www.uhasselt.be
Universiteit Hasselt
Campus Hasselt:
Martelarenlaan 42 | 3500 Hasselt
Campus Diepenbeek:
Agoralaan Gebouw D | 3590 Diepenbeek

Faculteit Geneeskunde en Levenswetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Actual and perceived upper limb performance after a task-oriented training in people with MS

Jessie Hollandts
Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij neurologische aandoeningen

PROMOTOR :
Prof. dr. Peter FEYS

COPROMOTOR :
dr. Ilse LAMERS

2016
2017

Faculteit Geneeskunde en Levenswetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Actual and perceived upper limb performance after a task-oriented training in people with MS

Jessie Hollandts

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij neurologische aandoeningen

PROMOTOR :

Prof. dr. Peter FEYS

COPROMOTOR :

dr. Ilse LAMERS

Acknowledgement

Upon obtaining my master’s degree in Rehabilitation Sciences and Physical Therapy at the University of Hasselt, I would like to express my sincere gratitude and appreciation to everybody who supported me during the writing of this master thesis.

First, my promotor and co-promotor, Prof. dr. Peter Feys and dr. Ilse Lamers, who guided me during the past two years through this master thesis with the necessary support, supervision, accessibility and valuable feedback to bring this study into success.

The occupational therapists of the Rehabilitation and MS centre Overpelt, for their generous support, time and advice during the training sessions and the assessments.

Dr. Francesca Solmi, whose time and statistical advice were highly appreciated and has been a helpful contribution.

Finally, two fellow students, Jan Spaas and Michaël Meulemans, conducted the analyses of the clinical tests regarding upper limb capacity, and this has turned into a pleasant cooperation for over the past two years.

I would also like to thank the participants, whose commitment and willingness during the intervention has been vital to complete this study to further explore rehabilitation in MS.

During the past two years, it has been a pleasure to study the science and application of actual upper limb performance in neurological rehabilitation, and I believe that the insights gained during this study have been, and will be, a major benefit to our future careers.

Lastly, I wish Prof. dr. Peter Feys and dr. Ilse Lamers the best luck with the continuation and publication of the current pilot RCT, as well as their future research projects, with the purpose to explore further the effects of upper limb rehabilitation in MS.

Thank you.
Jessie

Tessenderlo, August 16, 2017 *J.H.*

1 Research context

The present master thesis involves the domain of neurological rehabilitation. Neurological disorders affect several domains of human functioning, causing range of long-term disabilities. Hundred million people are affected by neurological disorders worldwide, of which approximately more than two million people have multiple sclerosis [1]. Therefore, the disease is the most common neurological disorder among young adults. In Flanders, the prevalence of multiple sclerosis was given as 74/100.000 in 1994 [2], which increased upon 88/100.000 with a growth of 430 new diagnoses per year in Belgium [3]. Overall, the prevalence is increasing due to a longer survival and a true increase in incidence [4].

People with multiple sclerosis present with a varied range of symptoms depending on the location and severity of demyelination and neural atrophy. These patients can suffer from sensorimotor impairments, cognitive malfunction, visual disturbances, speech problems, autonomous dysregulation and fatigue [5]. Upper limb disabilities manifest through a combination of sensory disturbances, muscle weakness, tremor, spasticity/rigidity, fatigability etc [6]. Physical rehabilitations aim to reduce these impairments to maintain the patient's level of functioning. Several approaches in upper limb rehabilitation can be effective in MS [7]. However, more interest on actual upper limb performance has been developed recently. Clinicians claim that an improvement on upper limb capacity does not directly transfers into a favorable progression of daily upper limb use at home. To close this gap between upper limb movements in the clinical setting and upper limb behavior at home, the assessment of actual upper limb performance through accelerometers has been investigated. Unfortunately, the application of the accelerometer in upper limb assessment is not obvious yet. Still, actual upper limb performance is believed to be an important construct in upper limb assessment, because improvements on daily upper limb use are the main goals of rehabilitation.

In the first year of the master's degree, a literature review was conducted on actual upper limb performance in neurological disorders. However, large heterogeneity regarding the parameters of the accelerometer, limited comparisons between studies. Guidelines or recommendations to apply the accelerometers in clinical studies are lacking. Recent studies in stroke failed to show significant improvement on actual upper limb performance after intervention [8-11]. Further, none of the current studies in MS has incorporated accelerometers to assess actual upper limb performance.

In the second year of the master's degree, the research question focused on the effects of technology-support task-oriented training on actual and perceived upper limb performance in multiple sclerosis, and whether these effects are intensity-dependent (i.e. dose-response relation). The current study was conducted at the Rehabilitation and MS centre Overpelt (January 2016 – December 2017) and serves as a pilot study within a larger research project regarding 'the clinical and neural effects of task-oriented upper limb rehabilitation in multiple sclerosis'. This pilot study is still ongoing and to date 22 participants have completed the interventions. The article will be published once a sample of 30 patients has been included. The master thesis was prepared under the supervision of dr. Ilse Lamers and Prof. dr. Peter Feys, who both have great expertise in the assessment and rehabilitation of upper limb disabilities in multiple sclerosis.

The research protocol was largely developed by dr. Ilse Lamers before October 2015. I was not involved in the participant recruitment at the Rehabilitation and MS centre Overpelt. Potential participants were screened regarding inclusion and exclusion criteria by the treating neurologist. I also did not participate at the baseline and post assessments, which were conducted by a blinded assessor, nor at the training sessions, which were performed through the occupational therapists of the centre. However, two fellow students supervised the training sessions, so information regarding the intervention was passed along to me. Before the statistical analyses, I have experienced problems with the MATLAB script, necessary for analyzing the accelerometer output. Eventually, Catherine Lang was willing to help us and handed over their MATLAB script. Hereafter, the experimental measures could be analyzed and converted into Excel files. The results on the clinical tests of upper limb capacity were handed over by the two fellow students, who analyzed these outcome measures. Eventually, I presented preliminary results during a team meeting with my co-promotor, where I received feedback and suggestions. Here, the decision was made to perform statistical analyses only on the accelerometer data from Friday. The academic writing was done independently, as well as the design of the tables and figures. During the writing process, feedback and suggestions were provided by the promotor and co-promotor, for which I would like to express my sincere gratitude.

1. World Health Organization: Atlas multiple sclerosis resources in the world, 2008. Geneva: WHO Press; 2008
2. van Ooteghem, P., et al., P*revalence of multiple sclerosis in Flanders, Belgium.* Neuroepidemiology, 1994. 1**3(**5): p. 220-5.
3. Prevalence and incidence rate http://www.fondation-charcot.org/nl/multiple-sclerose-charcot-stichting
4. Koch-Henriksen, N. and P.S. Sorensen, T*he changing demographic pattern of multiple sclerosis epidemiology.* Lancet Neurol, 2010. 9**(**5): p. 520-32.
5. O'Sullivan, S.B., G.D. Fulk, and T.J. Schmitz, Physical rehabilitation. 2014.
6. Bertoni, R., et al., U*nilateral and bilateral upper limb dysfunction at body functions, activity and participation levels in people with multiple sclerosis.* Mult Scler, 2015. 2**1(**12): p. 1566-74.
7. Lamers, I., et al., U*pper Limb Rehabilitation in People With Multiple Sclerosis: A Systematic Review.* Neurorehabil Neural Repair, 2016. 3**0(**8): p. 773-93.
8. Liao, W.W., et al., E*ffects of robot-assisted upper limb rehabilitation on daily function and real-world arm activity in patients with chronic stroke: a randomized controlled trial.* Clin Rehabil, 2012. 2**6(**2): p. 111-20.
9. Hsieh, Y.W., et al., B*ilateral robotic priming before task-oriented approach in subacute stroke rehabilitation: A pilot randomized controlled trial.* Clin Rehabil, 2016.
10. Shim, S. and J. Jung, E*ffects of bilateral training on motor function, amount of activity and activity intensity measured with an accelerometer of patients with stroke.* J Phys Ther Sci, 2015. 2**7(**3): p. 751-4.
11. Lemmens, R.J., et al., A*ccelerometry measuring the outcome of robot-supported upper limb training in chronic stroke: a randomized controlled trial.* PLoS One, 2014. 9**(**5): p. e96414.

2 Abstract

Background: Upper limb rehabilitation can be effective in people with multiple sclerosis, but none of the current studies included accelerometers to evaluate intervention effects on actual upper limb performance. In neurological diseases, effectiveness on actual upper limb performance is not convincing yet. Task-oriented training might be a valuable rehabilitation approach to improve actual upper limb performance.

Objective: What is the effect of task-oriented training at low and high intensity on the actual upper limb performance, compared to control intervention in people with MS? Additionally, are these changes on actual upper limb performance related to the changes on capacity level and perceived performance?

Methods: 22 people with MS (EDSS range 5-8) were divided into three groups: task-oriented training at high intensity (TOT100 group), low intensity (TOT50 group) and usual occupational therapy (UOT group). Participants were also categorized according to level of upper limb dysfunction (mild, moderate, severe). Participants attended one-hour training sessions, five days/week, for eight weeks. Primary outcome measures were Actigraph and Manual Ability Measure-36 (MAM-36). Secondary outcome measures were Nine Hole Peg Test (NHPT), Action Research Arm Test (ARAT), Box and Block test (BBT) and Test d'Évaluation des Membres Supérieurs des Personnes Âgées (TEMPA).

Results: A mixed model analysis indicated that accelerometer variables did not improve after 8 weeks of training, except for magnitude ratio in the entire sample (p=0,0415) and within the TOT50 group (p<0,0001). The MAM-36 showed significant time effects for the entire sample (p=0,0206). However, none of the primary outcome measures changed between the TOT100 and TOT50 group. Overall, the correlations coefficients between changes on accelerometer variables and changes on capacity measures and MAM-36 were low and not significant, except for Box and Block test.

Conclusion: Actual upper limb performance is an important aspect in upper limb assessment, which is probably not related to other ICF levels. However, task-oriented training does not seem to improve actual upper limb performance, but accelerometers could have failed to capture a minimal change in daily UL use.

3 Introduction

Multiple sclerosis (MS) is an auto-immune disease, characterized by chronic inflammation and destruction of myelin in the Central Nervous System (CNS) [1]. Depending on the extent of neurodegenerative plaques in the cortex, cerebellum or spinal cord, the level of disability vary widely from sensorimotor impairments, visual problems, cognitive decline, fatigue, cerebellar symptoms and autonomous impairments [2].

Upper limb (UL) deficits are quite common in people with multiple sclerosis (pwMS), starting off in the early stages of the disease and increasing with overall disability. Kister, Bacon et al (2013) [3] reported that an impaired hand function is the most frequent symptom in the first year of the disease in 60% of pwMS. According to Bertoni, Lamers et al (2015) [4], bilateral UL abnormalities regarding reduced muscle strength (41%) and altered sensibility (62%) are frequent in severe disease severities (EDSS>5.5). Thereby, 76% of pwMS with UL dysfunctions, experience problems with manual dexterity and manipulating objects in daily life [5]. Bilateral UL symptoms reduces the possibility of coping with the malfunctioning of the most impaired UL with the other one. Studies confirmed that a loss of manual dexterity is associated with a decreased independence in ADL [6] and social activities [7]. Hence, the UL disabilities and manual dexterity problems result in a decreased quality of life [8].

