration might not been long enough. Furthermore, participants may have performed less during the unsupervised training sessions due to the absence of the motivating and undivided attention of a therapist. Future research to assess and evaluate the number of repetitions to determine training intensity similar as in current trials on task-oriented training [57,58] is needed. Finally, one can comment on the uncontrolled study design or relatively small sample size. However, we opted for a proof-of-concept phase II trial, focusing on efficacy, given lessons learned of negative results in a previous study with a prototype of the I-TRAVLE system [30]. Next steps in pwMS are to design studies comparing different treatment modalities and intensities for different disability levels in order to define optimal dosage and responders.

CONCLUSION

This cohort study demonstrated beneficial effects on upper limb improvement after 8-weeks of robot-mediated I-TRAVLE training in pwMS. Furthermore, pwMS seemed to improve more on body functions and structures and activity level in comparison with chronic stroke patients who merely improved on robot-generated outcome measures.

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DECLARATION OF INTEREST

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The authors report no conflicts of interest.

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TABLES

Table 1. Demographic characteristics of included participants (n=27).

Subject	EDSS	Type of MS	Disease duration (yrs)	Age	Gender (F/M)	Wheelchair-bound	Hand dominance	Arm trained	SDMT	NFI
MS (n=13)										
1	3.5	SP	3	38	F	No	Right	Left	46	20
2	7.5	PP	17	66	M	Yes	Left	Left	38	7
3	6.5	RP	4	22	F	Yes	Right	Left	59	28
4	7	RP	9	38	M	Yes	Right	Left	34	27
5	7	SP	28	52	F	Yes	Right	Left	41	25
6	6.5	RR	27	49	F	Yes	Right	Left	32	16
7	2.5	RR	4	55	F	No	Right	Right	25	25
8	7.5	SP	21	39	F	Yes	Right	Right	10	30
9	8	SP	30	57	M	Yes	Right	Right	14	28
10	7.5	SP	17	54	F	Yes	Left	Left	37	21
11	5	SP	6	61	F	No	Right	Right	32	23
12	6	PP	7	63	M	Yes	Right	Left	30	20
13	3	RR	31	63	F	No	Right	Right	34	27
Median	6.5		17	54					34	25
IQR	5-7.5		6-27	39-61					30-38	20-27
Stroke (n=14)										
1			4	54	M	No	Right	Left	37	13
2			9	59	M	No	Right	Left	25	15
3			2	64	M	Yes	Left	Right	6	12
4			3	74	M	Yes	Right	Right	16	3
5			1	55	M	No	Right	Left	22	14
6			5.4	64	F	No	Left	Right	37	13
7			2	74	M	No	Right	Left	29	10
8			2	60	F	No	Right	Left	22	17
9			1.6	58	M	No	Right	Left	21	24
10			2.2	72	F	No	Right	Left	22	14
11			14.5	59	F	No	Left	Right	15	17
12			14.7	64	F	No	Left	Right	31	14
13			0.7	38	F	No	Left	Right	41	10
14			1.3	56	M	No	Left	Right	37	
Median			2	59,5					23,5	14
IQR			1.7-5.1	56-64					21.2-35.5	12-15

Values reported are median and interquartile range, or number; yrs= years; F= female; M=male; SP= secondary progressive MS; RR= relapsing remitting MS; PP= primary progressive MS; RP=relapsing progressive MS; SDMT= Symbol Digit Modalities Test; NFI= Neurological Fatigue Index.

Table 2. Clinical outcome measures before and after the intervention, and at 3 months follow-up.

