2013•2014
FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de revalidatiewetenschappen en de kinesitherapie

Masterproef

Robot-assisted therapy of the upper limbs in Multiple Sclerosis: Relationship of robot-generated with clinical outcome measures and effect of intervention

Promotor :
Prof. dr. Peter FEYS

Copromotor :
dr. Anneleen MARIS

Vicky Minten

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

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universiteit hasselt
KNOWLEDGE IN ACTION

Woord vooraf

Deze masterproef is het resultaat van het onderzoek dat ik uitgevoerd heb ter afsluiting van mijn masteropleiding ‘Revalidatiewetenschappen en Kinesitherapie in de Neurologische Revalidatie’ aan de Universiteit Hasselt.

Dit onderzoek was niet tot een goed einde gekomen zonder de steun en hulp van meerdere personen. Woorden van dank gaan uit naar deze mensen.
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Om niemand te vergeten wil ik ten slotte iedereen bedanken die mij, op welke manier dan ook, geholpen heeft bij het realiseren van deze masterproef. Hartelijk dank aan jullie allen!

Velm, 14 Augustus 2014 V.M.

Background

This research covers the domains neurorehabilitation and rehabilitation technology. Persons with Multiple Sclerosis experiencing upper extremity dysfunctions are of interest in this master thesis. Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by demyelisation and damage in white matter, cortex, deep grey matter nuclei and the spinal cord. This makes it a heterogeneous disease, with very individual patterns of symptoms being presented depending on the place of lesions. [1]

Because of these chronic inflammations, damaging axons in the central nervous system, we see a lot of functional impairments in this group of patients. Disabilities are found throughout the whole body. [2] Upper limb dysfunctions are found in at least 66% of persons with MS and impairments in manual dexterity even in 76%. [3,4] The latter was found to be an important predictor of overall activity and participation, so upper extremity impairments will have a great impact on a person's quality of life. [5] This shows the great need for attention to these problems and a need for rehabilitation programs to tackle upper extremity functional impairments. Long time, MS patients were advised not to participate in physical exercise. Recent research established proving the possible beneficial effects of participation in exercise. [6]

Nowadays, more and more research is being performed regarding upper limb function and beneficial effects of exercise training, while earlier research mostly focused on lower limb function. Kwakkel et al. indicated the importance of training duration and intensity for successful neurological rehabilitation. [7] A highly intensive, repetitive and task specific approach is needed when working with persons with MS. In this framework, robotic devices can have an important purpose, being very easy to tailor to individual needs and able to provide intensive therapy. [8] Early examples of these robotic devices for the upper extremity are the MIT-MANUS and MIME. [9] These have shown already to be effective in a population of stroke patients. [10]

The experiments included in this master thesis are embedded within the research performed at REVAL- Rehabilitation research centre of BIOMED, Hasselt University in collaboration with EDM-Hasselt University and other partners, like the Rehabilitation and MS Centre in Overpelt (RMSC). BIOMED is multidisciplinary institute in which fundamental and applied scientific research, innovation and education in the domain of life sciences is performed.

The Expertise centre of Digital Media (EDM-UHasselt) performs research in computer science (ICT). Two additional core competences are the focus of their research namely, visual computing and human-computing interaction. In this framework, staff of EDM helped with the Haptic Master device and evaluation module used in the present study. All research was performed in the Rehabilitation and MS Centre in Overpelt. This centre is known for their expertise in care, treatment and support for patients with MS and other degenerative neurological diseases.

The dataset of this project consists of data coming from 3 different experiments. All three included experiments were part of the Interreg Projects IVA-VLANED-1.14.

Interreg is European trans-boundary project collaboration between partners in Southern Netherlands and Flanders, strengthening the socio-economic structures and innovations in health care.

In this framework fit organizations like COST Action TD1006. They focus on the growing use of robotic devices in rehabilitation settings. The core objective of this organization is to develop new, efficient robot-assisted therapies, adapted to the patient's needs. Their second goal is to provide a structured and clear summary about existing and emerging therapies assisted by robots. An interdisciplinary team of leading researchers from robot engineering, clinical motor neurorehabilitation, computational neuroscience and motor neuroimaging focuses on these goals.

The first aim of this master thesis is to investigate the relationship between clinical outcome measures and robot-generated outcome measures for the upper extremity in persons with Multiple Sclerosis (PwMS). We wanted to investigate the relevance of using robotic outcome measures to assess upper limb function and performance. The robotic outcome measures were collected during specific tasks using the Haptic Master. For this first part we used data from the first 2 experiments. In these cross-sectional analyses, correlations were calculated between clinical outcome measures and robotic measured outcome measures. The first experiment was a RCT study, covering robot-supported upper limb training in a virtual learning environment, performed in 2011. This pilot randomised controlled trial was embedded in the Interreg III project "Rehabilitation Robotics" and was performed by UHasselt-REVAL, UHasselt-EDM and RMSC. The second part of the dataset was retrieved from a cross-sectional observational study, investigating motor fatigue of the shoulder muscles during repetitive robot-based training in PwMS. This experiment by Dr. Deborah Severijns (December 2012) was performed in corporation with partners of the Interreg IV Project "Rehabilitation Robotics II" resulting in the I-TRAVLE approach and system. It was an extended consortium done by PHL-REVAL, UHasselt-EDM, Tue, UM, KULeuven, RMSC, Adelante and BLIX. The second part of the present study aimed at investigating the effect of robot-assisted training using pre-post measurements. For this purpose we used data from the first and a third experiment. The third experiment consisted of an ongoing research project embedded in the Interreg IV project "Autonomous and personalized use of the I-TRAVLE concept for people with MS and stroke". Partners for this study were UHasselt-Biomed, UHasselt-EDM, RMSC and Adelante. It focussed towards personalized rehabilitation and rehabilitation at home. The intervention consisted of an 8 week during training of arm function and arm skill performance using the Haptic Master. Participants attended trainings sessions on 5 days per 2 weeks. Each training session consisted of 2 sets of 30 minutes of I-TRAVLE-assisted therapy. We performed analyses with data of the first and third experiment for this purpose.

This master thesis was performed by one person. For the third experiment that was already ongoing during master thesis 1, the student attended work meetings discussing the research protocol. The student helped collecting data for the second experiment included in this master thesis. Data was collected and inserted in an excel-file for statistical calculations. Additional statistical analyses were performed for other research projects on behalf of Prof. Dr. Feys using the included data of the present study. Data from the third ongoing study were collected by co-promotor Dr. Anneleen Maris and the therapists from the RMSC in Overpelt. Data-analyses were performed by the student, as well the academic writing of this paper.

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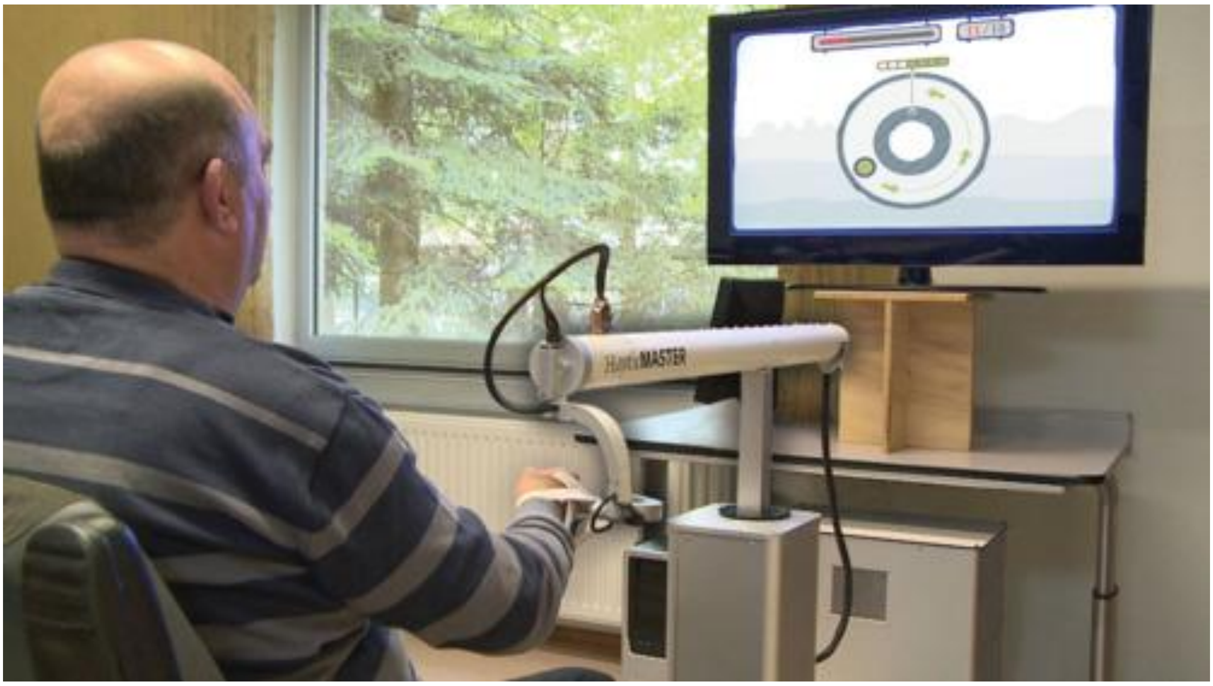

Robot-assisted therapy of the upper limbs in Multiple Sclerosis: relationship of robot-generated with clinical outcome measures and effect of intervention

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Robot-assisted therapy of the upper limbs in Multiple Sclerosis: relationship of robot-generated with clinical outcome measures and effect of intervention

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Abstract

Background: Use of robotic devices in rehabilitation is nowadays commonplace, but the clinical significance of the robot-generated outcome measures is still unknown. The first part of the present study aims to identify the relationship between clinical outcome measures and robotic outcome measures for the upper extremity in PwMS. The second part researches the effect of a training intervention with a robotic device, the Haptic Master (HM).