Since there is no pharmacological treatment to cure the disease itself, medicine focus on slowing down the disease course [9]. Consequently, rehabilitation is the main tool to improve or stabilize symptoms related to MS to maintain physical functioning. However, there is a substantial lack of evidence-based interventions, aiming to improve UL abnormalities and manual dexterity in pwMS. Research concerning lower limbs in MS or UL function in other neurological diseases, such as stroke, are more expanded. Lamers, Maris et al. (2016) [10] reported an overview of different rehabilitation strategies for UL function in pwMS. Here, interventions are classified according to the levels of the International Classification of Functioning, disability and health (ICF). To conclude, UL rehabilitation can be effective in pwMS. More interestingly, UL function improves on the same ICF level as the rehabilitation program that it focused on, thus effects on body function are not being transferred to other activity levels, and vice versa. Further superior therapy modalities could not be indicated due to methodological heterogeneity.

To our knowledge, none of the current studies in MS included measures of actual UL performance to evaluate their intervention effects. Though, it is important to know whether gains made in UL capacity further translates into improved UL performance. Capacity describes an individual's ability to execute a task within a structured environment at a single moment. Actual and perceived performance describe a different construct regarding how individuals actually use their UL in their current home environment over a longer period. Although correlations between performance and capacity measures in MS vary from low to high for the dominant hand [11], thus research emphasizes the importance of measuring capacity and performance separately. In the end, the main goal of rehabilitation is to enhance the daily use of the most impaired UL during ADL at home.

Task-oriented approach assumes that patients learn by actively attempting to solve the problems inherent in a functional task rather than by repetitively practicing normal patterns of movement. This approach could be beneficial due to the high specificity of the training components associated with the practice of a meaningful ADL task, whereby the individual adapts the execution to the environment [12, 13]. Task-oriented training in stroke indicates promising effectiveness for UL function [14-16], but effects on actual UL performance are variable. Four Randomized Controlled Trials (RCT) in stroke investigated the effects on actual UL performance after technology-assisted task-oriented training. Two of them revealed significant improvement on amount of arm-hand use after bilateral training with functional tasks [17] and robot-assisted with additional task-oriented training [18], while other two studies regarding robot-assisted priming combined with task-oriented approach [19] and task-oriented training with support of Haptic Master [20] were not significant. Two observational cohorts, investigating individualized, high-repetition, task-specific training, also revealed several significant accelerometer variables [21, 22]. In pwMS, studies investigating task-oriented training are scarce, despite promising results in stroke. In general, little is known about the effectiveness of rehabilitation on actual UL performance in pwMS.

In this single-blind, pilot Randomised Controlled Trial, the main objective is to explore the intensity-dependent effects of task-oriented training on the actual UL performance, compared to usual occupational therapy in a small sample of pwMS. Additionally, the relationship between the changes on actual UL performance and the changes on capacity level and perceived performance are further investigated.

4 Methods

The task-oriented training program and the principles of training progress were based on the successful protocols described for stroke, but never applied in MS [23, 24].

4.1 Participants

Participants (n=22) were recruited at the 'Rehabilitation and MS centre Overpelt' in Belgium. Both hospitalized and ambulatory pwMS referred for UL rehabilitation by the treating neurologist, were allowed for participation in the study. Adults patients (age > 18y), diagnosed with multiple sclerosis according to the McDonald criteria [25] with different levels of self-reported UL dysfunction (six-point Likert scale), were selected. Participants were excluded if they had; (1) a relapse or relapse-related treatment within the last three months prior to the study; (2) complete paralysis of both ULs; (3) severe cognitive or visual deficits interfering with testing and training; (4) other medical conditions interfering with UL function, like orthopaedic or rheumatoid impairments. After an elucidation of the study design and a two-week reflection period, the participants gave their written consent. This pilot study was conducted from January 2016 until December 2017 and was registered at clinicaltrials.gov (NCTO2688231). All procedures were approved by the Medical Ethics Committee of the University of Leuven, Hasselt University and 'Mariaziekenhuis Noord-Limburg' (17/12/2015).

4.2 Study protocol

Participants were stratified into three blocks of UL dysfunction (mild, moderate, severe) based on the capability of raising the arms to 90° anteflexion for 20 seconds and a cut-off score of 33.3 sec on the NHPT [26]. See figure 1 in Appendix for more details. Next, participants were randomized into two groups, namely a higher and a lower intensity task-oriented training group, by an independent staff member using a randomized complete block design. Participants were also blinded, because they were not aware that different treatment intensities were applied.

Before the start of the intervention, participants were asked to choose three tasks from a list of 46 ADL, based on the items of the ABILHAND and Manual Ability Measure-36 (MAM-36). See table 1 in Appendix. Hereafter, the participant's individual maximum number of repetitions was determined for each chosen task during a single session of 60 minutes. The difficulty of the task was adapted to the participant's capabilities and the task was repeated until the individual maximum number of repetitions was reached. Description of these procedures are listed in table 2 in Appendix. During the following training sessions, participants practiced their three tasks at an intensity of 100% of their individual maximum number of repetitions in the *'Task-Oriented Training 100% group'* (TOT100) and at an intensity of 50% of their individual maximum number of repetitions in the *'Task-Oriented Training 50% group'* (TOT50). Participants attended one-hour training sessions, five days/week, for eight weeks. Within a training session, participants completed the repetitions of one task before advancing to another task (blocked practice order) and few rest intervals were allowed (massed practice). More details on the principle of motor learning that were applied during the training sessions are described in table 3 in Appendix. Training sessions were individually guided and supervised by a therapist. The order in which the three tasks were practiced was randomly chosen before each training session. The progression of task difficulty and the introduction of new tasks throughout the training sessions is based on fixed, pre-defined rules for up- and downgrading of the difficulty level. See table 4 in Appendix. To compare both experimental groups with a control intervention, a third, not-randomized group was incorporated during a period when no task-oriented training sessions were given. The 'Usual Occupational Therapy group' (UOT) received usual occupational therapy focusing on UL rehabilitation, with an equal training frequency and duration as the TOT100 and TOT50 group (8 weeks, 5 session/week, 60 minutes). Furthermore, participants from all three groups received their usual physical therapy sessions focusing on lower limb function, gait and balance at the rehabilitation centre, which accounts for additional therapy of 60 minutes, 5 sessions/week for 8 weeks. A complete overview of the study design is given in figure 2 in Appendix.

A technological device, the TagTrainer [27], was used to assist the task-oriented training with real-life objects in both experimental groups. See figure 3 in Appendix for more information. The TagTrainer is a sensor-based tabletop device placed in front of the participant and allows object manipulation on an interactive 24x24 cm board by marking objects with a tag. As such, training tasks are very similar with and without the additional technological support. Colored LED lights on the board provides visual feedback when tags are detected or provide new targets for object placement/movement. The current and target number of repetitions were displayed on a computer screen nearby the participant. A maximum of three TagTrainers could be connected to each other, depending on the demands of the task. For some complex tasks, the TagTrainer was only used to count the number of repetitions (e.g. unbuttoning a shirt). Additionally, a second device, the Diego (Tyromotion), was used for participants who require anti-gravity support during the performance of different UL tasks. The Diego can provide uni- or bilateral support, and does not impede the use of real-life objects.

4.3 Outcome measures

Outcome measures were taken the week before and after the intervention during two sessions of 60 minutes on two consecutive days. All assessments were performed by an assessor blinded for group allocation, except for UOT group. The sequence of the assessment was randomized to avoid order effects. Unilateral tests were completed with both ULs.

4.3.1 Descriptive outcome measures

At baseline, the following demographic and MS-specific characteristics were described; sex, age, hand dominance by Edinburgh Handedness Inventory [28] (ambidextrous participants were regarded as right handed), type of MS, time since diagnosis, neurological severity by EDSS [29], spasticity by modified Ashworth Scale [30], fatigue by modified Fatigue Impact Scale [31] and intention/postural tremor by Fahn's Tremor Rating Scale [32].

4.3.2 Experimental outcome measures

Primary outcome measures – actual performance

The main primary outcome measure for actual UL performance is the accelerometer. Validity and reliability of accelerometer is established in stroke [33-35], but not yet in MS. Here, accelerometers were worn on both wrists (GT3X+, Actigraph) for 5 days, starting from Wednesday 9:00 till Monday 9:00, before and after the 8-week intervention. These sensors record acceleration along three axes in activity counts where 1 count = 0.001664 g. Data were sampled at 30 Hz and activity counts were binned into 1-second epochs for each axis. The devices were also worn during the night (sleeping) and those data are part of the five days or 120 hours. UL movements associated with walking, accelerations through driving and other not goal-directed UL movements, were also included in out calculations. These factors may result in an overestimation of the non-ratio variables for MS, but also in stroke patients [36]. Accelerometers were returned the next Monday after the intervention and the data were downloaded using ActiLife 6 software. However, only accelerometer data from Friday was used for statistical analyses to account for possible placebo effect of the accelerometer. In collaboration with C. Lang, who designed a custom-written software program based on MATLAB script for research in stroke (Waddell et al, 2016), the same MATLAB script derived 6 variables from accelerometer data. Each of these variables quantifies a related aspect of UL activity. In table 5 in Appendix, the 6 variables from the MATLAB script are described in detail: (a) duration of use of the dominant and non-dominant hand; (b) use ratio for the contribution of the most impaired UL relative to the less impaired UL; (c) magnitude ratio for the contribution of both UL to general activity; (d) bilateral magnitude for the intensity of UL movements; (e) median acceleration for overall movement of the most impaired UL; and (f) acceleration variability for the variability of the most impaired UL activity [37]. These variables can detect differences between participants with stroke [38], and with the exception of bilateral magnitude, are responsive to change on UL function following a task-related intervention in individuals post-stroke [21]. However, responsiveness to change on UL function following motor training in pwMS has not been established yet.

Primary outcome measures – perceived performance

Next to actual UL performance, perceived UL performance was measures through Manual Ability Measure-36 (MAM-36). Manual ability measure-36 is a questionnaire, in which patients rate 36 uni- and bilateral task with a four-point scale (0 to 100 points). The sum score is converted into a ‘manual ability measure’ by Rasch-calibration (0 to 100). Validity and reliability is established in MS [39, 40].

Secondary outcome measures – capacity level

Four secondary outcome measures are chosen at capacity level of ICF. The Nine Hole Peg Test (NHPT) is a unilateral assessment of the time, needed to insert and remove nine pegs as fast as possible [39, 40]. The mean time was calculated based on two trials performed with each hand. The Box and Block test (BBT) requires participants to pick up, transport over a wall and release as many blocks as possible from one side of a box to other side within 60 seconds [40, 41]. The score reflects the total number of blocks transported by each hand. The Action Research Arm Test (ARAT) addresses four unilateral subscales: grasp, grip, pinch, gross arm movements [40, 41]. Nineteen items get a score from 0 to 3 with a maximum score of 57. Test d’Évaluation des Membres supérieurs des Personnes Âgées (TEMPA) measures the time and extent of difficulty (from 0 till -3) on four unilateral and five bilateral ADL [40, 42]. Only the level of difficulty score was used for statistical analysis.

4.4 Data analysis

Statistical analyses were performed with SAS JMP Pro 12.2.0. The significant level was set at 0.05. Baseline characteristics of the three groups were compared using non-parametric Kruskal-Wallis for continuous variables and non-parametric Fisher Exact test for categorical variables. Here, the dominant and non-dominant test scores of unilateral tests were analyzed together to obtain a larger data set. For the primary outcome measures, a mixed model analysis was performed to investigate time, group and the group*time interaction as fixed effects. The participant was added as a random effect to account for repeated measurements. The side (dominant vs non-dominant) was nested within the random participant effect to account for the existence of multiple scores on 'the hours of use' of the accelerometer. For the other five accelerometer variables and MAM-36, the dominant and non-dominant UL were blend together into one. Multiple comparisons were performed to test the evolution of score within each group, combined with a correction for multiple testing with Tukey HSD. To check for correct model analyses, normality of the residuals was visually inspected by the normal quantile plots. If normality of residuals was not met, a log transformation was performed after which normal distribution was achieved. This assumption was not met for the magnitude ratio, thus a log transformation was executed. For correlations between changes on actual performance and changes on capacity level and perceived performance, a correlation analysis was performed with the spearman rho correlation coefficients. Non-parametric correlation coefficients were preferred, due to small sample size and lack of normality of the changes on outcome measures. No distinction between groups were made in the sample for the correlations analyses to obtain a lager data set. Moreover, a scatterplot was drawn for visual inspection of the relationship between the changes on the outcome measures.