ICF	Outcome measures		PRE		POST		*p*-value ǂ	Follow-up		*p*-value †
PwMS (n=13)										
Function	Active Range of Motion	Maximum anteflexion (°)	110.0	[97.0-132.0]	137.0	[112.0-144.0]	<0.05	117.0	[87.2-144.0]	NS
		Sustained anteflexion (°)	102.0	[92.0-120.0]	129.0	[100.0-138.0]	<0.05	105.0	[81.9-137.0]	NS
		Maximum abduction (°)	106.0	[76.0-118.0]	108.0	[77.0-128.0]	NS	85.4	[63.9-133.0]	NS
		Sustained abduction (°)	102.0	[62.0-106.0]	88.0	[74.0-125.0]	NS	84.6	[52.0-128.0]	NS
	Strength	Motricity Index (0-100)	76.0	[70.0-83.0]	76.0	[72.0-84.0]	NS	76.0	[66.0-100.0]	NS
		Handgrip (kg)	13.2	[9.1-16.2]	14.8	[11.2-20.2]	<0.05	13.6	[11.6-18.6]	<0.05
		Perceived strength (VAS)	3.9	[3.0-4.6]	7.4	[5.1-8.6]	<0.05	7.5	[3.8-8.3]	NS
	Fatigue	Perceived fatigue (VAS)	3.6	[1.8-5.1]	1.7	[0.7-5.6]	NS	0.8	[0.3-3.7]	<0.05
Activity	Capacity	WMFT time (s)	2.4	[1.5-4.8]	1.6	[1.0-1.7]	<0.01	1.4	[1.0-2.0]	<0.05
		WMFT FA	4.0	[3.4-5.0]	5.0	[4.5-5.0]	<0.05	5.0	[4.5-5.0]	<0.05
	Perceived performance	ABILHAND	0.5	[-1.3-1.8]	0.9	[-0.6-1.8]	NS	0.1	[-1.2-1.3]	NS
Stroke (n=14)										
Function	Active Range of Motion	Maximum anteflexion (°)	70.8	[44.3-84.1]	61.3	[49.8-73.4]	NS	64.8	[51.7-85.3]	NS
		Sustained anteflexion (°)	69.3	[38.7-82.6]	57.5	[46.8-70.0]	NS	60.1	[49.0-81.3]	NS
		Maximum abduction (°)	65.4	[51.3-81.4]	62.6	[43.1-85.1]	NS	71.5	[48.4-85.1]	NS
		Sustained abduction (°)	63.7	[47.4-87.1]	58.0	[41.8-86.0]	NS	67.6	[47.3-83.7]	NS
	Strength	MI	51.5	[39.0-59.8]	55.0	[39.0-63.3]	NS	56.5	[40.3-65.5]	NS
		Handgrip (kg)	9.0	[7.8-16.5]	9.6	[7.0-15.0]	NS	13.6	[8.8-16.3]	NS
		Perceived strength (VAS)	4.6	[3.9-4.9]	5.1	[4.8-6.3]	<0.05	5.2	[4.9-5.7]	<0.05
	Fatigue	Perceived fatigue (VAS)	1.1	[0.5-3.4]	1.8	[0.0-2.5]	NS	1.1	[0.0-2.7]	NS
Activity	Capacity	WMFT time (s)	39.7	[7.8-120.0]	11.6	[5.2-120.0]	NS	9.7	[5.1-120.0]	NS
		WMFT FA	2.0	[0.0-3.0]	2.0	[0.0-3.25]	NS	2.0	[0.0-3.0]	NS
	Perceived performance	ABILHAND	0.5	[0.2-1.5]	1.3	[1.0-2.2]	NS	1.1	[0.0-1.5]	NS

Values are median and [interquartile range], ǂ =significance level between pre and post testing, † =significance level between pre and follow-up testing.
°= degrees range of motion; kg= kilogram; VAS= Visual Analogue Scale; WMFT= Wolf Motor Function Test; s= seconds; FA= Functional Ability.

Table 3. Robot-generated outcome measures before and after the intervention.