Methods: Data were used from 3 previous experiments in PwMS: 1) a pilot RCT researching robot-supported upper limb training in a virtual learning environment [11], 2) researched fatigue of shoulder muscles during repetitive robot-based training [12] 3) researched if robot-assisted I-TRAVLE training improves arm function. [13] The first part of the present study consists of a cross-sectional analysis including 19 PwMS, using the first two experiments. Robot-generated parameters were obtained using the evaluation software embedded in the Haptic Master. Motricity Index (MI), Brunnstrom Fugl-Meyer (BFM), Jamar handheld dynamometer, Action Research Arm Test (ARAt) and Motor Activity Log (MAL) clinical outcome measures were used. Calculations were performed using Pearson product-moment correlation coefficient. The second part consists of an effect study using data from the first and third experiment. Analyses were performed using Wilcoxon signed-rank test.

Results: Patient characteristics of the first and second experiment were significantly different. The first and third experiments were comparable at both evaluation moments.
Correlation analyses of the first experiment and pooled dataset showed little significant results. Results were mainly visible for ROM in all three directions. The second experiment showed no significant correlations at all. Effects of intervention were found for ROM and movement duration during transporting in both experiments, and for speed in the first experiment only. Reaching skill component showed only trends towards significance in the first experiment and no significant results in the third. Both experiments showed a significant change in movement duration and a trend towards significance for speed during lifting.

Conclusion: Robot-generated range of motion was found to be a fair indicator of upper limb function when compared with five clinical tests. Main effects of robot-assisted training were found in movement duration and speed.

KEYWORDS:
Multiple Sclerosis, robot, clinical, robot-generated, outcome measures, relationship, effect

Background

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system. A multifocal demyelisation and axonal damage is found in the white matter, cortex, deep grey matter nuclei and even the spinal cord. [1]

MS has a course which is characterized by multiple acute episodes of neurological impairment. These episodes are followed by partial or complete recovery, with clinical stable periods between the attacks. This phase of the disease is defined as the relapsing-remitting phase, with a mean duration of 10 years. The relapsing-remitting phase is followed by the secondary progressive phase. There is a progression of the clinical impairments visible, with or without superimposed relapses and remissions, leading to irreversible disability. Only 10-15% of MS patients present a progressive disability from the start. This type of MS is referred to as primary progressive MS. [14]

Impairments are visible in all parts of the body and are very individual for each MS-patient. Clinical impairments can be presented as sensory-motor disintegration, motor impairments, problems with postural balance, intention tremor, ataxia and impaired motor coordination. A functional relevant cerebellar deficit, e.g. ataxia and tremor, is found in about 30% of the MS population.[15] A study performed on 205 persons with MS (PwMS) found more than 50% of the subjects reported impairment or restriction in upper limb functioning. The highest prevalence of upper limb dysfunction was found in the group with the progressive type. [16] 'Goodkin et al' found at least 66% of persons with MS presenting upper limb dysfunction; with disability of manual dexterity found in 76% by Johansson et al. [3,4] These functional limitations have a great impact on individual's daily life. [2] Manual dexterity was found to be an important predictor of overall activity and participation within the community by Kierkegaard et al. These upper limb dysfunctions lead to reduced ability to perform ADL activities, which results in a decreased independence and quality of life. [5] This proves the importance of paying attention to upper limb function in PwMS by clinicians and researchers. [17]

For a long time, patients with Multiple Sclerosis were discouraged to participate in physical exercise, believing this may increase risk of relapses. Existing research has proven the importance and beneficial effects for this population to engage in physical activity. [6]

The effectiveness of multidisciplinary rehabilitation in MS is supported in a recently updated systematic review. Both inpatient and ambulatory settings showed effective improvements in activity and participation. [18] Exercise programmes using active and passive training showed positive results on muscle power, exercise tolerance and mobility related activities.[19] Neurophysiological-based physiotherapy or a combined training (physiotherapy with aerobic graining) showed significant improvements in impairment and fatigue. [20] Other interventions which proved to be effective in patients with MS are among others: hydrotherapy, cooling devices, low frequency magnetic field, TENS, neurorehabilitation and a many more. [19] Although the positive influence reported on exercise, little research focuses on the effects on upper limb function specifically. They report beneficial effects on fitness and quality of life but not on aspects like muscle strength, endurance, range of motion.

According to Kwakkel et al. training duration and intensity of exercise programs are considerate key components for a successful neurological rehabilitation. In this framework, robotic devices can serve their purpose. They can be used for a controlled, repetitive, intensive and motivating feedback-guided rehabilitation program.[10] Robotics may also be very appropriate because of the high inter-individual variability making them able to adapt the very individual pattern of symptoms, often seen in PwMS. [15] Worldwide use and presence of robotic devices is nowadays becoming commonplace. What started with a proof-of-concept testing in the 1990's, is now getting widespread acceptance among many researchers and clinicians. These devices are used in the treatment of both upper and lower extremity impairments. They do not only serve the purpose of training devices, because they have precise instruments measuring a wide variety of variables like forces and positions. [21] These properties make them also usable for diagnose and assessment of motor impairments. They are able to accurately measure and track the patient's impairments throughout the rehabilitation period. Clinical scales are subjective and often suffer from poor interrater reliability. Robotic devices measure continuous variables which makes them possibly a more subjective measurement tool. [21]
There are 2 clear types of robotic devices, namely an exoskeleton and an end-effector. Early examples of robot devices used in rehabilitation include the MIT-MANUS and MIME, both end-effectors. [9]

One of the first multicentre RCT studies about rehabilitation robotics was performed using the MIT-Manus in a population of stroke patients. Results showed that robot therapy was effective, likely because of the great amount of repetitions. The effects were equivalent to that of a high intensity training program and bigger than the standard training program. [10]
Robotic devices can be used together with virtual realities and environments in which the patient can interact. These environments are a motivation to modulate the reorganisation of the brain. This can be achieved by a combination of visual, somatosensory (haptic) and auditory feedback. [22] The combination of these feedback systems gives a more realistic interaction with (virtual) objects and targets. Despite all the advantages, these systems use complex technologies. This makes for the limited range in available robotic devices. [22]
Additionally, research about the effect of these technologies are still very limited, especially in patients with MS. we found research mostly done on patients after stroke.
The goals of the present study are to investigate (a) the relationship between clinical outcome measures and robotic measured outcome measures for the upper extremity in persons with MS and (b) in a second part the effect of robotic therapies on clinical outcome measures.

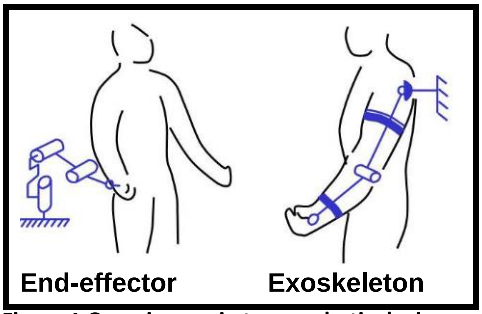


Figure 1 Overview main types robotic devices

Methods

Participants

All participants were recruited from the Rehabilitation and MS center in Overpelt, experiencing functional deficits of the upper extremity as a result of MS. These participants consisted of 3 groups each participating in a different experiment within a framework of 3 years. All subjects gave informed consent. Inclusion and exclusion criteria of all three experiments were similar.

The first experiment included 17 PwMS diagnosed according to the McDonald criteria. The Motricity Index was used to determine upper limb weakness, scoring <85. Exclusion criteria were: 1) (nearly) total paralysis of the upper extremity, 2) visual or mental dysfunctions interfering with task execution, 3) occurrence a relapse in the last month before study onset and 4) receiving relapse-related glucocorticoid treatment. The second experiment included 16 PwMS and 16 healthy subjects. Inclusion criteria for the third study were similar to those of the first two: 1) age ≥ 18, 2) clinically diagnosed with MS at entry in the study, 3) latestrelapse more than 3 months ago, 4) having completed their active clinical rehabilitation program, 5) hemiparesis, 6) fair cognitive level, 7) able to understand the questionnaires and measurement instructions, 8) able to read and understand Dutch. Exclusion criteria were: 1) severe spasticity of the arm (MAS elbow and wrist each ≥3), 2) severe visual impairment and/or severe cognitive impairment which may interfere with the execution of the arm-hand tasks or the measurements, 3) severe neglect in the near extra personal space (established by the letter cancellation test and Bell's test), 4) severe apraxia and 5) no informed consent. A clinically relevant improvement in arm-hand use in persons with MS is considered to be present when exceeding 10% of baseline values compared to post-intervention values. Use of the most affected arm was measured using average number of accelerometer-based activity counts as primary outcome measure. Given a mean difference of at least 10% between baseline and post-measurements, an expected standard deviation in both pre-training and post-training data of 12%, a 2-tailed test for repeated-measures, an alpha of .05, a power of .80 and a loss to follow-up of 10% gave use a sample size of at least 15 participants needed to be included in the study. Participants were measured on multiple occasions throughout the 8 week training protocol. Baseline clinical measurements were performed 3 times prior to starting the intervention. Due to the possibility of unexpected relapses, these baseline measurements were interspaced by 1 week to obtain information about baseline stability. After the 8 weeks, training measurements were retrieved directly post-training and 12 weeks post-training. The training period consisted of 6 week of I-TRAVLE assisted practice.