5 Results

Baseline descriptive characteristics at baseline are given in table 6. Overall, the median score of 7 on EDSS indicated an advanced disease stage (IQR 5.5 – 7.5). This represents an average pwMS who can walk with walking aid, but no more than 5 meters, thus wheelchair use is more assigned for daily use [43]. Further, more than half of the participants (55%) had moderate level of UL dysfunction. High p-values indicates no significant differences between TOT100 (n=7), TOT50 (n=7) and UOT (n=6), except for modified Ashworth Scale.

The causes for the drop-out of two participants (9.1%) was not related to the intervention. One participant in the TOT50 group stopped after seven weeks of the intervention, due to a relapse. One participant in the UOT group withdrew from the study prior to the first training sessions because lack of motivation. Further, post measurements of the accelerometers were missing from two participants, due to refusal to wear the accelerometer and due to faults during the registration process of the data on the computer. In total, complete data of baseline and post measurements were collected from 18 participants (81.8%). Available data from the missing data were included to apply intention-to-treat analysis.

5.1 Training tasks during intervention

The total number of tasks trained was 79, with a mean number of tasks per participant of 5.27 (range 3 to 8). Twenty-four of the 46 training tasks were chosen by at least one participant from the TOT100 or TOT50 group (table 1). The most frequently chosen training tasks were ‘buttoning clothes’, ‘writing sentences’, ‘cutting meat with fork and a knife’ and ‘opening a jar’. One participant with severe UL dysfunction preferred one alternative task that was not included in the list, to improve the active range of motion of elbow extension in the most affected UL (‘wiping off’ sensors on TagTrainer with a tag attached to the finger or a glove).

The number of task repetitions performed during one training session varied substantially between different participants and between different tasks, but a higher median value of 47 repetitions was consistent in the TOT100 group (IQR 38-87) compared to 32 repetitions in the TOT50 group (IQR 26-58). The total number of repetitions performed per participant was also higher in the TOT100 group (median 1569, IQR 1134-2353), compared to the TOT50 group (median 1035, IQR 588-1706) after the 8-week intervention. However, participants in the TOT50 group completed a larger percentage of their target number of repetitions compared to participants in the TOT100 group, with a respectively median of 88% (IQR 82-96) and 72% (IQR 69-76).

Two participants from the TOT50 and TOT100 group started the training sessions with additional, antigravity support from the Diego (Tyromotion), but the assistance could be gradually reduced after two to seven weeks of the intervention.

5.2 Changes on actual and perceived UL performance after intervention

Results on primary outcome measures are presented in table 7 and 8 and figure 4 and 5. Overall, there was no change on actual UL performance on any of the six accelerometer variables, except for the log data of the magnitude ratio. The contribution of each UL to general UL activity was significant improved after 8-week intervention (p=0.04), with a trend toward differences between the groups (p=0.06). Though, significant group*time interaction effects were also found (p<0.001). Multiple comparisons revealed a significant effect in the TOT50 group from baseline to post-intervention (mean difference of -2.87; p<0.0001), compared to a small change in the TOT100 group (mean difference of -0.03; p=0.99) and in the UOT group (mean difference of 0.33; p=0.99). Other group and time effects were not significant for magnitude ratio.

For perceived performance, a significant time effect was found on MAM-36 (p=0.02) without a difference between the interventions (p=0.32). The time*group interaction effect was not significant (p=0.42). Although time effects were also limited, none of the primary outcome measures illustrated significant between-group effects.

Considering the pilot nature of this study with an associated small sample size, an observation analysis is eligible. The change on the accelerometer variables and MAM-36 after intervention, were plotted in a boxplot graph (figure 4 and 5). For each participant, the percentage of change on a test was calculated as: $\%change = \frac{post-pre}{pre} * 100$. The hours of use appear to decline in all groups, except for the most impaired UL in TOT50 group (mean change of 14%). However, the use of the less impaired UL in TOT50 group decreased by 12%. One participant from TOT100 group used their most impaired UL less than 1 hour over 24 hours, while the less impaired UL was used more. No significant effects were found on the use ratio. However, the boxplot graph illustrates a large increase in the TOT50 group (mean change of 44%). In TOT50 group, the use ratio of two participants increased from 0.95 and 0.65 to 2.06 and 1.42

respectively. This indicates that both participants used their most impaired UL more after intervention. Between-group comparisons of the log data of the magnitude ratio revealed significant effect in the TOT50 group, which is also illustrated in the boxplot graph. In TOT50 group, the magnitude ratio of two participants increased from -0.06 and -1.3 to 7 and 0.83 respectively. This indicates an improvement of the amount of most impaired UL use. Here, one participant from TOT100 group reached the minimal value of -7 on the magnitude ratio, which indicates a great amount of less impaired UL activity. For median acceleration, no significant effects were found. However, the boxplot graph illustrates an increase in the TOT50 group (mean change of 69%). Three of five participants in the TOT50 group showed a greater amount of overall activity of the most impaired UL, but one participant in particular increased from 11 to 41. The MAM-36 improved after intervention in the entire sample, without any differences between the groups. Although, the boxplot graph illustrates an increase in the experimental groups. The TOT100 group increased with 8%, compared to 10% increase in the TOT50 group.

Figure 6 provides representative examples of the density plots, which reflects the proportion of the contribution of each UL to general UL activity. Symmetry in the curves of the plot indicates more or less equal UL activity of the most and less impaired UL. The absence of warmer colors indicates less UL movement overall. Often a noticeable peak in the center of the plot indicates more intense UL movements (i.e. larger and faster UL movements), compared to more flattened curves. While some participants showed fluctuations in the shape of the plot, none of the participants changed sustainable over time. In relation with clinical test, the density plots seemed to agree with change on UL capacity and perceived performance. The first four participants with strong density plots also improved on the clinical tests, while participant 5 and 6 show less improvement on the clinical tests, which is reflected in the flattened shape of the density plots.

5.3 Correlation between changes on actual UL performance and changes on capacity level and perceived performance

Correlation coefficients between changes on actual UL performance and changes on UL capacity and perceived performance are provided in table 10. Of all accelerometer variables, none of the correlation coefficients were significant, except for change on BBT (-0.52 for score of the dominant hand). Overall, all correlation coefficients were low.

6 Discussion

This pilot study is the first to explore the effects of task-oriented training on actual UL performance in pwMS, using two different training intensities. In general, accelerometer variables did not improve after 8 weeks of training, in contrast with the significant effects on the MAM-36 from baseline to post. Further, the TOT100 and TOT50 group did not change significantly to each other, so this may suggest that there is no difference between usual occupational therapy and task-oriented training, as well as no intensity-dependent effect (i.e. dose-response relation) regarding actual and perceived UL performance in pwMS. Below, a comprehensive discussion on the study finding is addressed.

6.1 Study findings

Changes on actual and perceived UL performance after intervention

In this pilot study, primary outcome measures addressed both actual and perceived UL performance on ICF activity level. Overall, time effects were found on one accelerometer variable and MAM-36, with a lack of group effects. The magnitude ratio, defined by the contribution of each UL to general UL activity, improved after the eight-week intervention period in the whole sample ($p=0.0415$) and within the TOT50 group ($p<0.0001$). This effect also manifests in the density plots, as magnitude ratio is presented on the x-as. The nearly symmetric plots indicate an equal contribution of each upper limb to UL activity, that improved from baseline to post. Although, it could be expected that duration of activity of each UL would also improve to accomplish a more equal UL contribution, this is not reflected in the duration of use and use ratio. It is possible that both the most and less impaired UL were more active, but not sufficient to reach a significant improvement on the duration of use of each UL separately. The median acceleration, which showed the overall movement of the most impaired UL, did also not increase. The lack of warm colors in the density plots confirmed this result. Further, the intensity of UL activity, defined by the bilateral magnitude, did not improve after 8 weeks in the entire sample, between or within groups. This tendency is noticeable in the density plots, as bilateral magnitude is represented on the y-as. At last, the variability of activity of the most impaired UL, defined by acceleration variability, did also not change over the entire intervention period.

Perceived UL performance also reported significant time effects from baseline to post-intervention for the entire sample (p=0,0206), but improvements were not different between the interventions. Although, several participants reported improvements in their daily arm-hand use through the training program (e.g. one participant mentioned she had less difficulties and was more confident in doing the dishes).

Considering this is the first study to evaluate the effects of task-oriented training on actual UL performance in pwMS, it is difficult to compare these results. In stroke, a recent RCT examined the changes on UL performance after a task-oriented training [37]. Waddell et al (2016) also found no changes on actual UL performance on any of the 6 accelerometer variables. Thereby, the overall amount of movement practice (i.e. 3200, 6400, 9600 or individualized maximum number of repetitions) did not influence the changes on actual UL performance. These results are consistent to our study findings. The accelerometer measurement was similar, except that Waddell et al (2016) conducted the assessments at weekly time interval to account for more than 8 follow-up measurements. The procedures regarding the task-oriented training (e.g. the choice of the tasks, the use of assistance etc.) were not clearly described in the study of Waddell et al (2016), but the training dosage was two, three to four times as high compared to our median of 1569 (TOT100) and 1035 (TOT50) number of repetitions. Nevertheless, no significant effects were found on different training intensities in Waddell et al (2016).

Other RCT's investigating the effects of task-oriented training in neurological diseases, were difficult to compare due to study heterogeneity. Especially, the parameters (e.g. the type, settings and variables) of the accelerometer varied strongly among these RCT's.

Correlation between changes on actual UL performance and changes on capacity level and perceived performance

Correlation analyses failed to reveal significant and high correlations between the changes on actual UL performance and changes on UL capacity and perceived performance, except for the BBT. These results may suggest that changes on UL capacity and perceived performance does not influence changes on actual UL performance. This tendency is consistent with the regression analyses of Waddell et al (2016)[37] and Doman et al (2016)[44], who also concluded that there were inconsistencies between changes on UL capacity and changes on UL performance.

One previous study by Lamers et al (2013) [11] investigated the relation between actual UL performance and clinical tests on different ICF levels in pwMS. For the dominant UL, none of the accelerometer variables were correlated with capacity measures and perceived performance. For the non-dominant hand, correlations between actual UL performance and clinical test were overall high and significant. Of all three accelerometer variables, intensity of movement (PIM) showed the highest correlation with clinical tests. Further, hand dominance influences the magnitude of the correlations. The discrepancy between our study findings and the results of Lamers et al (2013) could be explained through a different accelerometer type. The motionlogger extracted different variables from the accelerometer data, reflecting intensity of movement (PIM), movement frequency (ZC) and time spent in motion above the threshold (TAT). Further, Lamers et al (2013) was a cross-sectional study, in which participants were assessed at one moment. In our study, changes on UL assessment before and after task-oriented training were correlated to each other.

Based on the results of this study and the study in stroke [37], one may suggest that changes on capacity level and perceived performance are not correlated with changes on actual UL performance. This contradicts the clinical assumptions that improving UL capacity in the clinical setting, directly translates to an increased actual UL performance in daily life. It could be possible that changes on UL capacity may be insufficient to improve actual UL performance. Perhaps, UL capacity needs to reach a specific threshold to cause a change on actual UL performance [45, 46]. Moreover, self-perception of changes on UL performance might be a valuable component, but these scales may not reflect the actual performance because of cognitive dysfunctions and other biases. One may conclude that it is important to assess all different ICF levels to get a full image of the UL function. More evidence from larger trials with regression analyses are needed to make firm conclusions.