		Pre		Post		*p*-value
pwMS (n=11)						
Transporting	ROM (m)	0.55	[0.45-0.60]	0.56	[0.50-0.62]	ns
	Distance (m)	1.10	[1.02-1.20]	1.14	[1.04-1.19]	ns
	Velocity (m/s)	0.15	[0.12-0.20]	0.19	[0.17-0.27]	<0.05
	HPR	1.67	[1.61-1.84]	1.62	[1.59-1.70]	ns
	Duration (s)	8.65	[5.99-10.51]	5.44	[4.44-6.15]	<0.05
Reaching	ROM (m)	0.35	[0.21-0.40]	0.36	[0.24-0.41]	ns
	Distance (m)	0.63	[0.41-0.90]	0.84	[0.57-0.89]	ns
	Velocity (m/s)	0.11	[0.08-0.17]	0.17	[0.10-0.21]	ns
	HPR	2.30	[1.87-3.15]	2.20	[1.62-4.55]	ns
	Duration (s)	5.26	[3.52-8.23]	4.26	[3.28-7.15]	ns
Lifting	ROM (m)	0.45	[0.42-0.45]	0.45	[0.42-0.45]	ns
	Distance (m)	0.78	[0.69-0.94]	0.86	[0.69-0.90]	ns
	Velocity (m/s)	0.12	[0.10-0.13]	0.17	[0.13-0.22]	ns
	HPR	1.67	[1.50-1.85]	1.75	[1.56-1.98]	ns
	Duration (s)	7.80	[5.01-9.03]	5.29	[3.89-6.21]	<0.05
Stroke (n=14)						
Transporting	ROM (m)	0.56	[0.43-0.61]	0.49	[0.36-0.60]	ns
	Distance (m)	1.14	[1.08-1.28]	1.12	[0.84-1.48]	ns
	Velocity (m/s)	0.14	[0.08-0.19]	8.68	[6.26-11.6]	<0.05
	HPR	1.75	[1.59-3.59]	1.84	[1.65-2.59]	ns
	Duration (s)	9.38	[6.39-21.96]	7.21	[5.34-12.90]	<0.01
Reaching	ROM (m)	0.3	[0.16-0.36]	0.30	[0.21-3.36]	ns
	Distance (m)	0.95	[0.80-1.01]	0.81	[0.68-1.03]	ns
	Velocity (m/s)	0.09	[0.08-0.12]	0.16	[0.11-0.22]	<0.01
	HPR	4.07	[2.57-11.58]	2.7	[2.15-4.38]	ns
	Duration (s)	9.51	[8.48-17.81]	6.06	[4.84-17.79]	<0.05
Lifting	ROM (m)	0.43	[0.28-0.45]	0.38	[0.25-0.45]	<0.05
	Distance (m)	1.13	[0.83-1.52]	0.97	[0.7-1.38]	ns
	Velocity (m/s)	0.09	[0.07-0.12]	0.12	[0.09-0.18]	<0.05
	HPR	2.38	[2.01-5.09]	2.42	[1.68-5.16]	ns
	Duration (s)	13.15	[8.72-18.47]	8.68	[5.94-12.61]	<0.05

Values are median [IQR], significance level pre-post testing at 0.05. ROM= range of motion; HPR= hand path ratio.

FIGURES

Figure 1. General setup of the I-TRAVLE system and Haptic Master.

Figure 2. I-TRAVLE basic motor function exercise ‘lifting’ (a), ‘turning’ (b) and patient interface (c).

Figure 3. Serious game ‘chicken and egg’. The purpose of this serious game is to collect as many eggs as possible and push or pull the foxes away.