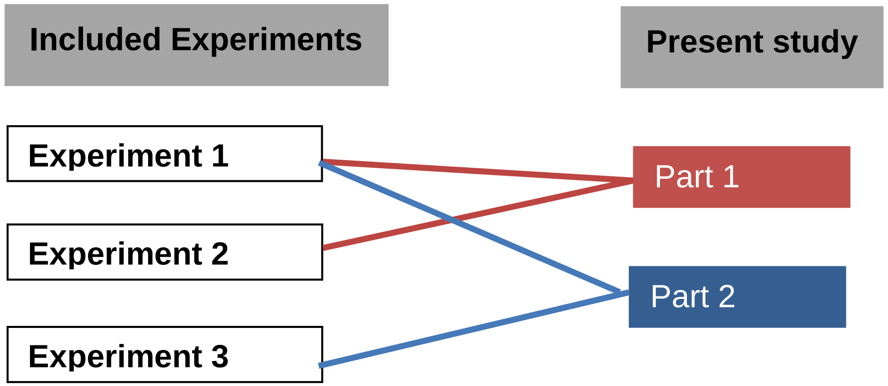
Experimental design and procedure

Figure 2 presents an overview of the different experiments included and post-hoc statistical analyses performed on these datasets. The present study consists of 2 parts each using different experiments for statistical analyses. Three experiments were included in which specific tasks were performed using the Haptic Master. The first experiment was a pilot randomized controlled trial study on robot-supported upper limb training in a virtual learning environment conducted on 17 PwMS. For the first aim of the present study we analysed outcome measures coming from 9 participants included in experiment 1. The second experiment was a cross-sectional study investigating fatigue of shoulder muscles during repetitive robot-based training in 16 PwMS. Only 10 participants were used for analyses during the present study. The third experiment included 11PwMS performing an I-TRAVLE-based training of arm function and arm skill performance. This experiment was used to cover the second part of the present study. Only matching outcome measures were retrieved from each experiment to perform analyses.

Correlations between clinical and robot-measured outcome measures were performed on the first 2 experiments. These analyses were performed for each experiment separately and on the pooled dataset covering the subjects of both experiments. Clinical outcome measures used in these calculations were: 1) Motricity Index, 2) Jamar Handheld Dynamometer, 3) Brunnstrom Fugl-Meyer, 4) Action Research Arm test and 5) Motor Activity Log. Four robot-measured outcome measures were used: 1) Range of Motion, 2) Time of Movement (movement duration), 3) speed of movements and 4) hand-path ratio.

The effect of intervention was calculated using experiment 1 and 3. For this part, each experiment was analysed separately. Calculations of change were primarily performed on the robot-generated outcome measures. These were similar to those used in the first part of this study.

Additionally, changes in clinical outcome measures were calculated and compared to changes in robot-generated outcome measures. The aim was to investigate the hypotheses that: robotic devices present outcome measures which are more objective and sensitive to changes of upper limb function in persons with MS compared to the standard and widely used clinical tests. Retrieval of clinical outcome measures of the third experiment was ongoing during the process of writing the present study. When available in time, these will also be included in the analyses.



	Part 1			Part 2	
	Experiment 1 n=9	***Experiment 2 n=10***	***Pooled n=19 (Experiment 1+2)***	***Experiment 1 n=9***	***Experiment 3 n=11***

Clinical outcome measures	- Motricity Index (MI)
	- Jamar Handheld Dynamometer
	- Brunnstrom Fugl-Meyer (BFM)
	- Action Research Arm test (ARAt)
	- Motor Activity Log
	  o Amount Of Use (AOU)
	  o Quality Of Movement (QOM)
	  o Total (Use)
				- Motricity Index (MI)
				- Jamar Handheld Dynamometer
				- Brunnstrom Fugl-Meyer (BFM)
				- Action Research Arm test (ARAt)
				- Motor Activity Log
				  o Amount Of Use (AOU)
				  o Quality Of Movement (QOM)
				  o Total (Use)
					- Motricity Index (MI)
					- Modified Ashworth Scale (MAS)
					- Active ROM
					- Wolf Motor Function Test (WMFT)
					  o Median Time
					  o Grip force
					- Perceived Fatigue
					- Perceived Force
					- Manual Ability Measure (MAM)

Robot-generated outcome measures	- Skill components
	  o Transporting
	  o Reaching
	  o Lifting
	- Robot-generated parameters
	  o Range Of Motion (ROM,°)
	  o Movement duration (s)
	  o Speed (m/s)
	  o Hand-Path Ration (HPR)
				- Skill components
				  o Idem part 1
				- Robot-generated parameters
				  o Range Of Motion (ROM,°)
				  o Movement duration (s)
				  o Speed (m/s)
				  o Hand-Path Ration (HPR)
				  o Distance	

Aim	Correlation between clinical and robot-generated outcome measures			Effect of intervention using pre- and post-training outcome measures	
Statistical Analyses	Pearson product-moment correlation coefficient			Wilcoxon signed-rank test	

Figure 2 Overview of different experiments and post-hoc statistical analyses

Clinical outcome measures

The following section presents the clinical outcome measures used in the included experiments. A brief explanation is given for each of the clinical tests. For the first two experiments the following clinical test were used: 1) Motricity Index (MI), 2) Jamar Handheld Dynamometer, 3) Brunnstrom Fugl-Meyer (BFM), 4) Action Research Arm test (ARAt) and 5) Motor Activity Log (MAL). The third experiment included: 1) Modified Ashworth Scale (MAS), 2) Perceived Fatigue 3) perceived Force, 4) active range of motion, 5) Wolf Motor Function Test (WMFT) and 6) Manual Ability Measure (MAM)

MOTRICITY INDEX (MI). Voluntary movements and isometric muscle strength are measured by the *Motricity Index*. The maximum score for the upper extremity section (or the lower extremity section) is 99 plus 1. To measure the severity of the hemiplegia the scores of the arm andleg are summed and divided by 2.6. Convergent validity, predictive validity and interrater reliability were proven for stroke. [23] It shows a good internal consistency and moderate test-retest reliability in patients with MS. [24]

JAMAR HANDHELD DYNAMOMETER. The Jamar handheld dynamometer measures the hand and forearm strength when applying isometric force. The subject is seated with the arm which wasn't tested on the lap. The tested arm is supported on the table with the lower part of the arm in neutral position, the elbow flexed and shoulder slightly flexed. Two hydraulic handles have to be squeezed together. The amount of muscle strength will be shown in kilograms. Nothing was found about the validity and reliability of the Jamar handheld dynamometer for patients with stroke and Multiple Sclerosis.

BRUNNSTROM FUGL-MEYER (BFM). The Brunnstrom Fugl-Meyer Assessment scale (BFM) assesses the ability to move the arm and its segments selectively. It also measures sensation and passive joint mobility. The included articles only used the upper section of this assessment scale consisting of 2 parts. For this section of research only the subsection 'motor function' was tested for correlations. This subsection gives a total score ranging from 0 to 66. A very high interrater reliability and convergent validity was found for patients with stroke. [23]

ACTION RESEARCH ARM TEST (ARAt). The Action Research Arm Test contains four subtests: 'grasp', 'grip', 'pinch' and 'gross movements'. This test compromises 19 items in total. In stroke the ARAt is extremely reliable for each of the subtests as well as for the tests in total. Reliability was shown in stroke as well as in MS. [25]

MOTOR ACTIVITY LOG (MAL). The MAL measures perceived arm performance using a structured patient-rated questionnaire. A total of 17 pre-defined activities were scored using an ordinal rating scale. The Amount of Use (AOU): 'How much did you use your arm for this activity in the last week?' and the Quality of Movement (QOM): 'How useful was your arm, when doing this activity in the last week?' were measured. Five was the normal score for both parts. The sum score (0-10) of AOU and QOM is referred to as 'USE'. Mean scores and total score were used for statistical analyses. In stroke responsiveness and validity are confirmed. [26]

MODIEFIED ASHWORTH SCALE The Ashworth Scale grades muscle tone or spasticity. A score of 0 means normal muscle tone, while a score of 4 means that the limb is rigid in flexion or extension. These are measures by manually feeling the resistance of the muscle to passive stretching of it. The scale had therefor face validity. Experience with the scale revealed that many patients with hemiplegia demonstrated scores in the lower part of the scale. Therefor the score 1 wasn't distinctive enough anymore. A modified version was made were an additional score is seen, namely +1. [27]

PERCEIVED FATIGUE/ PERCEIVED FORCE. Both parameters were presented on a 10cm Visual Analogue Scale (VAS). The purpose is to point out how tired the person feels (perceived fatigue) or how the person perceives the power in his arms at this moment (perceived force).

ACTIVE RANGE OF MOTION (AROM). AROM of the shoulder for anteflexion and abduction This was performed using a universal goniometer.

WOLF MOTOR FUNCTION TEST (WMFT). This test has two parts: the first contains 15 timed tasks and the second one 2 strength tasks. These strength tasks consist of lifting the weighted limb and measuring the "grip strength". Ordered by complexity, from simple to hard, this test is administered sequentially to each upper extremity. Quality of movement is rated using a 6-point functional ability scale. Zero meaning that there wasn't even an attempt and 5 meaning that normal movement can be observed. Appendix 11 shows a scoring form for this test. In stroke patients a high interrater reliability, internal consistency and test-retest reliability was found. [28]

MANUAL ABILITY MEASURE. This test is composed from the ABILHAND, Disabilities of the Arm, Shoulder and Hand; the TEMPA and the Solerman Grip Function Test. It's based on the ICF. Tasks are rated by a score: (1) unable, (2) very hard, (3) a little hard and (4) easy to perform.

Robotic system and virtual environment

Training of arm function and arm skill performance was performed using the robotic system Haptic Master(MOOG, Nieuw-Vennep, NL) with the assistance of the I-TRAVLE system. This device is an end-effector. The Haptic Master is a haptic device which is controlled according to the principle of 'admittance control'. This is a system in which the 'force' that is being applied to the system (i.e. arm of the haptic master) is measured, while 'position' (arm HM) is the end result. The paper by van der Linde et al [29] presents more technical details on this principle and on the Haptic Master. Wrist and forearm movements can be measured by controlling the ADL gimbal added on the Haptic Master. Proximal movements can be trained because of large workspace of the Haptic Master. Multiple studies used this system.

The Haptic Master was used in conjunction with the I-TRAVLE software. This creates a virtual environment in which the patients can train different skill components, e.g. reaching, lifting and transporting. All these skill components are necessary to perform ADL activities successfully. The latest version of the I-TRAVLE system has the possibility to self-adapt the training regime of the patient based on movement parameters (e.g. velocity, smoothness,…) sensed by the system. Automated personalization of the training content is one of the main new features of this system. This wasn't present in the previous Interreg-IV study. Also the number of virtual training environments and variety in difficulty level has been extended. Figure 3 presents a demonstration of the Haptic Master and I-TRAVLE system.