Actual upper limb performance

The lack of significant effects on actual UL performance could be explained through the intervention undertaken or through the responsiveness of accelerometers to change. It is possible that task-oriented UL training was not adequate to improve actual UL performance in daily life, despite promising effectiveness on UL capacity in stroke and pwMS. Adaptations towards the individual's training preferences and the specificity of the training could assume that participants were most likely to improve UL tasks that were trained, and thus change daily behavior at home. The intervention incorporated several principles of motor learning (table 3), in that way task-oriented training is expected to improve actual UL performance. These assumptions are enhanced by several participants, who reported that they used their UL more for daily activities.

Another factor that could explain these striking results is the responsiveness of the accelerometer to change. Accelerometers could have failed to capture changes that really occurred. Responsiveness of accelerometer has been illustrated in stroke patients [21], but not in pwMS. First, accelerometer parameters, such as the sample frequency and epoch, the wearing time and the variables play a key role. Thereby, wearing sensors on the ULs could potentially trigger participants to use their ULs more in daily life. Apart from the placebo effects, wearing adherence is another factor that could underestimate actual UL performance. Some studies asked participants to register their daily UL activities in a diary to solve the problems regarding adherence [35, 47]. Current studies pointed out the lack of guidelines or recommendations in using the accelerometers in clinical studies, taking placebo effects and wearing adherence into account.

Secondly, accelerometers mainly represent the amount of daily UL use, but are not capable to register quality of movement. An increase in the amount of daily UL use may not necessarily reflect a better quality of UL movements (e.g. speed, efficiency, accuracy). Perhaps some participants made small improvements in these parameters, that were not measured.

6.2 Methodological considerations

Training program and rehabilitation technology

Several principles of motor learning were implemented in the training to stimulate learning and transfer effects (table 3) [48, 49]. The training components 'random' and 'distributed' practice could be beneficial, but were not implemented due to practical concerns.

The addition of technology to support UL training is an upcoming approach in rehabilitation, and might gain several advantages such as increasing total therapy time and enabling independent and quantifiable training [24]. The TagTrainer allows training of functional ADL with both ULs using real-life objects on ICF activity level, which is different to most robot-assisted UL rehabilitation. Despite the lack of feedback of 'knowledge of performance', the feedback regarding the number of repetitions and the LED lights displaying errors or success in object placement, can be important in guiding the training and maintaining motivation of patient. The clinical usability of the TagTrainer was already investigated among therapists treating patients with stroke and tetraplegia [27]. To our knowledge, this study is the first clinical trial to integrate the TagTrainer in an UL training program.

Upper limb dysfunction levels

Participants were stratified intro three different UL dysfunction levels for two reasons. First, this classification had ensured a balanced distribution among groups (TOT100 and TOT50) through blocked randomization even in a small sample. Secondly, it was the aim to explore whether the response to task-oriented UL training differed for pwMS with varying levels of UL dysfunctions. However, due to small sample size, no statistical analyses were performed to answer this research objective.

Upper limb tests appear to be adequate to separate patient subgroups, but there is currently no gold standard test or procedure for UL available. Here, participants were classified based on their distal UL function with a cut-off value on NHPT, described in MS literature (33.3 sec)[26] , as well as their proximal UL function with a self-selected criterion for shoulder anteflexion (90° anteflexion for 20 sec). Using these criteria, most participants were classified as having mild (n=6) or moderate (n=11) UL dysfunctions, while the three participants with severe UL dysfunctions were distributed in each of the intervention groups (TOT100, TOT50 and UOT group). In general, sample was too small to draw conclusions, and observational analysis did not reveal clear difference in training response between the different levels of UL dysfunctions. It might be possible that a different classification method resulted in a different outcome [50].

Training intensity

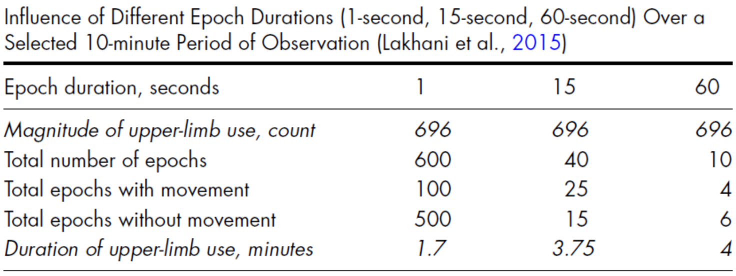
Training intensity act as one of key determinant of training dosage [51]. Previous research in stroke rehabilitation concluded that the time scheduled for therapy may not accurately reflect the actual practice time nor the number of movement repetitions performed [52], and as such does not reflect therapy dosage optimally. To date, there are no studies investigating the effects of UL training at different training intensities in pwMS (i.e. dose-response relation).

In the present study, training intensity was determined based on an individualized maximum number of repetitions as reference, instead of a fixed number of repetitions in previous studies [22, 23, 53]. This method was preferred to ensure feasibility of the training program, even in pwMS with severe UL dysfunctions. Participants from all UL dysfunction levels were capable to perform this high-intense task-oriented training for one hour without any adverse effects. However, participants from the TOT100 group had more difficulties to reach their target number of repetitions compared to the TOT50 group. This tendency could be explained through the difficulty of the tasks. Based on the results of Waddell et al (2016)[37], it could be assumed that a higher intensity does not necessarily influence the results. It is questionable whether this high dosage in stroke (i.e. 3200, 6400, 9600 or individualized maximum number of repetitions) is even feasible in pwMS, taking possible adverse effects and drop-outs into account. One may state that it is not necessary to request the patient to perform a task as many times as possible in clinical practice to accomplish an improvement.

Accelerometers

Like mentioned before, the responsiveness of the accelerometer to change is crucial in clinical trials, and is dependent on the selection of the parameters. The accelerometer is assumed to be a good assessment tool to register arm-hand movement, even small, dexterous movements of the fingers can be picked up by accelerometers [54]. First, the type of accelerometer is addressed. Hayward, Eng et al (2016) [55] recommended to use multiaxial accelerometer devices. Here, the Actigraph was preferred based on previous work investigating reliability, validity and responsiveness in stroke patients [21, 56]. However, psychometrics of accelerometers in pwMS are lacking.

Secondly, sample frequency and epoch duration are discussed. Here, data from the accelerometers were sampled at 30 Hz, based on the range of sample frequency [10 – 30 Hz] in previous studies in stroke [17-20]. However, studies investigating the correct sample frequency necessary to record small UL movements are lacking. It could be expected that a high sample rate is necessary to capture a minimal change on actual UL performance, thus it is possible that a frequency of 30 Hz is too low for an accurate registration of UL movements. Activity counts were binned into 1-second epochs for each axis, based on previous studies in stroke [21, 56, 57]. In Hayward, Eng et al (2016) [55], the influence of different epoch durations was illustrated in a table. These figures suggest that a longer epoch duration could lead to considerable errors in duration of use estimates, thus a short epoch is preferred for a more accurate representation of daily UL activity.



Influence of Different Epoch Durations (1-second, 15-second, 60-second) Over a Selected 10-minute Period of Observation (Lakhani et al., 2015)

Epoch duration, seconds	1	15	60
Magnitude of upper-limb use, count	*696*	*696*	*696*
Total number of epochs	600	40	10
Total epochs with movement	100	25	4
Total epochs without movement	500	15	6
Duration of upper-limb use, minutes	*1.7*	*3.75*	*4*

Table 10: Influence of different epoch durations

As a third parameter, the duration of the wearing period of the accelerometer is addressed. Hayward, Eng et al (2016) [55] preferred a multiple day assessment to counterbalance the variability in daily UL use, taking placebo effects into account. In general, a 3-day measurement was recommended over a 1 or 7-day assessment, but commitment and motivation of the patient is an important criterion. In addition, monitoring days should cover a single week- and weekend day, because of differences in employment and type of activities. Here, the accelerometers were worn from Wednesday till Monday to include a 5-day assessment with three weekdays and a full weekend. However, to compare results with other RCT's investigating actual UL performance in stroke [37], a single day assessment of 24 hours was preferred for statistical analysis. Friday was chosen, considering this is the last day of the week and the start of the weekend, with two days to counteract for placebo effects. Unfortunately, the benefits of multiple day assessment fades away. Despite, C. Lang suggested that a 24-hour measurement period is sufficient for a valid and representative outcome [58, 59].

The final parameter discussed, is the variables that can be derived from accelerometer data. Because the same MATLAB script from Waddell et al [37] was used in this study, the variables are similar. Despite that reliability, validity and responsiveness has been investigated in preliminary studies, it is still questionable whether the variables also quantify specific quality-related movement parameters (e.g. speed, efficiency, accuracy). Further, some pwMS in this study reached the minimum and maximum value of the magnitude ratio, which may indicate possible floor and ceiling effects. Floor and ceiling effects could be different in MS compared to stroke, because of more bilateral UL disabilities. Future research needs to explore more the different variables that can be derived from accelerometer data, to achieve a more accurate representation of the amount of daily UL use and the quality of the UL movements.

6.3 Study limitations

Several limitations need to be discussed. First, the number of participants was small (n=23), despite the broad inclusion criteria which were deliberately chosen for this pilot study. Large variability in the data limits generalization of the study findings. Therefore, the evaluation of outliers, and their possible influence on a small data set, is difficult. Second, group composition was not completely balanced, because the UOT group was recruited separately without randomization. An equal distribution of UL dysfunctions between the TOT100 and TOT50 group was achieved, in contrast to the UOT group. The pilot study is still ongoing with the aim to collect data of ten participants in each group. Third, missing data of accelerometer assessment from two participants in the TOT50 group were consequences of technological errors and the appearance of the accelerometer. Fourth, the content and intensity of the UOT training sessions were not registered. Fifth, therapists were not blinded for group allocation. The assessor was only blinded regarding the TOT100 and TOT500 group, but not for the UOT group, causing a possible bias. Sixth, therapy adherence seemed to be a problem during analyses, but the actual wearing time of the accelerometer could not be determined precisely. This limitation could underestimate an accurate representation of daily UL use.

6.4 Future research

This pilot study is the first to explore effects on actual and perceived UL performance after task-oriented training in pwMS. Power calculations for sample size should be made for larger RCT in the future. The dose-response relationship of task-oriented training in pwMS should be explored further with more differentiation between training intensities. Previous research has shown that neuroimaging can yield distinct outcomes from clinical test after UL rehabilitation in MS [50], so these neuroimaging techniques can be added in a larger RCT.

More importantly, there is an urgent need for recommendations or guidelines to implement accelerometer in clinical trials, especially for the selection of the parameters. Psychometrics of accelerometer needs to be expanded in other neurological diseases in larger trials. Responsiveness needs to be explore more in depth regarding the minimal detectable change (MDC) and minimal clinical important change (MCIC). Further, the applications of the accelerometer need to be explored widely for more quality-related variables. The future aim of accelerometer is more focused on the recognition of UL movement, linked to a certain type of task [60, 61].

6.5 Conclusion

Actual UL performance is an important construct in UL assessment, which could be best assessed separately from UL capacity during rehabilitation. Actual UL performance does not seem to improve after task-oriented training, despite promising effects on perceived UL performance and UL capacity. It could be assumed that accelerometers fail to capture minimal change of daily UL use after intervention. There is an urgent need for recommendations or guidelines to use accelerometers properly in clinical studies.