Figure 4. Study flowchart

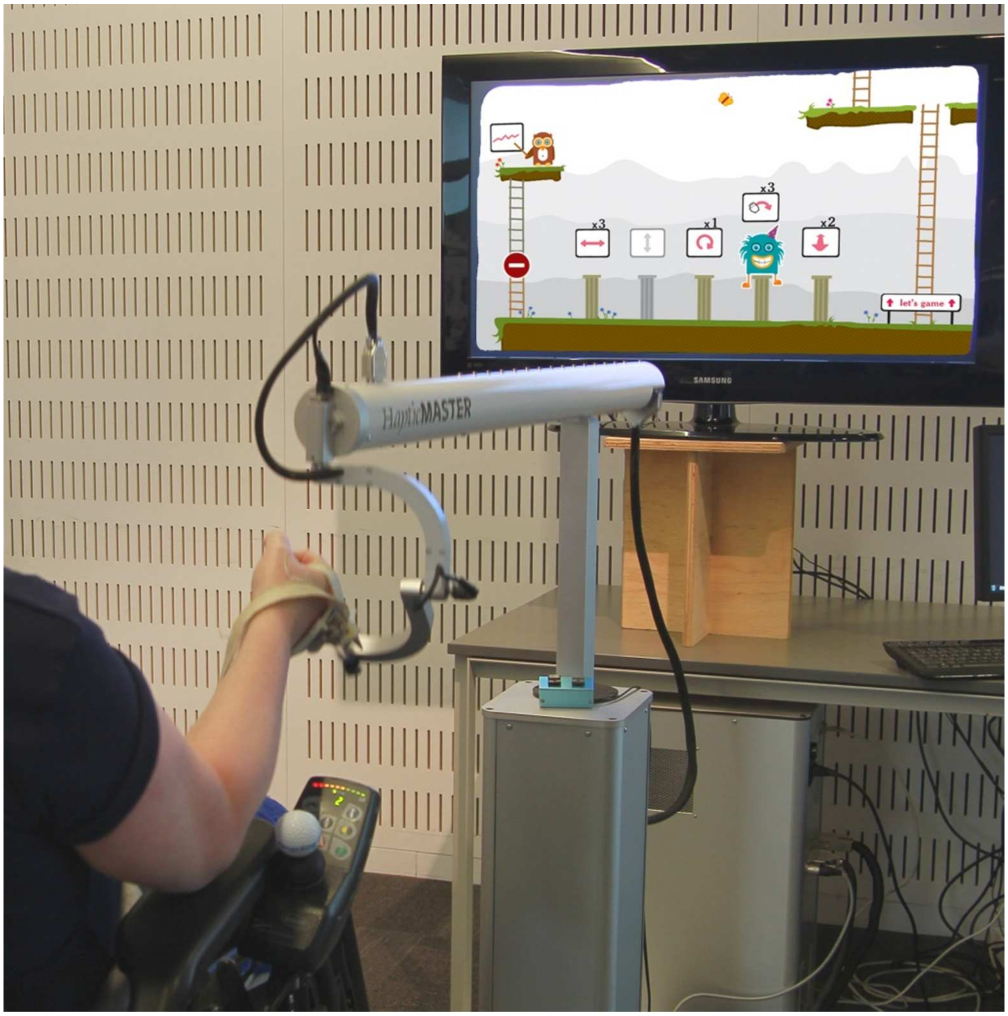

Figure 1. General setup of the I-TRAVLE system and Haptic Master.

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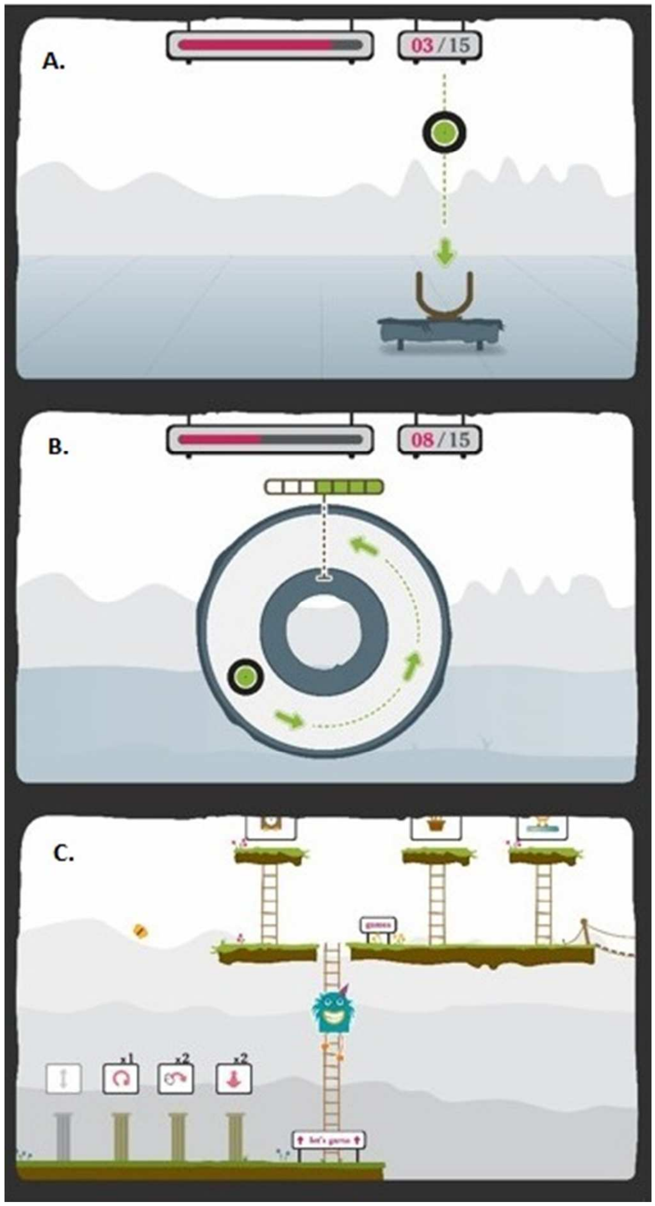