Figure 3Haptic Master and I-TRAVLE system

Robot-generated outcome measures

The evaluation module embedded in the Haptic Master measures three important skill components: transporting, reaching and lifting. The transporting component consists of the movement performed when moving left to right. For each of these skill components multiple movement parameters can be measured. Reaching is performed in a dimension from the front to the back, while lifting is performed by moving the robotic arm up and down.

Four gross movements parameters were used for the purpose of analyses namely: 1) range of motion (ROM; m), 2) movement duration (s), speed or velocity (m/s) and the hand-path ratio. The second part of the present study includes a fifth robotic movement parameter, namely distance (m). The range of motion was measured in degrees. The evaluation protocol measures the individual's range of motion first and is also used to calculate the workspace in which the robot-assisted training will be performed. After this evaluation the remaining three parameters were measured 3 times. Statistical analyses were performed using mean values of these 3 repetitions.

The movement duration was measures by the time needed to move between the starting point and target. This was measured in seconds. Hand-path ration (HPR) is the quotient between the actual hand trajectory and the straight-line distance between two targets. This looks for deviations from the shortest distance, a straight line, between 2 points.

Statistical analysis

Between group differences of the first and second research were calculated using independent samples t-test. This test examines whether there is a significant difference on a quantitative/numerical variable between 2 groups. To determine significant difference we need to examine several statistics, one of which is the p-value. Cut-off score is $p<0.05$. For this purpose we first have to determine whether equal variances are assumed between the two groups using The Levene's test. A non-significant result ($p>0.05$) assumes equality of variance. The first aim of this study was analysed using a non-parametric two-tailed design, namely the Pearson product-moment correlation coefficient. Each research was analysed separately, after which both populations were pooled together into one dataset. For this purpose 3 sets of correlation calculations were performed.

Missing data were analysed using missing data analysis and multiple imputations were performed. The multiple imputation analysis gave us a complete dataset with estimates for the missing values. For each missing value 5 imputations were performed. Correlation analyses were performed on this imputed dataset. This resulted in a correlation analysis for the original dataset, for each imputation separately and for the pooled data. The pooled data is the best estimate for the missing values and was used to present the results for the research for a relationship. This procedure was performed for all 3 sets of analysis.

The second part of this study involved calculating difference between pre- and post-measurements. A paired t-test and Wilcoxon Signed-Ranks were used. Only robotic-measured outcome measures were used to calculate effect of intervention. A third part can consist of a comparison between clinical change and robot-measured change from baseline to the end of the intervention. For this purpose non-parametric correlation analysis will also be performed.

Results

PART I. RELATION BETWEEN ROBOT-GENERATED AND CLINICAL OUTCOME MEASURES

Subjects

Table 1 presents the patient characteristics for each experiment. Characteristics were provided for Experiment 1 and 2 separately and for the pooled dataset of both studies. The population of the first experiment had a mean age of 61 (±8.8) years. Six males and 3 females were included with a mean EDSS score of 7.5 (±1.56). The mean disease duration was 21.11 (±9.9) years. Mean score for clinical tests were also presented in this table.
Subjects of the second experiment had a mean age of 53.7 (±5.9) years and mean disease duration of 11.4 (±8.3) years. The second experiment included more women compared to the first experiment. EDSS scores weren't available for the subjects included in the second experiment.

Results from the independent samples t-test, measuring between groups difference, showed that mean age and mean disease duration were significant different between the two research populations. Results of the clinical outcome measures were significantly different between groups for: Motricity Index ($t = -2.247$, $df = 17$, $p<0.05$), Brunnstrom Fugl-Meyer ($t = -1.31$, $df = 17$, $p <0.05$) and ARAt ($t = -2.89$, $df = 10.2$, $p<0.05$). The population of experiment 2 performed significantly better on the MI (M = 81.33, SD=12.76), BFM (M= 61.22, SD= 5.36) and ARAt (M= 51.78, SD = 6.78) compared to experiment 1. They were also significantly younger and have significantly shorter disease duration.

Table1. Patient Characteristics Experiment 1 and 2

	Experiment 1 n=9	Experiment 2 n=10	Experiment 1+2 n=19	Between group difference
Age (years)	61.0 ± 8.8	53.7 ± 5.9	57.3 ± 8.2	0.029*
Gender (m/f)	6/3	3/7	9/10	
EDSS score	7.5 ± 1.56			
Disease duration (years)	21.11 ± 9.9	11.4 ± 8.3	16.3 ± 10.2	0.025*
Clinical outcome measures				
MI (0-100)	69.67 ± 12.16	81.33 ± 12.76	75.5 ± 13.5	0.038*
JAMAR (kg)	18.35 ± 12.46	24.33± 9.12	21.34 ± 11.03	ns
BFM (0-66)	50.78 ± 11.84	61.22 ± 5.36	56.0 ± 10.41	0.034*
ARAt (0-57)	35.11 ± 16.62	51.78 ± 6.78	43.44 ± 15.01	0.016*
MAL_AOU	2.74 ± 1.32	3.67 ± 1.59	3.20 ± 1.49	ns
MAL_QOM	2.25 ± 1.54	3.14 ± 1.58	2.83 ± 1.55	ns
MAL_Use	5.25 ± 2.79	6.81 ± 3.06	6.03 ± 2.96	
(0-10)				ns

Values are mean ± standard deviation

Abbreviations m: male, f:female, EDSS: Expanded Disability Status Score, R: Right, L:Left, IQR: Interquartile range, MI: Motricity Index, JAMAR: Jamar Handheld Dynamometer, BFM: Brunnstrom Fugl-Meyer, ARAT: Action Research Arm Test, MAL: Motor Activity Log, AOU: Amount Of Use, QOM: Quality of movement

*** significant at p<0.05**
ns: not significant

Results analyses

Table 2 presents the results for the first part of the present study. Correlations were calculated using a non-parametric design. Analyses were performed on each experiment separately and on the pooled dataset of both experiments. The robot-generated outcome measures were grouped per gross skill component namely: transporting, reaching and lifting. Each skill component was divided into four separate robot-generated parameters. Each parameter will be discussed separately.

The second experiment showed no significant correlations, so only results for the first experiment and pooled dataset will be presented beneath.

1. Transporting

The transporting skill component showed the greatest amount of significant correlations.

RANGE OF MOTION. The first experiment showed a significant correlation with MI at $p<0.01$. MAL_AOU showed a significant correlation at $p<0.05$. Trends towards significance were found for ARAt, MAL_QOM and MAL_Use.

The pooled dataset showed significant correlations at $p<0.01$ with MI and ARAt. Jamar and BFM showed significant correlations at $p<0.05$. Trends towards significance were found with MAL_QOM and MAL_Use.

MOVEMENT DURATION. A trend towards significance was found in the first experiment with Jamar handheld dynamometer, measuring hand grip strength.

SPEED. Trends towards significance were found with MI and BFM in the pooled dataset.

HAND-PATH RATIO. Experiment 1 showed a significant correlation at $p<0.05$ with BFM. Only a trend towards significance could be found for the BFM in the pooled dataset.

2. Reaching

The reaching skill component only showed significant correlations for range of motion and movement duration.

RANGE OF MOTION. The first experiment showed a significant correlation with ARAt at $p<0.01$ and with hand grip force (Jamar) at $p<0.05$. Trends towards significance were found for the same clinical outcome measures in the pooled dataset.

MOVEMENT DURATION. A trend towards significance was found in the first experiment with MAL_AOU. The pooled experiment presented a significant correlation at $p<0.01$ with MI and at $p<0.05$ with ARAt.

3. Lifting

RANGE OF MOTION. Significant correlations with MI and ARAt were found at $p<0.05$ in the pooled dataset.

MOVEMENT DURATION. The first experiment only showed a trend towards significance with ARAt. The pooled dataset showed a significant correlation with MI at $p<0.05$. Trends towards significance were found for BFM and ARAt.

SPEED. Trends towards significance were found with MAL_AOU in the first experiment and with BFM for the pooled dataset.

HAND-PATH RATIO. HPR showed a significant correlation with ARAt in the first experiment at $p<0.05$.

Table 2. Results for Part 1 Correlation Analyses

		Transporting (left-right)				***Reaching (front-back)***				***Lifting (Up-Down)***			
	Experiment	**ROM (°)**	**Duration (s)**	**Speed (m/s)**	**HPR**	**ROM (°)**	**Duration (s)**	**Speed (m/s)**	**HPR**	**ROM (°)**	**Duration (s)**	**Speed (m/s)**	**HPR**
MI (0-100)	Exp. 1	-0.826**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	Exp. 2	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	Pooled (1&2)	-0.662**	ns	-0.478†	ns	ns	0.640**	ns	ns	0.545*	0.546*	ns	ns
JAMAR (kg)	Exp. 1	ns	-0.628†	ns	ns	0.703*	ns	ns	ns	ns	ns	ns	ns
	Exp. 2	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	Pooled (1&2)	-0.510*	ns	ns	ns	0.402†	ns	ns	ns	ns	ns	ns	ns
BFM (0-66)	Exp. 1	ns	ns	ns	-0.705*	ns	ns	ns	ns	ns	ns	ns	ns
	Exp. 2	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	Pooled (1&2)	-0.496*	ns	-0.433†	-0.428†	ns	0.438†	ns	ns	ns	0,396†	-0.428†	ns
ARAt (0-57)	Exp. 1	-0.611†	ns	ns	ns	0,795**	ns	ns	ns	ns	-0.594†	ns	-0.720*
	Exp. 2	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	Pooled (1&2)	-0.676**	ns	ns	ns	0.449†	0.518*	ns	ns	0.544*	0.406†	ns	ns
MAL_AOU	Exp. 1	-0.686*	ns	ns	ns	ns	0.637†	ns	ns	ns	ns	-0.611†	ns
	Exp. 2	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	Pooled (1&2)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
MAL_QOM	Exp. 1	-0.617†	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	Exp. 2	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	Pooled (1&2)	-0.409†	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
MAL_Use (0-10)	Exp. 1	-0.633†	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	Exp. 2	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	Pooled (1&2)	-0.428†	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

Abbreviations *ROM: Range Of Motion; HPR: Hand-path ratio; MI: Motricity Index; JAMAR: Jamar Handheld Dynamometer; BFM: Brunnstrom Fugl-Meyer; ARAt: Action Research Arm Test; MAL: Motor Activity Log, AOU: Amount Of Use, QOM: Quality Of Movement*

***** Correlation is significant at the 0.01 level (2-tailed)***
**** Correlation is significant at the 0.05 level (2-tailed)***
† trend towards significance 0.05<p< 0.1

PART II. EFFECT OF ROBOT-ASSISTED TRAINING ON FUNCTION AND PERFORMANCE OF THE UPPER LIMBS

Subjects

Table 3 presents the descriptive characteristics for experiment 1 and 3. Robot-measured outcome measures are presented for both pre- and post-training measurements.