7 References

1. MeSH definition from PubMed https://www.ncbi.nlm.nih.gov/mesh/68009103
2. O'Sullivan, S.B., G.D. Fulk, and T.J. Schmitz, Physical rehabilitation. 2014
3. Kister, I., et al., *Natural history of multiple sclerosis symptoms.* Int J MS Care, 2013. **15**(3): p. 146-58.
4. Bertoni, R., et al., *Unilateral and bilateral upper limb dysfunction at body functions, activity and participation levels in people with multiple sclerosis.* Mult Scler, 2015. **21**(12): p. 1566-74.
5. Johansson, S., et al., *High concurrent presence of disability in multiple sclerosis. Associations with perceived health.* J Neurol, 2007. **254**(6): p. 767-73.
6. Chen, C.C., et al., *Hand strength and perceived manual ability among patients with multiple sclerosis.* Arch Phys Med Rehabil, 2007. **88**(6): p. 794-7.
7. Yozbatiran, N., et al., *Motor assessment of upper extremity function and its relation with fatigue, cognitive function and quality of life in multiple sclerosis patients.* J Neurol Sci, 2006. **246**(1-2): p. 117-22.
8. Kierkegaard, M., et al., *The relationship between walking, manual dexterity, cognition and activity/participation in persons with multiple sclerosis.* Mult Scler, 2012. **18**(5): p. 639-46.
9. Nandoskar, A., et al., *Pharmacological Approaches to the Management of Secondary Progressive Multiple Sclerosis.* Drugs, 2017.
10. Lamers, I., et al., *Upper Limb Rehabilitation in People With Multiple Sclerosis: A Systematic Review.* Neurorehabil Neural Repair, 2016. **30**(8): p. 773-93.
11. Lamers, I., et al., *Perceived and actual arm performance in multiple sclerosis: relationship with clinical tests according to hand dominance.* Mult Scler, 2013. **19**(10): p. 1341-8.
12. Wade, E. and C.J. Winstein, *Virtual reality and robotics for stroke rehabilitation: where do we go from here?* Top Stroke Rehabil, 2011. **18**(6): p. 685-700.
13. Rensink, M., et al., *Task-oriented training in rehabilitation after stroke: systematic review.* J Adv Nurs, 2009. **65**(4): p. 737-54.
14. Timmermans, A.A., et al., *Effects of task-oriented robot training on arm function, activity, and quality of life in chronic stroke patients: a randomized controlled trial.* J Neuroeng Rehabil, 2014. **11**: p. 45.
15. Winstein, C.J., et al., *Effect of a Task-Oriented Rehabilitation Program on Upper Extremity Recovery Following Motor Stroke: The ICARE Randomized Clinical Trial.* Jama, 2016. **315**(6): p. 571-81.
16. Hubbard, I.J., et al., *Task-specific training: evidence for and translation to clinical practice.* Occup Ther Int, 2009. **16**(3-4): p. 175-89.
17. Shim, S. and J. Jung, *Effects of bilateral training on motor function, amount of activity and activity intensity measured with an accelerometer of patients with stroke.* J Phys Ther Sci, 2015. **27**(3): p. 751-4.
18. Liao, W.W., et al., *Effects of robot-assisted upper limb rehabilitation on daily function and real-world arm activity in patients with chronic stroke: a randomized controlled trial.* Clin Rehabil, 2012. **26**(2): p. 111-20.
19. Hsieh, Y.W., et al., *Bilateral robotic priming before task-oriented approach in subacute stroke rehabilitation: A pilot randomized controlled trial.* Clin Rehabil, 2016.
20. Lemmens, R.J., et al., *Accelerometry measuring the outcome of robot-supported upper limb training in chronic stroke: a randomized controlled trial.* PLoS One, 2014. **9**(5): p. e96414.
21. Urbin, M.A., K.J. Waddell, and C.E. Lang, *Acceleration metrics are responsive to change in upper extremity function of stroke survivors.* Arch Phys Med Rehabil, 2015. **96**(5): p. 854-61.
22. Waddell, K.J., et al., *Feasibility of High-Repetition, Task-Specific Training for Individuals With Upper-Extremity Paresis.* American Journal of Occupational Therapy, 2014. **68**(4): p. 444-453.
23. Birkenmeier, R.L., E.M. Prager, and C.E. Lang, *Translating animal doses of task-specific training to people with chronic stroke in 1-hour therapy sessions: a proof-of-concept study.* Neurorehabil Neural Repair, 2010. **24**(7): p. 620-35.

24. Timmermans, A.A., et al., *Technology-assisted training of arm-hand skills in stroke: concepts on reacquisition of motor control and therapist guidelines for rehabilitation technology design.* J Neuroeng Rehabil, 2009. **6**: p. 1.
25. Polman, C.H., et al., *Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria.* Ann Neurol, 2011. **69**(2): p. 292-302.
26. Lamers, I., et al., *Associations of upper limb disability measures on different levels of the International Classification of Functioning, Disability and Health in people with multiple sclerosis.* Phys Ther, 2015. **95**(1): p. 65-75.
27. Tetteroo, D., et al., *TagTrainer: supporting exercise variability and tailoring in technology supported upper limb training.* J Neuroeng Rehabil, 2014. **11**: p. 140.
28. Oldfield, R.C., *The assessment and analysis of handedness: the Edinburgh inventory.* Neuropsychologia, 1971. **9**(1): p. 97-113.
29. Kurtzke, J.F., *Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS).* Neurology, 1983. **33**(11): p. 1444-52.
30. Bohannon RW, S.M., *Interrater reliability of a modified Ashworth scale of muscle spasticity.* Phys Ther 67(2):206-7, Feb 1987.
31. Kos, D., et al., *Assessing fatigue in multiple sclerosis: Dutch modified fatigue impact scale.* Acta Neurol Belg, 2003. **103**(4): p. 185-91.
32. Hooper, J., et al., *Rater reliability of Fahn's tremor rating scale in patients with multiple sclerosis.* Arch Phys Med Rehabil, 1998. **79**(9): p. 1076-9.
33. Uswatte, G., et al., *Validity of accelerometry for monitoring real-world arm activity in patients with subacute stroke: evidence from the extremity constraint-induced therapy evaluation trial.* Arch Phys Med Rehabil, 2006. **87**(10): p. 1340-5.
34. Reiterer, V., et al., *Actigraphy--a useful tool for motor activity monitoring in stroke patients.* Eur Neurol, 2008. **60**(6): p. 285-91.
35. van der Pas, S.C., et al., *Assessment of arm activity using triaxial accelerometry in patients with a stroke.* Arch Phys Med Rehabil, 2011. **92**(9): p. 1437-42.
36. Uswatte, G., et al., *Ambulatory monitoring of arm movement using accelerometry: an objective measure of upper-extremity rehabilitation in persons with chronic stroke.* Arch Phys Med Rehabil, 2005. **86**(7): p. 1498-501.
37. Kimberly J Waddell, M., OTR/L1; Michael J Strube, PhD2; Ryan R Bailey, PhD, OTR/L1, Joseph W Klaesner, PhD1, Rebecca L Birkenmeier, OTD, OTR/L1,3,4; Alexander W Dromerick, MD5; Catherine E Lang, PT, PhD1,3,4, *Does task-specific training improve upper limb performance in daily life post-stroke.* Neurorehabilitation and Neural Repair.
38. Bailey, R.R., J.W. Klaesner, and C.E. Lang, *Quantifying Real-World Upper-Limb Activity in Nondisabled Adults and Adults With Chronic Stroke.* Neurorehabil Neural Repair, 2015. **29**(10): p. 969-78.
39. Lamers, I. and P. Feys, *Assessing upper limb function in multiple sclerosis.* Mult Scler, 2014. **20**(7): p. 775-84.
40. Lamers, I., et al., *Upper limb assessment in multiple sclerosis: a systematic review of outcome measures and their psychometric properties.* Arch Phys Med Rehabil, 2014. **95**(6): p. 1184-200.
41. Platz, T., et al., *Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer Test, Action Research Arm Test and Box and Block Test: a multicentre study.* Clin Rehabil, 2005. **19**(4): p. 404-11.
42. Feys, P., et al., *Validity of the TEMPA for the measurement of upper limb function in multiple sclerosis.* Clin Rehabil, 2002. **16**(2): p. 166-73.
43. EDSS scale on National MS fonds https://www.nationaalmsfonds.nl/over-ms/prognose/edss
44. Doman, C.A., et al., *Changes in Upper-Extremity Functional Capacity and Daily Performance During Outpatient Occupational Therapy for People With Stroke.* Am J Occup Ther, 2016. **70**(3): p. 7003290040p1-7003290040p11.

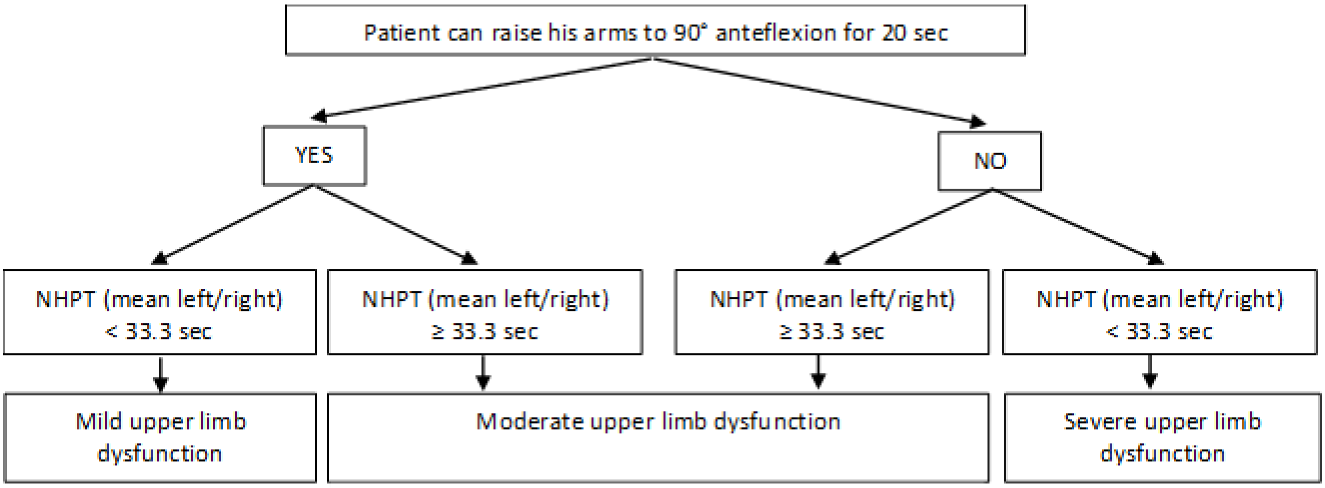
45. Hidaka, Y., et al., *Use it and improve it or lose it: interactions between arm function and use in humans post-stroke.* PLoS Comput Biol, 2012. **8**(2): p. e1002343.
46. Schweighofer, N., et al., *A functional threshold for long-term use of hand and arm function can be determined: predictions from a computational model and supporting data from the Extremity Constraint-Induced Therapy Evaluation (EXCITE) Trial.* Phys Ther, 2009. **89**(12): p. 1327-36.
47. Thrane, G., et al., *Arm use in patients with subacute stroke monitored by accelerometry: association with motor impairment and influence on self-dependence.* J Rehabil Med, 2011. **43**(4): p. 299-304.
48. Spooren, A.I., A.A. Timmermans, and H.A. Seelen, *Motor training programs of arm and hand in patients with MS according to different levels of the ICF: a systematic review.* BMC Neurol, 2012. **12**: p. 49.
49. Timmermans, A.A., et al., *Influence of task-oriented training content on skilled arm-hand performance in stroke: a systematic review.* Neurorehabil Neural Repair, 2010. **24**(9): p. 858-70.
50. Bonzano, L., et al., *Upper limb motor rehabilitation impacts white matter microstructure in multiple sclerosis.* Neuroimage, 2014. **90**: p. 107-16.
51. Page, S.J., A. Schmid, and J.E. Harris, *Optimizing terminology for stroke motor rehabilitation: recommendations from the American Congress of Rehabilitation Medicine Stroke Movement Interventions Subcommittee.* Arch Phys Med Rehabil, 2012. **93**(8): p. 1395-9.
52. Lohse, K.R., C.E. Lang, and L.A. Boyd, *Is more better? Using metadata to explore dose-response relationships in stroke rehabilitation.* Stroke, 2014. **45**(7): p. 2053-8.
53. Lang, C.E., et al., *Dose response of task-specific upper limb training in people at least 6 months poststroke: A phase II, single-blind, randomized, controlled trial.* Ann Neurol, 2016. **80**(3): p. 342-54.
54. Rowe, J.B., et al., *The variable relationship between arm and hand use: a rationale for using finger magnetometry to complement wrist accelerometry when measuring daily use of the upper extremity.* Conf Proc IEEE Eng Med Biol Soc, 2014. **2014**: p. 4087-90.
55. Hayward, K.S., et al., *Exploring the Role of Accelerometers in the Measurement of Real World Upper-Limb Use After Stroke.* Brain Impairment, 2016. **17**(1): p. 16-33.
56. Urbin, M.A., R.R. Bailey, and C.E. Lang, *Validity of body-worn sensor acceleration metrics to index upper extremity function in hemiparetic stroke.* J Neurol Phys Ther, 2015. **39**(2): p. 111-8.
57. Bailey, R.R., J.W. Klaesner, and C.E. Lang, *An accelerometry-based methodology for assessment of real-world bilateral upper extremity activity.* PLoS One, 2014. **9**(7): p. e103135.
58. Bailey, R.R. and C.E. Lang, *Upper-limb activity in adults: referent values using accelerometry.* J Rehabil Res Dev, 2013. **50**(9): p. 1213-22.
59. Michielsen, M.E., et al., *Quantifying nonuse in chronic stroke patients: a study into paretic, nonparetic, and bimanual upper-limb use in daily life.* Arch Phys Med Rehabil, 2012. **93**(11): p. 1975-81.
60. Biswas, D., et al., *Recognition of elementary arm movements using orientation of a tri-axial accelerometer located near the wrist.* Physiol Meas, 2014. **35**(9): p. 1751-68.
61. Lemmens, R.J., et al., *Recognizing complex upper extremity activities using body worn sensors.* PLoS One, 2015. **10**(3): p. e0118642.