Figure 2. I-TRAVLE basic motor function exercise 'lifting' (a), 'turning' (b) and patient interface (c).

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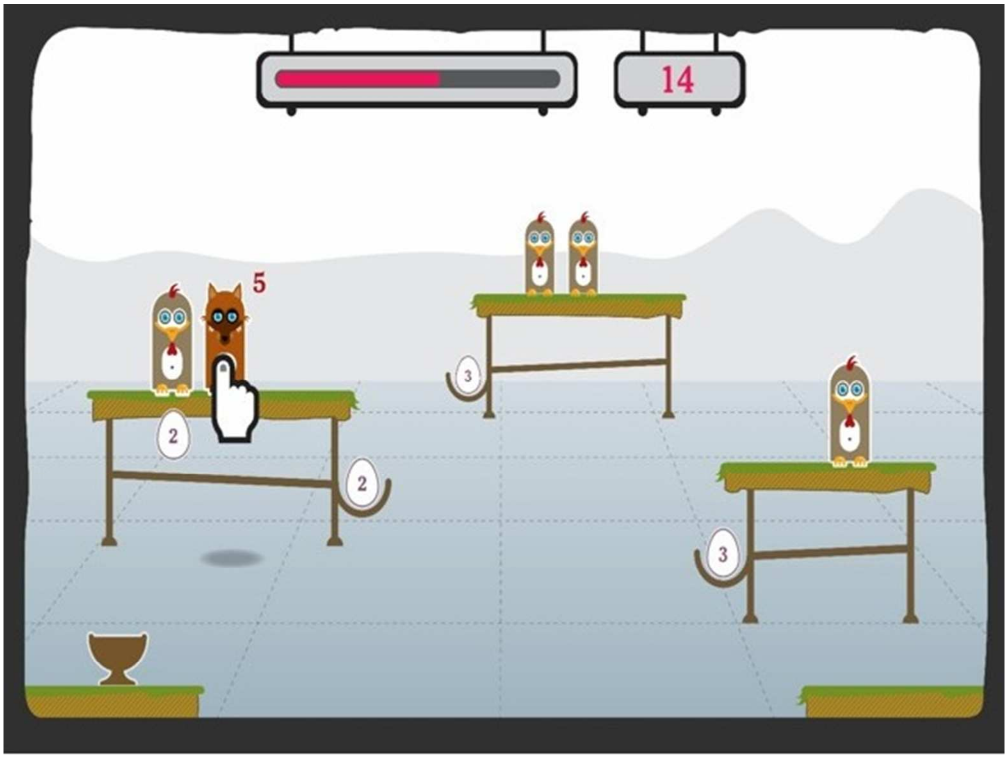
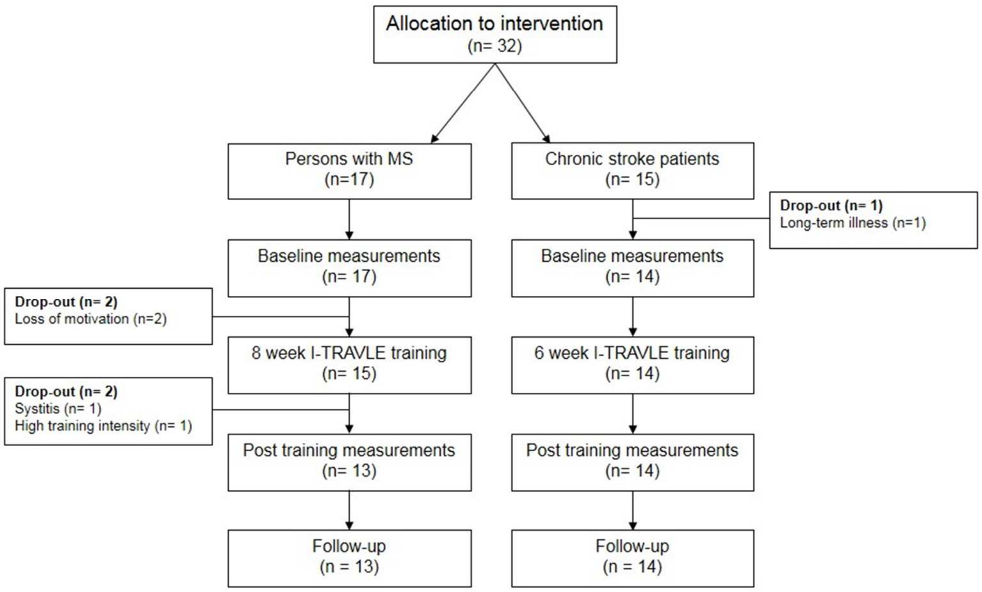