Subjects of the first experiment had a mean age of 61 ± 8.8 years, a mean EDSS score of 7.5 ± 1.56 and a mean disease duration of 21.11 ± 9.9 years. Subjects of the third experiment, when compared to the first experiment, were younger (53.11 ± 9.69 years), had a lower EDSS score (5.5 ± 2.1) and finally a shorter disease duration (14.89 ±11.59 years). Both groups weren't significantly different from each other, but age and EDSS score showed a trend towards significance.

When comparing robot-generated outcome measures between groups we saw significant differences in the transporting skill component. Subject of the third experiment (Pre: M = 0.543, SD = ± 0.081; Post: M = 0.560, SD = ± 0.077) had a significant lower range of motion compared to those of experiment one (Pre: M = 0.621, SD = ± 0.105; Post: M= 0.627, SD = ± 0.120) for both pre- and post-training robot-generated outcome measures. Also the post-training outcome measure for hand-path ratio was significant different between groups. Experiment 1 (M = 1.189, SD = ±0.262) had a significant smaller hand-path ratio compared to experiment 3 (M=1.664, SD = ±0.171).

The male to female ratio shows us that experiment 3 included more women (n=7) compared to the first experiment (n=3).

Motricity Index was the only clinical outcome measure in the third experiment corresponding to the ones included in the first experiment. These results are only preliminary results, because of the fact that the dataset contained a lot of missing data used during analysis. These data were missing because calculations and final checks of the clinical dataset were still ongoing during the process of the present study.

Subjects of the third experiment seemed to have higher mean Motricity Index scores compared to those of the first experiment. Upper limb dysfunction might have been lower in the third experiment. Calculations for between group differences showed a significant difference in post-training MI score. The post-training MI score was significantly lower in the first experiment, compared to the third experiment.

Table 3. Patient Characteristics Experiment 1 and 3

		Experiment 1 n=9		Experiment 3 n=11		Between group difference	
Age (Years)		61 ± 8.8		53.11 ± 9.69		0.087†	
Gender (M/F)		6/3		4/7			
EDSS score		7.5 ± 1.56		5.5 ± 2.1		0.064†	
Disease Duration (Years)		21.11 ± 9.9		14.89 ± 11.59		ns	
Clinical outcome measures		**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
	MI (0-100)	69.67 ± 12.16	68.33 ±12.10	77.47 ± 12.54	80.91 ± 13.69	ns	0.043*
	JAMAR (kg)	18.35 ± 12.46	18.83 ± 11.99				
	BFM (0-66)	50.78 ± 11.84	51.71 ± 10.32				
	ARAt (0-57)	35.11 ± 16.62	37.00 ± 14.80				
	MAL_AOU	2.74 ± 1.32	2.77 ± 1.19				
	MAL_QOM	2.25 ± 1.54	2.14 ± 1.08				
	MAL_Use	5.25 ± 2.79	4.91 ± 2.20				
Outcome measures robot		**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Transporting (Left-Right)	*ROM (°)*	0.621 ± 0.105	0.627 ± 0.120	0.543 ± 0.081	0.560 ± 0.077	0.039*	0.034*
	Duration (s)	12.604 ± 8.262	6.571 ± 0.589	8.066 ± 2.575	5.241 ± 1.058	ns	ns
	Speed (m/s)	0.159 ± 0.014	0.207 ± 0.035	0.164 ± 0.071	0.225 ± 0.059	ns	ns
	HPR	2.231 ± 1.083	1.189 ± 0.262	1.797 ± 0.293	1.664 ± 0.171	ns	0.000**
	Distance (m)	1.774 ± 1.025	1.292 ± 0.099	1.165 ± 0.253	1.116 ± 0.115	0.059†	0.066†
Reaching (Front-Back)	*ROM (°)*	0.358 ± 0.071	0.370 ± 0.058	0.333 ± 0.091	0.345 ± 0.091	ns	ns
	Duration (s)	8.280 ± 4.501	5.540 ± 1.439	5.535 ± 2.873	5.104 ± 2.716	ns	ns
	Speed (m/s)	0.119 ± 0.053	0.148 ±0.031	0.150 ± 0.076	0.186 ± 0.072	ns	ns
	HPR	2.246 ± 0.530	2.050 ± 0.261	2.257 ± 0.558	2.876 ± 2.098	ns	ns
	Distance (m)	0.806 ± 0.138	0.794 ± 0.136	0.745 ± 0.317	0.786 ± 0.161	ns	ns
Lifting (Up-Down)	*ROM (°)*	0.436 ± 0.000	0.426 ± 0.019	0.430 ± 0.043	0.425 ± 0.050	ns	ns
	Duration (s)	8.605 ± 2.377	6.213 ± 2.950	7.161 ± 3.003	4.916 ± 1.391	ns	ns
	Speed (m/s)	0.125 ± 0.043	0.158 ± 0.056	0.140 ± 0.073	0.183 ± 0.059	ns	ns
	HPR	2.102 ± 0.909	1.811 ± 0.409	1.657 ± 0.277	1.709 ± 0.242	ns	ns
	Distance (m)	1.038 ± 0.449	0.861 ± 0.165	0.799 ± 0.169	0.807 ± 0.134	ns	ns

Values are Mean ± Standard Deviation (SD)

Abbreviations: M: Male, F: Female, EDSS: Expanded Disability Status Score, MI: Motricity Index, JAMAR: Jamar handheld dynamometer, BFM: Brunnstrom Fugl-Meyer, MAL: Motor Activity Log, AOM: Amount Of Use, QOM: Quality Of Movement, ROM: Range of Motion, HPR: Hand-Path Ratio

**** Significant at p<0.05, ** Significant at p<0.01, † trend towards significance 0.05<p<0.1, ns: not significant***

Results analyses

Table 4 presents the results for effect of training for the first experiment. Each performance skill is presented with all the related gross movement parameters. Figure 4 show graphs for the significant results in the first experiment.

The skill component 'transporting' showed significant results at $p<0.05$ for movement duration ($p=0.043$), speed ($p=0.018$) and hand-path ratio ($p=0.017$).

Only trends towards significance were found during reaching movements for movement duration ($p=0.063$) and hand-path ratio ($p=0.091$).

A significant effect of training was found at $p<0.01$ for movement duration ($p=0.008$) when evaluating the lifting skill component. A trend towards significance was found for speed ($p=0.051$).

Other movement parameters showed no significant effects of training when comparing pre- to post-training robot-generated outcome measures. For ROM and distance no difference was found between the two measurement points. On ROM almost all subjects scored identical, reaching full ROM possible with the Haptic Master device. This maximum score was already achieved pre-training, so post-training ROM couldn't increase anymore. Training with the robotic device, couldn't have an additional effect on this parameter anymore. This is also visible in the post-training scores of all subjects being identical to pre-training, except for one subject.

Post-hoc analysis of pre- and post-training clinical outcome measures presented no significant effect of training. Subjects already had high levels of upper limb function, making it less plausible for the robot-assisted training to induce improvements in upper extremity performance.

Table 5 presents results of the effect of intervention for experiment 3. Figure 5 gives an overview of the graphs for the significant results found in the third experiment. The transporting skill component showed significant correlations at $p<0.05$ for movement duration ($p=0.017$) and speed ($p=0.028$). A trend towards significance was visible for hand-path ration ($p=0.059$).

The lifting movement showed only significant results for movement duration ($p=0.028$). A trend towards significance was found for speed ($p=0.086$).

Reaching movements showed no significant effect of intervention when comparing pre- to post-training outcome measures.

Preliminary clinical outcome measures from the third experiment show significant effect of training for perceived force and WMFT median time and grip force. These results were only temporarily. Still a lot of data had to be processed and was missing during analysis. The final dataset with clinical outcome measure would include more clinical outcome measures and may present other results. The results found at this stage do show significant changes in clinical outcome measures. The first experiment couldn't present these changes. A hypothesis may be that the clinical tests used in the third experiment were more subjective en sensitive to change compared to those of the first experiment. Also these clinical outcome measures might be more comparable with the robot-generated outcome measures, measuring almost the same aspect of upper limb function.