8 Appendix

8.1 Figures

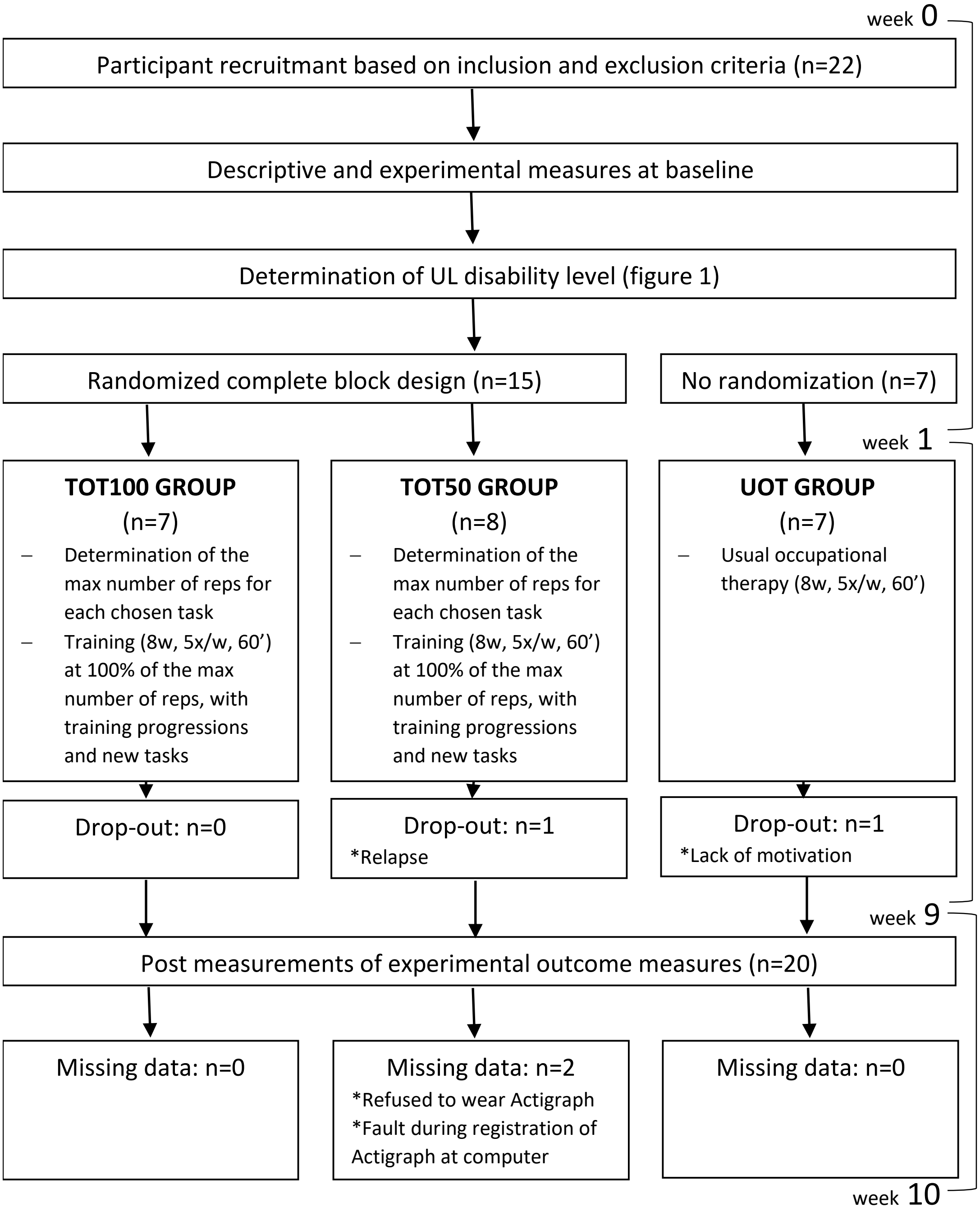
8.2 Tables

8.1.1. **Figure 1:** Determination of the upper limb dysfunction level



NHPT = Nine Hole Peg Test

8.1.2. **Figure 2:** Study design



8.1.3. **Figure 3:** Description and illustrations of the training set-up with the equipment

A participant practicing the task 'taking the cap off a bottle'. The Diego (Tyromotion) is used for antigravity support of both upper limbs and the TagTrainer provides targets for placement of the cap and the bottle through LED lights. The participant must place the tag (placed on top of the cap) on the blue LED light. The current and target number of repetitions are displayed on a computer screen.

8.1.4. **Figure 4:** Actual upper limb performance for all 6 accelerometer variables by group

a) Hours of use (less impaired vs most impaired UL)

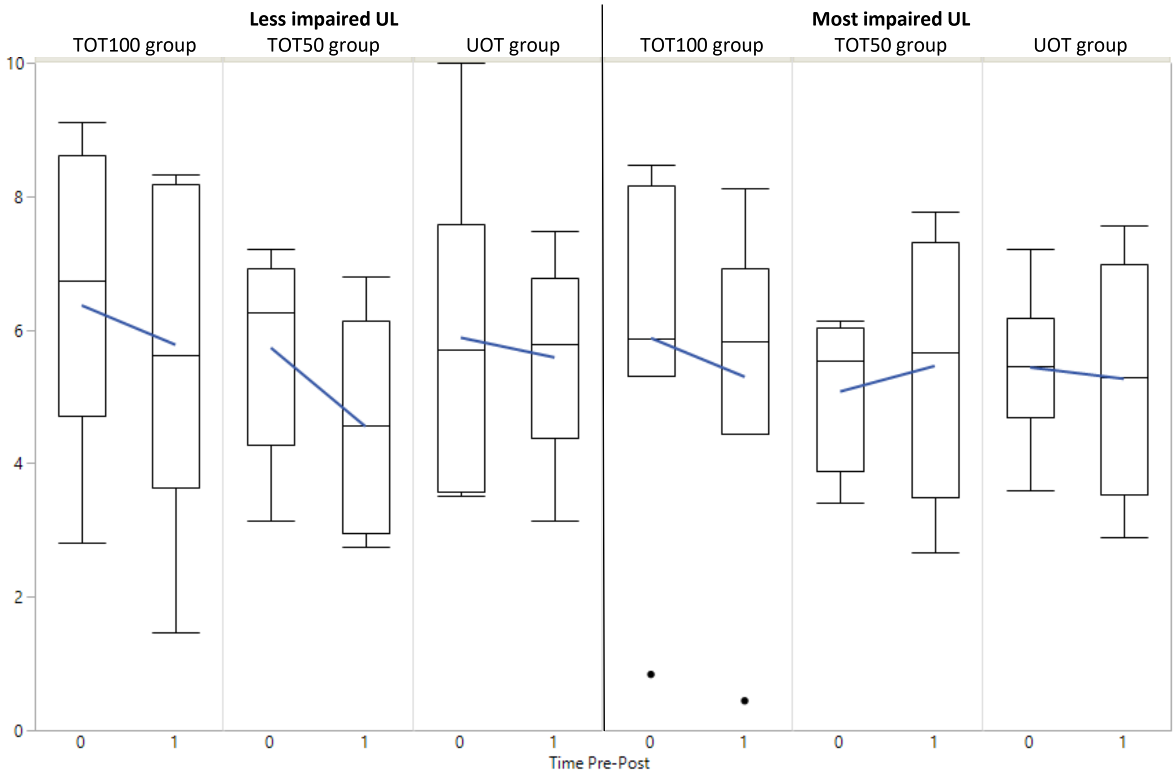


Figure 4a: Boxplot represents median and IQR. Blue line indicates group mean scores between baseline and post measurement. Note two drop-out in the TOT50 group and UOT group, two participants with missing post-data in the TOT50 group. Black points indicate a participant in TOT100 group, who used their most impaired UL for less than one hour for 24 hours.