Figure 3. Serious game ‘chicken and egg’. The purpose of this serious game is to collect as many eggs as possible and push or pull the foxes away.

169x127mm (96 x 96 DPI)



247x154mm (96 x 96 DPI)

IMPLICATIONS FOR REHABILITATION

- Robot-mediated training improved strength, active range of motion and upper limb capacity in pwMS.
- Robot-mediated therapy allows for adapted training difficulty.

Dear reviewer,

We would like to thank you for this constructive feedback and the valuable comments that have certainly contributed to improve the quality and readability of the manuscript. We have tried to maximally adjust the manuscript according to the suggestions made. All additions or changes in the revised manuscript are highlighted.

An itemized response to all points raised is given below. All the suggestions and remarks are numbered and the corresponding answer is stated beneath starting with **A/**.

We hope to have given a satisfactory answer to the different comments. If there are any further questions, we are prepared to provide further information or make adaptations if requested.

Sincerely,

The authors

Reviewer 1

Minor revisions

1. Abstract: In methods there are named clinical outcome measures and robot-generated outcome measures (velocity, range of motion and distance), whereas in results first it is stated that no significant change in clinical outcome was found in SP, except for perceived strength. But then it is stated that significant improvement in speed and movement duration was found for all. A bit confusing. We suggest to separate before-after and follow-up, since e.g. in results you describe "upper limb function at baseline" and in next sentence, "...significant improvements were found in a...." - if it is improvement, was it after training or at follow-up? From second and third sentence in abstract - results cannot be clearly understood when they happened. What about follow-up? In the paper it is presented more clearly.

A/ *The abstract has been adjusted. Information regarding post-training improvement in clinical measures was formulated more clearly and follow-up data was added instead of baseline information.*

2. Methods (p. 7, line 50): "By means of an ADL gimbal (MOOG, the Netherlands) to fixate the hand..." please explain (write more clearly) "ADL gimbal".

A/ *Thank you for this comment. We removed the word "ADL" since only gross motor function of the upper limb was trained with the Haptic Master in this study. Furthermore, we explained the gimbal more clearly and replaced "ADL gimbal" with "gimbal to fixate the hand and offer support throughout movements of the upper limb during games based on activities of daily living (ADL)".*

3. In Methods and in Discussion it is written that stroke patients had 6 weeks of training, however on Figure 4 it is written 8 weeks of I-TRAVLE training for both groups.

A/ *We apologize for the confusion and corrected the error in figure 4.*

4. Methods (p. 13, line 32): "squeeze the ADL gimbal during all basic motor function", write more clearly "the ADL gimbal".

A/ *We removed "ADL" in "ADL gimbal" since activities of daily living were not trained with the Haptic Master in this study, and extended gimbal with gimbal which supports the hand during all basic motor function exercises and serious games.*