Table 4. Results post-hoc analyses robot-generated and clinical outcome measures for part 2 Experiment 1

		Median Pre (IQR)	Median Post (IQR)	∆	p
ROBOT-GENERATED OUTCOME MEASURES					
Transporting (Left-Right)	*ROM (°)*	0.666 (0.197)	0.622 (0.232)	-0.044	ns
	Duration (s)	8.459 (15.369)	6.853 (1.087)	-1.606	0.043*
	Speed (m/s)	0.163 (0.024)	0.206 (0.060)	0.043	0.018*
	HPR	1.554 (2.025)	1.088 (0.473)	-0.466	0.017*
	Distance (m)	1.304 (1.974)	1.307 (0.186)	0.003	ns
Reaching (Front-Back)	*ROM (°)*	0.375 (0.103)	0.405 (0.093)	0.030	ns
	Duration (s)	7.575 (8.168)	5.802 (2.735)	-1.773	0.063†
	Speed (m/s)	0.103 (0.103)	0.146 (0.058)	0.043	ns
	HPR	2.114 (0.858)	1.894 (0.423)	-0.220	0.091†
	Distance (m)	0.782 (0,248)	0.848 (0.249)	0.066	ns
Lifting (Up-Down)	*ROM (°)*	0.436 (0.000)	0.436 (0.025)	0.000	ns
	Duration (s)	9.137 (4.663)	6.319 (5.838)	-2.818	0.008**
	Speed (m/s)	0.128 (0.084)	0.152 (0.110)	0.024	0.051†
	HPR	1.639 (1.292)	1.668 (0.796)	0.029	ns
	Distance (m)	0.810 (0.638)	0.810 (0.316)	0.000	ns
CLINICAL OUTCOME MEASURES					
MI (0-100)		66.0 (21.0)	60.0 (28.0)	-6.0	ns
JAMAR (kg)		21.3 (11.7)	21.0 (15.7)	-0.3	ns
BFM (0-66)		52.0 (20.0)	52.0 (20.0)	0	ns
ARAt (0-57)		40.0 (22.0)	38.0 (20.0)	-2	ns
MAL_AOU		3.0 (2.8)	2.8 (2.4)	-0.2	ns
MAL_QOM		2.3 (3.1)	2.0 (1.7)	-0.3	ns
MAL_Use (0-10)		5.3 (6.0)	5.0 (4.3)	-0.3	ns

Abbreviations: IQR: Interquartile Range, ROM: Range of Motion, HPR: Hand-Path Ratio, MI: Motricity Index, JAMAR: Jamar Handheld Dynamometer, BFM: Brunnstrom Fugl-Meyer, ARAt: Action Research Arm test, MAL: Motor Activity Log, AOU: Amount Of Use, QOM: Quality Of Movement

****   significant at p<0.05***
***** significant at p<0.01***
† trend towards significance 0.05<p<0.1
ns: not significant

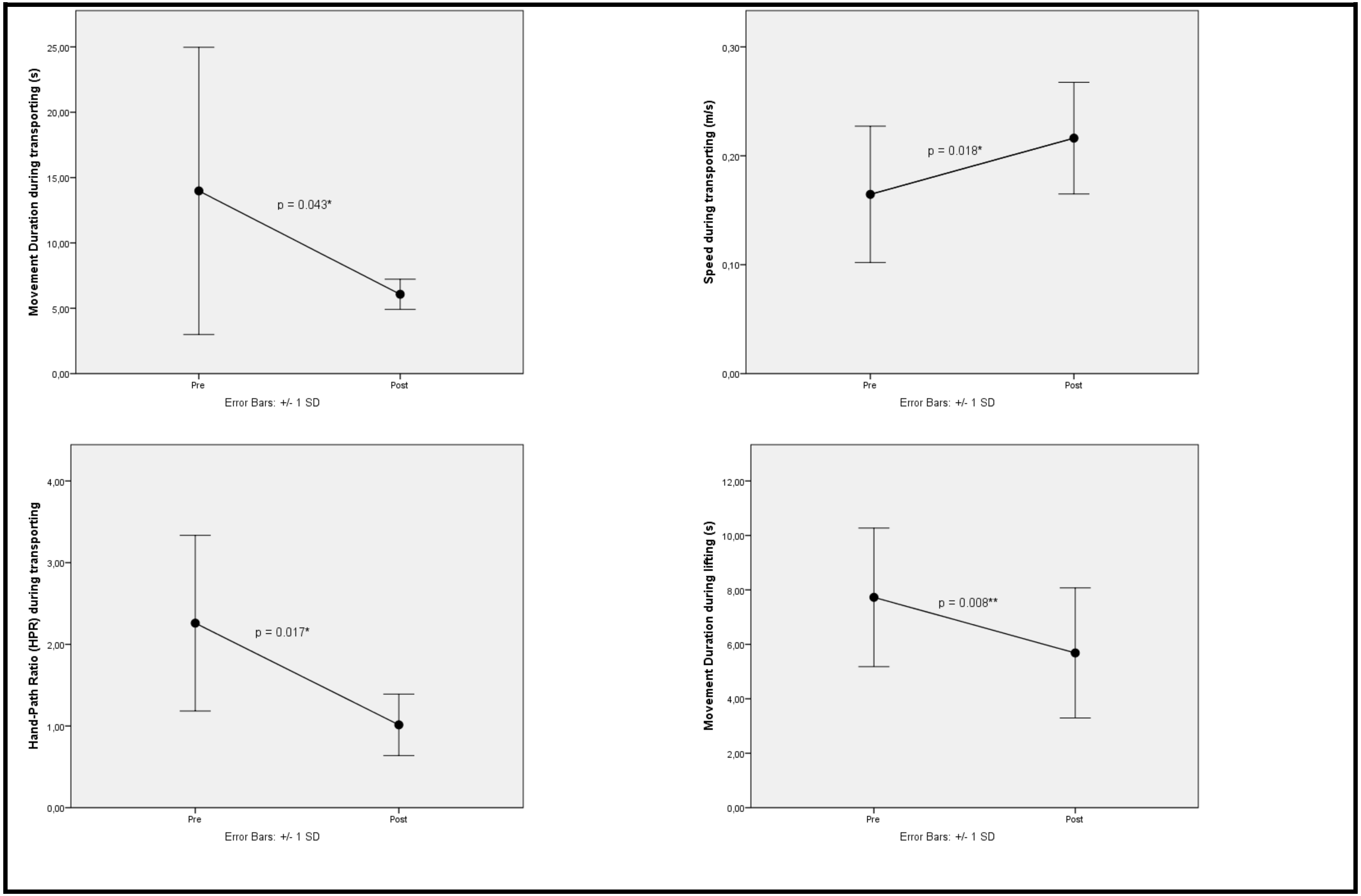


Figure 4 Graphs presenting significant results for Experiment 1

Table 5. Results post-hoc analyses robot-generated and clinical outcome measures for part 2 Experiment 3

		Median Pre (IQR)	Median Post (IQR)	Δ	p
ROBOT-GENERATED OUTCOME MEASURES					
Transporting (Left-Right)	*ROM (°)*	0.554 (0.115)	0.572 (0.115)	-0.018	ns
	Duration (s)	8.613 (4.905)	5.436 (1.431)	-3,177	0.017*
	Speed (m/s)	0.164 (0.085)	0.207 (0.098)	0,043	0.028*
	HPR	1.684 (0.454)	1.650 (0.200)	-0,034	0.059†
	Distance (m)	1.093 (0.262)	1.158 (0.173)	0,065	ns
Reaching (Front-Back)	*ROM (°)*	0.387 (0.172)	0.381 (0.126)	-0,006	ns
	Duration (s)	5.257 (3.470)	3.774 (3.864)	-1,483	ns
	Speed (m/s)	0.116 (0.077)	0.189 (0.128)	0,073	ns
	HPR	2.180 (0.899)	1.964 (1.994)	-0,216	ns
	Distance (m)	0.790 (0.453)	0.882 (0.276)	0,092	ns
Lifting (Up-Down)	*ROM (°)*	0.446 (0.011)	0.446 (0.023)	0.000	ns
	Duration (s)	7.453 (5.232)	4.879 (2.272)	-2,574	0.028*
	Speed (m/s)	0.118 (0.051)	0.175 (0.093)	0,057	0.086†
	HPR	1.575 (0.416)	1.745 (0.315)	0,170	ns
	Distance (m)	0.765 (0.261)	0.840 (0.228)	0,075	ns
CLINICAL OUTCOME MEASURES					
Motricity Index (0-100)		77.42 (6.75)	76.50 (34.50)	-0.92	ns
Modified Ashworth Scale (0-4)		0 (1)	0 (0)	0	ns
Active ROM	*Anteflexion*	116.50 (29.38)	137.50 (32.50)	21	ns
	Abduction	110.33 (29.75)	117.00 (48.25)	6.67	ns
Perceived Fatigue (0-10)		2.90 (5.48)	1.95 (5.65)	-0.95	ns
Perceived Force (0-10)		4.02 (0.94)	5.35 (4.30)	1.33	0.041*
WMFT	*Median Time*	2.09 (59.45)	1.49 (0.98)	-0.6	0.050*
	Grip force	15.07 (8.21)	14.81 (5.0)	-0.26	0.028*
MAM	*Raw Score*	101.67 (58.42)	53.25 (24.00)	-48.42	ns
	Measure	101.50 (54.75)	53.00 (23.38)	-48.5	ns

Abbreviations: IQR: Interquartile Range, ROM: Range of Motion, HPR: Hand-Path Ratio, WMFT: Wolf Motor Function Test, MAM: Manual Ability Measure