b) Use ratio

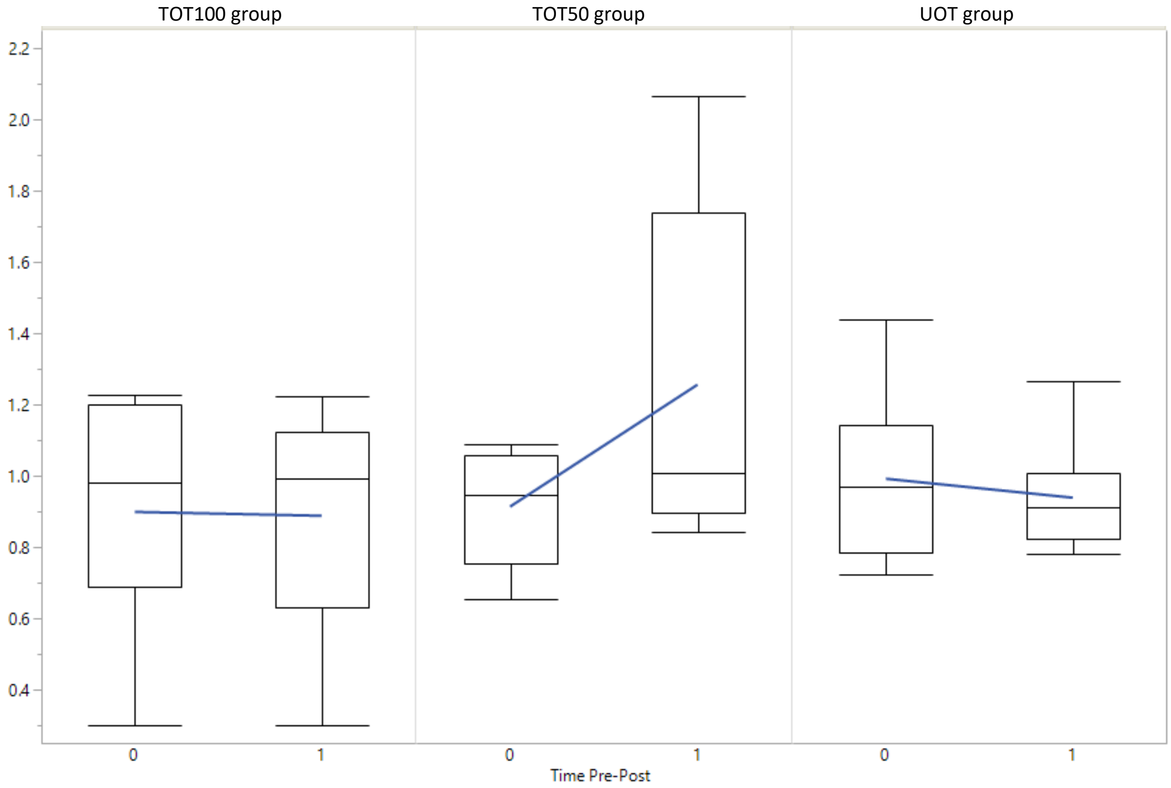


Figure 4b: Boxplot represents median and IQR. Blue line indicates group mean scores between baseline and post measurement. Note two drop-out in the TOT50 group and UOT group, two participants with missing post-data in the TOT50 group.

c) Magnitude ratio

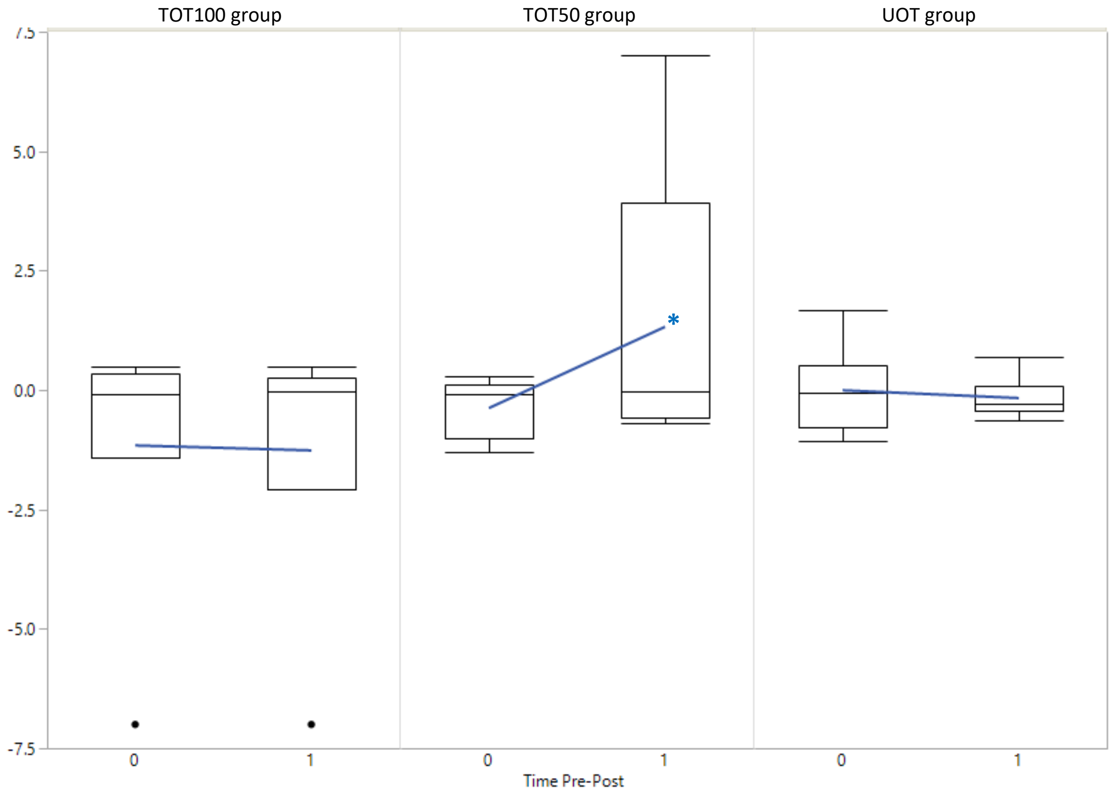


Figure 4c: Boxplot represents median and IQR. Blue line indicates group mean scores between baseline and post measurement. Note two drop-out in the TOT50 group and UOT group, two participants with missing post-data in the TOT50 group. Black points indicate a participant in TOT100 group with a great amount of less impaired UL activity.
*significant time effect in the TOT50 group (mean difference of -2.87; p<0.0001)

d) Bilateral magnitude

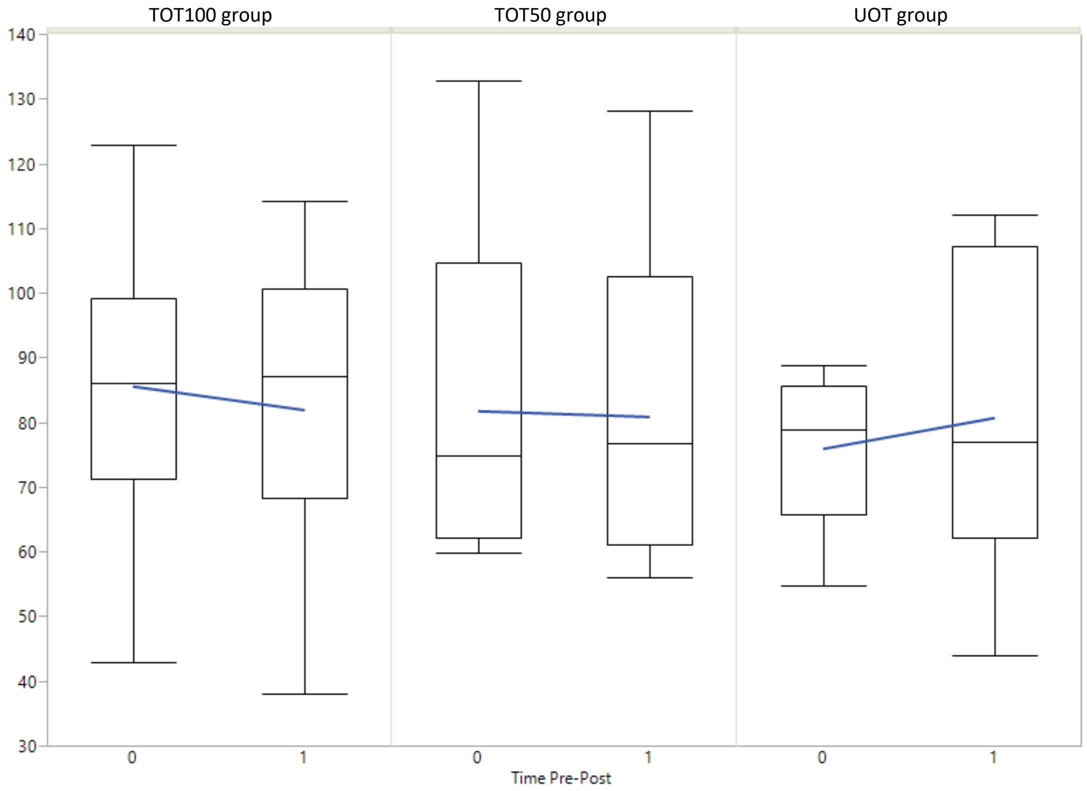


Figure 4d: Boxplot represents median and IQR. Blue line indicates group mean scores between baseline and post measurement. Note two drop-out in the TOT50 group and UOT group, two participants with missing post-data in the TOT50 group.

e) Median acceleration

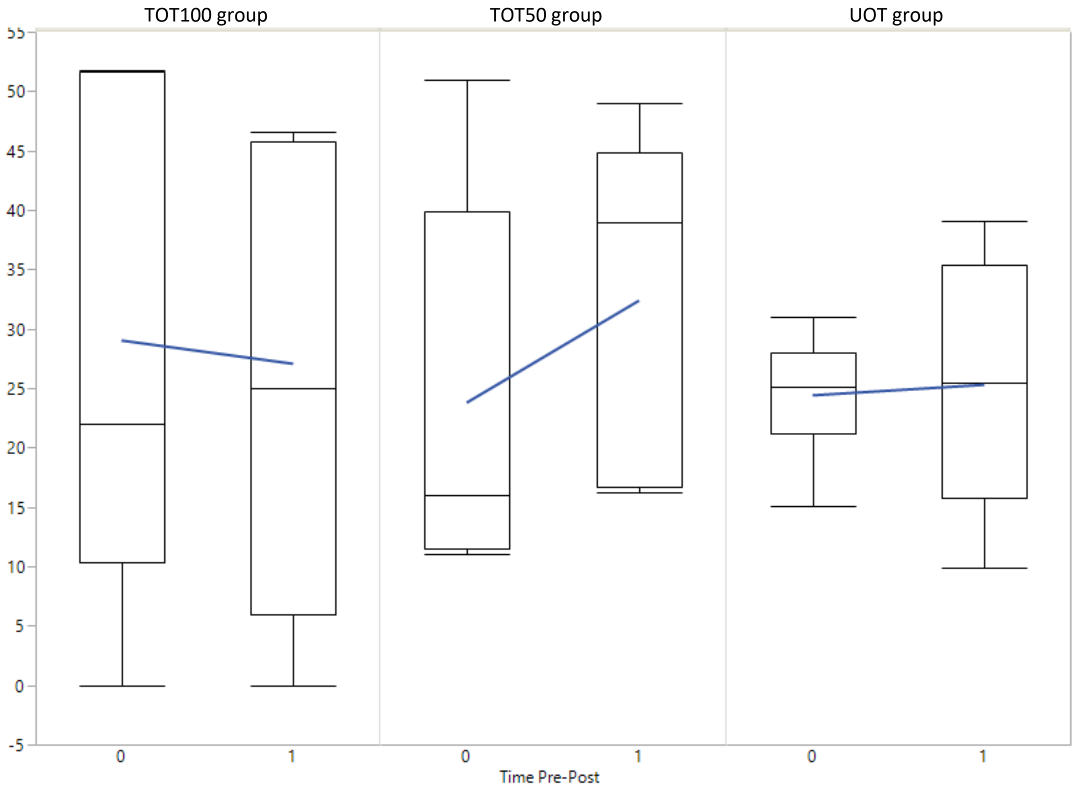


Figure 4e: Boxplot represents median and IQR. Blue line indicates group mean scores between baseline and post measurement. Note two drop-out in the TOT50 group and UOT group, two participants with missing post-data in the TOT50 group.