**** significant at p<0.05***
***** significant at p<0.01***
† trend towards significance 0.05<p<0.1
ns: not significant

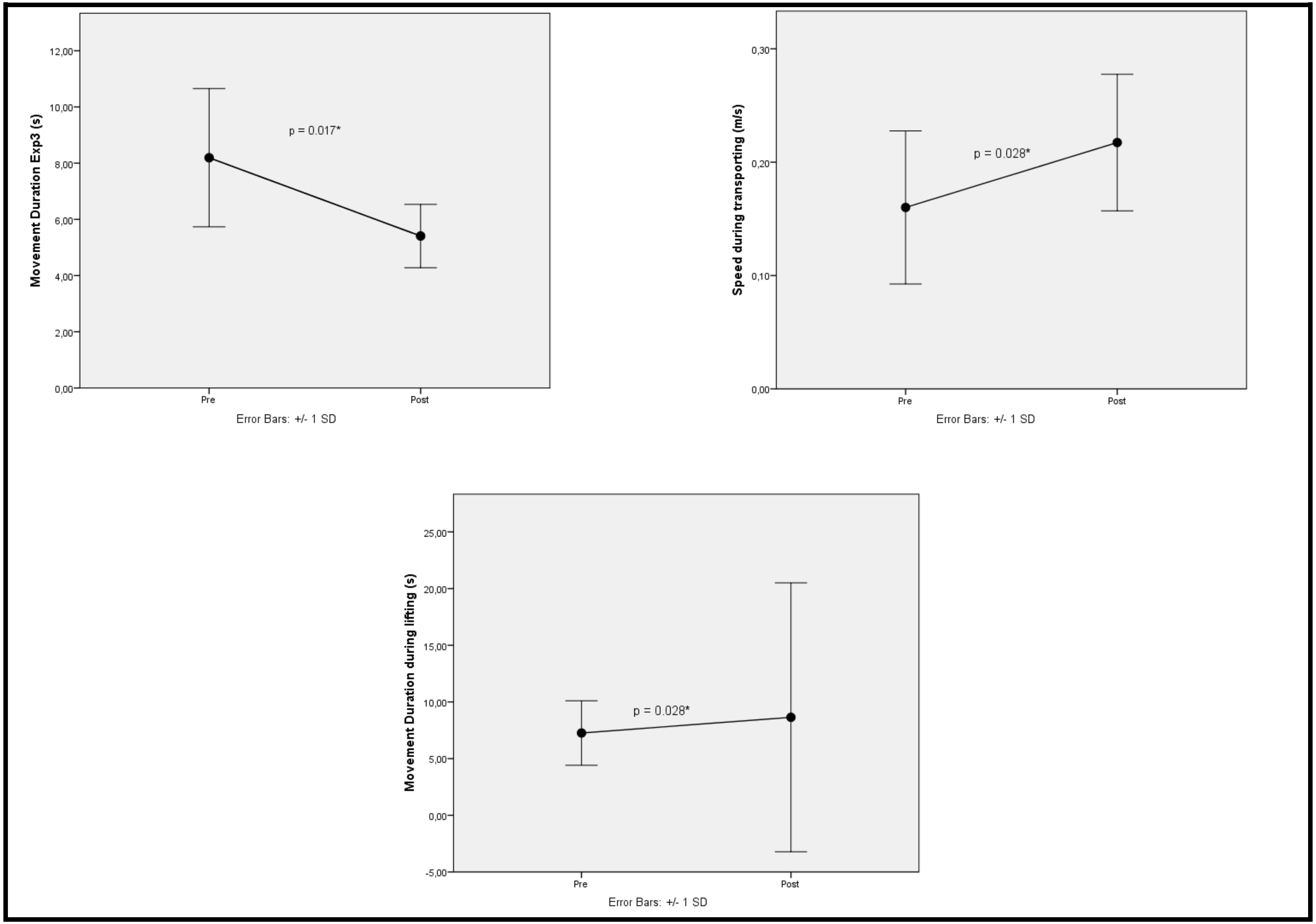


Figure 5 Graphs presenting significant results for Experiment 3

Discussion

PART I. RELATION BETWEEN ROBOT-GENERATED AND CLINICAL OUTCOME MEASURES

This part aimed to investigate the relationship between robot-generated and clinical outcome measures for upper extremity function in persons with MS. The purpose was to investigate the relevance of robot-generated outcome measures for the assessment of upper limb function. Results concerning patient characteristics and correlation analysis will be discussed separately.

Subjects

For this purpose experiment 1, 2 and a pooled dataset of both experiments were used. When comparing subjects of experiment 1 and 2, we found significant differences between both. The population of the second study was significantly younger and had a shorter disease duration compared to the first experiment. Motricity index, Brunnstrom Fugl-Meyer and ARAt were also significantly better. Experiment 2 included subjects with a lower degree of upper limb impairment measured with the MI, BFM and ARAt, compared to those of the first experiment.
For this reason pooling both experiments gave the possibility to include a wider spectrum of upper extremity dysfunction. This was also reflected in the results, showing no significant correlations in the second experiment. Only significant correlations were found in the first experiment and pooled dataset. A score of 27 or lower on the MI is indicative for severe hemiparesis/hemiparalyse. Mean scores of all included experiments were much higher, reflecting the fact that upper limb dysfunction measured with MI, wasn't severe in the included subjects. They were also able to perform relatively well on all other clinical outcome measures.

Correlation analyses

Significant correlations were found in experiment 1 and the pooled dataset, only. A possible explanation may be found in fact that the second experiment had a significant better upper limb function compared to the first. When looking at the first experiment upper limb dysfunction already wasn't as severe. The population of the first experiment showed just moderate to mild impairments. The second experiment scored even better, so upper limb dysfunction was even lower.

MOTRICITY INDEX. Motricity Index showed significant correlations in the first experiment at $p<0.01$ with ROM during the transporting. The pooled dataset showed significant correlations at $p<0.01$ with ROM of the transporting skill component and movement duration of the reaching skill component. At $p<0.05$, significant correlations were found in the lifting skill component for ROM and movement duration. Trends towards significance were found for speed during transporting.
The strong correlations with range of motion can be explained by the fact that the MI measures voluntary movements. A high score on the MI represents a great ability to perform voluntary movements, so automatically range of motion will be good as well.

JAMAR HANDHELD DYNAMOMETER. The Jamar handheld dynamometer measured the hand grip force in kg. We found significant correlations in the first experiment with ROM during reaching and in the pooled experiment with ROM during transporting phase. Trends towards significance were found in the first experiment for movement duration during transporting movements and for ROM in the pooled dataset while reaching. The lifting skill component didn't show any significant correlation at all. No robot-generated parameters measuring force or power were included in the evaluation module and dataset of the present study. This may also explain why our analyses resulted in little correlations. Hand grip strength seems to have some influence on the ROM. This may be logical because of the fact that hand grip strength is needed to manipulate the end-effector in an effective way. Low grip strength will result in a decreased ability to move the end-effector. Research has been performed on the relation of relative shoulder flexion and hand grip strength for upper limb function in stroke. This research supports the hypothesis that muscle weakness, especially hand grip strength, and shoulder flexion are related to paretic upper limb function. [30] Another explanation may be found in the fact that hand grip force isn't really trained during the robot-assisted I-TRAVLE training. Only haptic forces counteracting or resisting movements of the whole arm were implemented. This lack of specific strength training might partly explain the small amount of significant correlations.

BRUNNSTROM FUGL-MEYER. The Brunnstrom Fugl-Meyer assessment scale assesses the ability to move the arm and its segments selectively. A good selectivity of movements will be represented in a better range of motion, lower movement duration, higher speed and better trajectory.
The first experiment only showed a significant correlation of the Brunnstrom Fugl-Meyer with the Hand-path ratio during transporting. The pooled dataset showed significant correlations with range of motion during transporting. Speed and HPR during transporting, movement duration during reaching and movement duration and speed during lifting showed trends towards significance.
The present study showed only trends toward significance for speed, this is in contrast to the studies performed by Colombo et al. Both studies showed significant correlations at $p<0.05$ in persons after stroke. [8,31] The first study, performed in 2005, used two groups (group 1 n=7; group 2 n=9) each handling a different type of device, a wrist rehabilitation device and a shoulder-elbow device respectively. Fugl-Meyer scores were collected from a modified version by Lindmark. This modified version of the Brunnstrom Fugl-Meyer Assessment score upper limb function using a scale ranging from 0 to 115. [8] The second experiment compared scores of recent and chronic stroke patients. [31] Movement duration only showed trends towards significance in the pooled dataset of the present study. In contrast, studies performed in persons after stroke did show significant correlations. Both Frisoli et al. and Zollo et al. found a significant correlation between execution time and BFM at $p<0.05$. Both authors used the standard upper limb part of the BFM assessment with a score ranging from 0 to 66. [32-35] Subjects included in the study by Frisoli et al. had a mean and maximum BFM score of 21.1 and 36, respectively. [32,33] The population included in the study by Zollo et al had a mean score of 22.2 and also a maximum of 36. [34,35] This shows that both studies had a population with a significantly lower BFM score (M= 21.1 and M= 22.2) compared to our pooled dataset (M=56).

This difference may explain why significant correlations were found in both studies with a population with a more pronounced severity of upper limb impairment compared to our present study, with moderate to mild impairments, showing only trends towards significance.

Trajectory error or hand-path ratio showed significant correlations in two studies performed by Celik et al. [9,36] Our study showed a significant correlation in the first experiment and a trend towards significance in the pooled dataset for the transporting skill component. Again these studies were performed in stroke patients in contrast to our population of PwMS. When looking at patient characteristics of those two studies we saw that mean BFM scores were 36.25 and 40.4, respectively. These were again significantly lower compared to the mean score found in experiment 1 (M=50.78) and the pooled dataset (56.0). The higher BFM scores resulted in only a trend towards significance in the pooled dataset. Correlations in these stroke experiments were stronger, with a $p<0.01$, compared to the one of the present study ($p<0.05$). [9,36]

ACTION RESEARCH ARM TEST. We found significant correlations at $p<0.01$ for range of motion while transporting (pooled) and reaching (experiment1). Correlations at $p<0.05$ were found in the first experiment for HPR during lifting. The pooled dataset showed significant correlations for movement duration during reaching and range of motion during lifting. Trends towards significance were found in the first experiment for ROM during transporting and for movement duration during lifting. The pooled dataset showed trends towards significance for ROM during reaching and movement duration during lifting.

A study performed in patients after stroke by Celik et al. (2010) showed significant correlations with trajectory error at $p<0.01$. [9] Our present study showed the same correlation, when looking at hand-path ratio, in the first experiment at $p<0.05$. Comparing patient characteristics showed us that experiment 1 and the stroke population had comparable mean ARAt scores, 35.11 and 35.78 respectively. Although experiment 1 scored a little lower on the ARAt, correlations were not as strong as those of Celik et al. [9] Previously, we hypothesized that populations with more severe functional deficits showed more significant relationships between robot-generated and clinical outcome measures. This hypothesis may be rejected because of the findings that our study subjects, with lower ARAt scores, showed no stronger relationships compared of those by Celik et al. Important in this framework is to take in account the other clinical outcome measures in which our subjects scored better. We can conclude that although ARAt score was relatively low, upper limb function was still better in our patients.

A pilot study performed on PwMS found a moderate to good correlation for movement duration in a trajectory task and object manipulation task.[37] These tasks were performed using the stylus of the PHANTOM 1.5 haptic device. Both tasks combined the transporting and reaching skill components. These findings support the results we found, with $p<0.01$ for those two skill components.

Action Research Arm test consists of four subtests: grasp, grip, pinch and gross movements. Tasks consist out of reaching tasks, transporting objects, etc. All three skill components are covered by the Action Research Arm test.

We saw that ROM in all three skill components showed significant correlations. An impaired ROM will compromise most of the tasks described in the ARAt, like putting different types of objects on top of the case e.g. wooden block.
All tasks are timed and scored according to the required time to perform a certain task. This may be the reason why a significant correlation during reaching and a trend towards significance during lifting is found for movement duration. The correlation with HPR during lifting may represent the importance of a straight line trajectory from starting position towards the target. The more deviation from this straight line, the higher the score for HPR, the more time it costs to perform the task, the lower the ARAt score.

MOTOR ACTIVITY LOG. Scores were divided in two sub-scores: ‘Amount of use (AOU)’ and ‘Quality of movement (QOM)’. Total score was referred to as ‘Use’.
The sub-score ‘amount of use’ showed a significant correlation with ROM during transporting. Only trends towards significance were found for movement duration during reaching and for speed during lifting. Movement quality and total scores showed only trends towards significance for ROM during transporting. This is in contrast to the study by Celik et al, which found a fair correlation for trajectory error and a good correlation for movement smoothness. Trajectory error is comparable to the HPR parameter we used in our study. [9,36] None of the skill components showed significant correlations for HPR.
This subjective measuring scale showed little correlations with robot-generated outcome measures. A reason for this may be the fact that a significant better performance during robot-mediated tasks may not transfer to ADL activities. These do not only require upper limb function, but also other components like postural control, lower limb function, etc.

When comparing existing research with our results we can hypothesis that our present study only showed little correlations because of study population having only mild impairments. Existing research was mainly performed on patients after stroke. These included a population scoring significantly lower on clinical outcome measures compared to our study population, except for the ARAt. Most of these studies showed significant correlations when our results only presented weak correlations or trends towards correlations. Little research has been done looking for correlations between clinical and robot-generated outcome measures in PwMS. This hypothesis could not be investigated using existing studies in this population. More research is needed, using a population with more severe upper limb impairments, to see if more correlations can be found. Additionally, force and power measurements should be included in evaluation modules of robotic devices. According to Mercier, shoulder flexor strength and handgrip strength are indicative for upper limb function. These parameters can have their relevance when assessing upper extremity performance.
At last, the relevance of these robot-generated outcome measures are already described in multiple studies using acute and stroke populations. The lack of research performed in persons with Multiple Sclerosis, makes this another point of advice for future research. More research has to focus on the relevance of these robot-generated outcome measures in PwMS.

PART II. EFFECT OF ROBOT-ASSISTED TRAINING ON FUNCTION AND PERFORMANCE OF THE UPPER LIMBS

This part aimed to investigate the effect of robot-assisted training using robot-generated outcome measure, primarily. Additional effects of the same robot-assisted training on clinical outcome measures were investigated. For this purpose experiment 1 and 3 were used.

Subjects

In general subjects included in experiment 3 were younger (53.11 ± 9.69 years) compared to experiment 1 (61.0 ± 8.8 years). Experiment 3 included a population with a lower EDSS score and shorter disease duration. Analysis showed that both groups weren't significantly different.
Robot-generated outcome measures showed significant differences in transporting skill component only. Pre- and post-training ROM was significantly different between populations of the first and third experiment. Hand-path ratio was only significantly different for post-training outcomes. Trends towards significance were found for both pre- and post-training distance measures.
Descriptive characteristics and robot-generated outcome measures showed both groups being comparable.
The protocol composed for experiment 3 calculated a sample size of 15 subjects needed to be included to get satisfying power. Only 13 subjects were included, of which 2 were excluded from analysis because of too little available outcome measures. This compromises the power of the third experiment.

Analyses for effect of robot-assisted training

Analyses were performed using Wilcoxon Signed-Rank test. Experiment 1 showed significant effects of training for the transport and lifting skill components. Movement duration and HPR during transporting significantly decreased at $p<0.05$. Subjects became significantly faster post-training compared to pre-training. Lifting skill component showed significant effect of training by a decrease of movement duration. A trend towards significance could be found for speed. Movement duration and HPR during reaching showed trends towards significance.
Subjects became significantly faster, more accurate and movements were shorter when performing movements from left to right. Also performing a lifting movement took less time.
Comparable research has been performed early on populations of stroke patients. Similar results were found by Celik et al. for trajectory error, comparable to HPR, and mean tangential speed. [9,36] Mean tangential speed is similar to the mean speed we retrieved from the evaluation module of the Haptic Master. In this perspective, the tangential measures the speed of all movements and not necessarily the movements toward the target. [9]
Colombo et al. found significant effect of training on mean velocity in studies performed in 2005 and 2011. [8,31] A study performed by Frisoli et al. used 3 positions towards which reaching movements had to be performed using the L-Exos, namely contralateral (towards the contralateral side of the training arm), central and ipsilateral (towards the side of the trained arm). The contralateral and ipsilateral reaching movements match the transporting skill component presented in our study.

The central reaching task corresponds to the reaching skill component in the Haptic Master evaluation module. Results showed a significant decrease in execution time (movement duration) in all three directions. A second study performed by the same author showed also significant decrease in execution time. Our study found similar result for the transporting movement, but not for the reaching movement. Additionally, Zollo et al. found significant effect of training on movement duration and path length (distance). [34,35]

When we look at the data of the first experiment, we see that for ROM during lifting all subjects scored identical. We can conclude that the maximum ROM possible with the Haptic Master was achieved by all subjects. This maximum score was already achieved in the pre-training evaluations, making it impossible to have additional beneficial effect of the robot-assisted training on this parameter. This was visible in the post-training scores, where all but one subject scored the maximum score all over again. This couldn’t give us an indication of the beneficial effect robot-assisted training could have on lifting performance in persons with multiple sclerosis. We do see that robot-assisted therapy didn’t have a negative effect either.
The same phenomenon presented itself in the third experiment, with almost all subjects reaching the maximum score for ROM during lifting pre- and post-training.
In this light, the Haptic Master device may have a limitation, reaching maximum lifting range of motion very easily. Enlarging the possibility of the mechanism to ensuring the possibility of larger up-down movements, may give additional effect on upper limb function measured with clinical outcome measures and perceived during ADL activities by patients with MS.

For the first experiment we also looked at changes in five clinical outcome measures when comparing pre- to post-training measurements. No significant changes were found in MI, hand grip strength (Jamar), BFM, ARAt and MAL. This may prove our hypothesis that robot-generated outcome measures are more sensitive and subjective to change compared to the classic clinical tests.

The third experiment showed relatively similar results to the first experiment. Movement duration and speed during transporting were significantly different at post-training. In contrast, this experiment showed no significant change in HPR. Reaching movements showed only trends towards significance in the first experiment, but in the third experiment no significant change was found at all. Changes in lifting skill component were the same as in experiment 1, with a significant decrease of movement duration and a trend towards significant increase of speed.
Existing research in stroke patients supports our findings. When looking at existing research on persons with MS, Carpinella at al. found significant changes in movement duration and lateral deviation (HPR) in a study performed in 2009. [38] A study performed in 2012, investigated the effects of 8 sessions of robot-based therapy. [39] Two types of trails were used: (1) null field trials (no force field) and (2) force field trials. The null field trials found significant effect for reaching duration (movement duration) and mean lateral deviation (HPR). The force field trials showed a significant decrease in duration and lateral deviation. [39] These finding also correspond to our findings, mainly movement duration and HPR show significant effect of training.

For all robot-generated parameters, except ROM, the mean of 3 repetitions was used to perform analyses. One extreme value, or lesser performance, may have intervened with the final results. Patients may have experienced an effect of intervention, but one extreme value made them score worse than actually was the case. Significant effects of training may have gone lost because of this.

Calculations on temporary clinical outcome measures of the third experiment showed significant changes of upper limb function after robot-assisted training. Wolf Motor Function test and perceived force showed significant changes. This is contrast to the results found in the third experiment. Despite, these results were only temporary. Still a lot of missing data was included because not all data was processed. Results may be different when the full dataset is available and analysed. A hypothesis for these significant changes may be that these clinical tests are more sensitive to change compared to those included in the first experiment.

When we look at existing research covering these two aims in both stroke and persons with MS, a great variety of robot-generated parameters is identified. Often, parameters are device specific and different between research projects. Different naming but also different definitions are used, making it difficult to compare results of multiple researches. It is advisable that a consensus is made discussing and resolving this problem, making future research more clear and conform.

Conclusion

Robot-generated range of motion was found to be a fair indicator of upper limb function when compared with five clinical tests. Research should be performed on populations experiencing more severe upper limb impairments compared to those included in our research. Existing research performed on stroke patients showed additional correlations in populations experiencing lower levels of function. Research on stroke patients is already well established. Unlike in patients with MS, where there is still a lack of research investigating the relationship between robot-generated and clinical outcome measures for the upper extremity.

Main effects of robot-assisted training were found in movement duration and speed. Further research should also include parameters like force and power, because of the determining effects weakness in shoulder anteflexion strength and hand grip strength on upper limb function. Robotic devices also have to be adapted so maximum performance can be achieved and isn't limited by the mechanism.

List of abbreviations

MS: Multiple Sclerosis; PwMS: person with Multiple Sclerosis; RCT: randomized controlled trial; MI: Motricity Index; BFM: Brunnstrom Fugl-Meyer; ARAt: Action Research Arm test; MAL: Motor Activity Log; AOU: Amount of use; QOM: Quality of movement; (A) ROM: (Active) range of motion ; RMSC: Rehabilitation and Multiple Sclerosis Centre; MAS: Modified Ashworth Scale; ADL: Activities of Daily Living; m: male; f: female; EDSS: Expanded Disability Status Score; M: mean, WMFT: Wolf Motor Function Test; MAM: Manual Ability Test

Competing interests

The authors report no conflicts of interest.

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Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij neurologische aandoeningen**
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