f) Acceleration variability

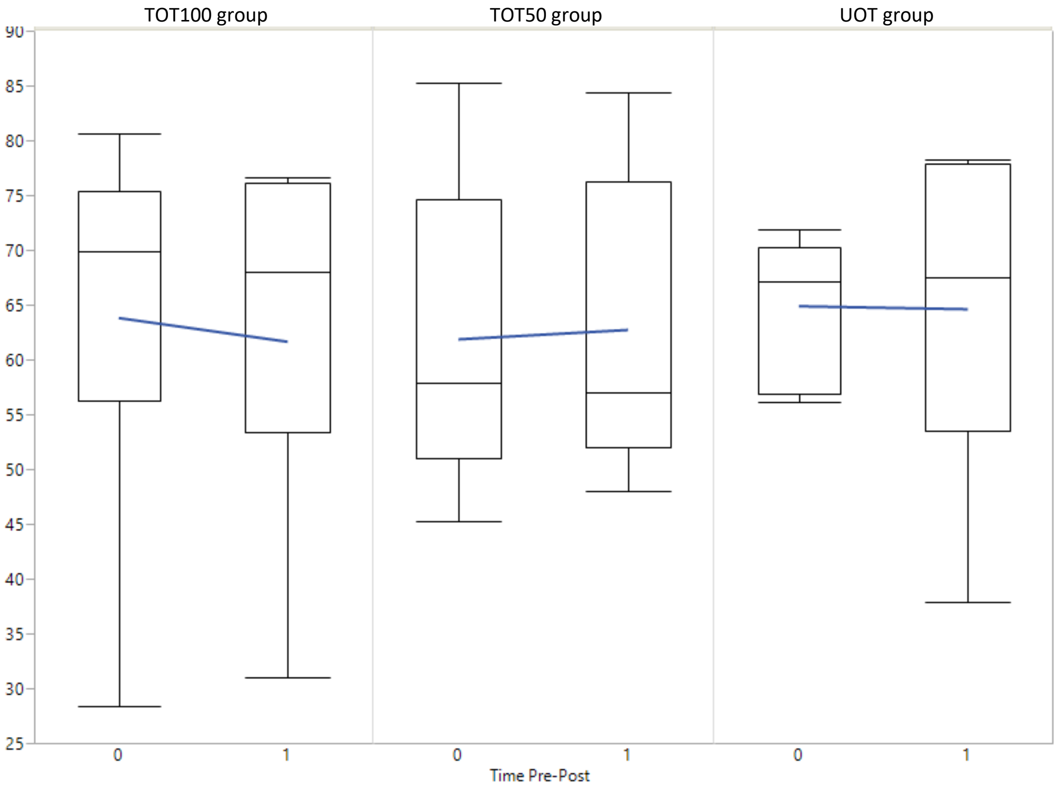


Figure 4f: Boxplot represents median and IQR. Blue line indicates group mean scores between baseline and post measurement. Note two drop-out in the TOT50 group and UOT group, two participants with missing post-data in the TOT50 group.

8.1.5. **Figure 5:** Perceived upper limb performance for MAM-36 by group

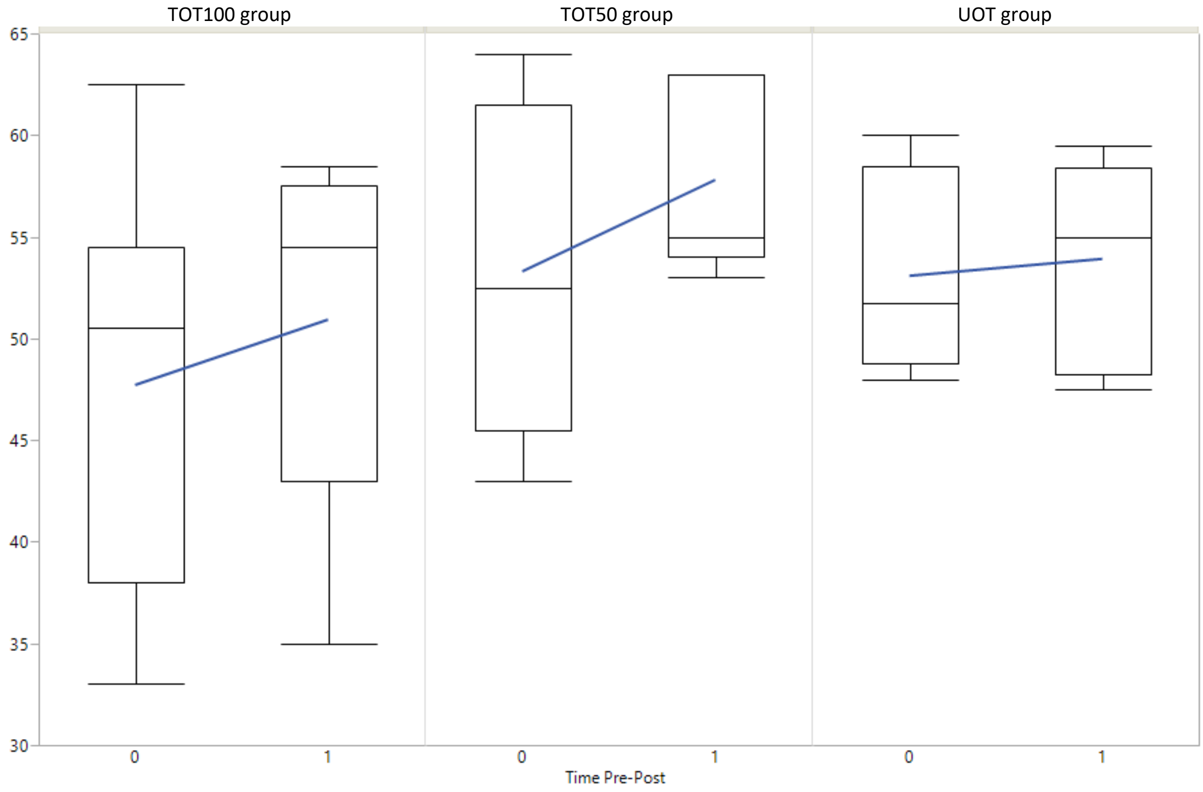
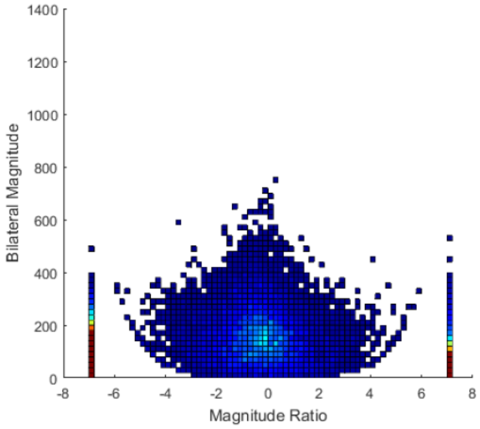
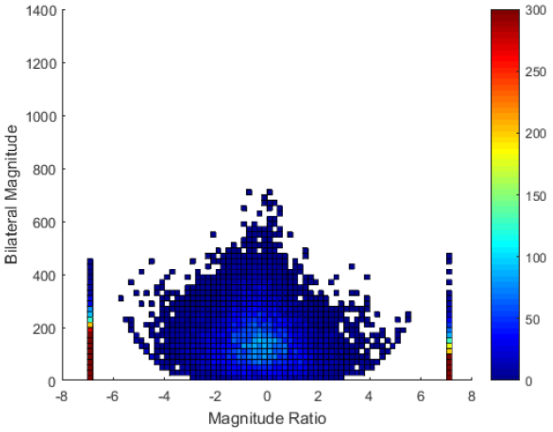
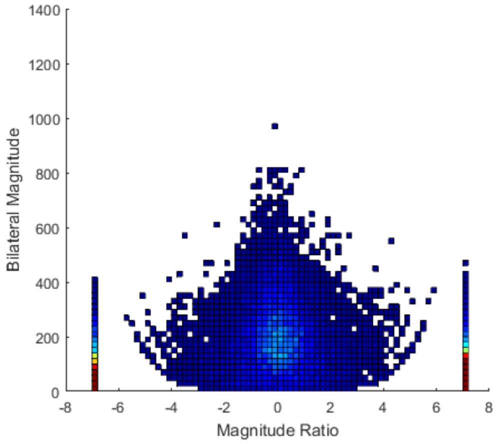
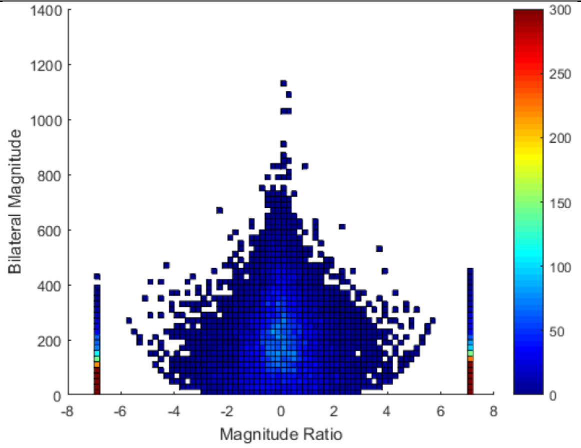
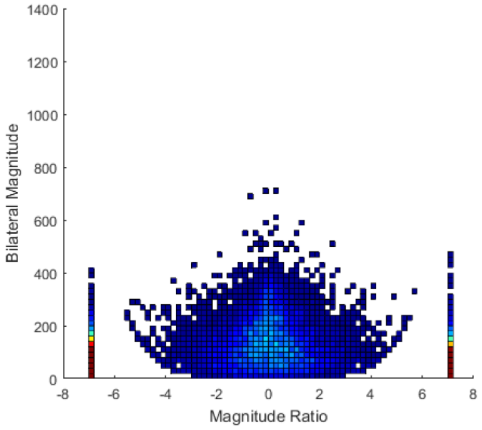
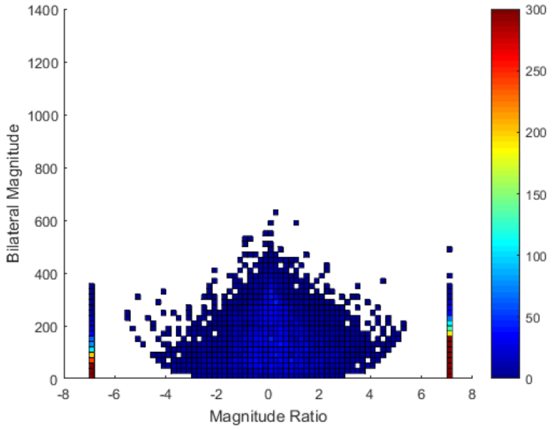
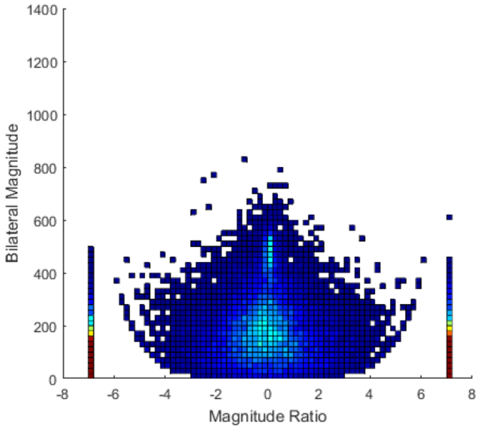
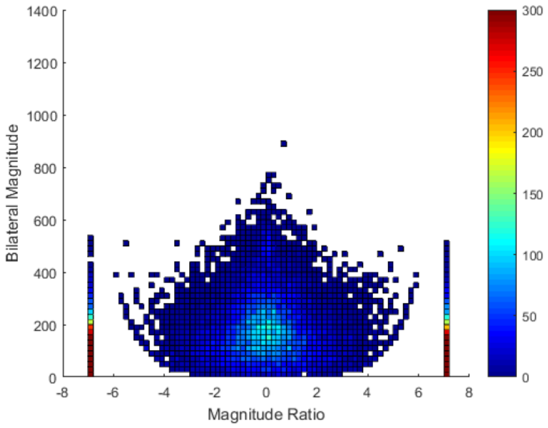
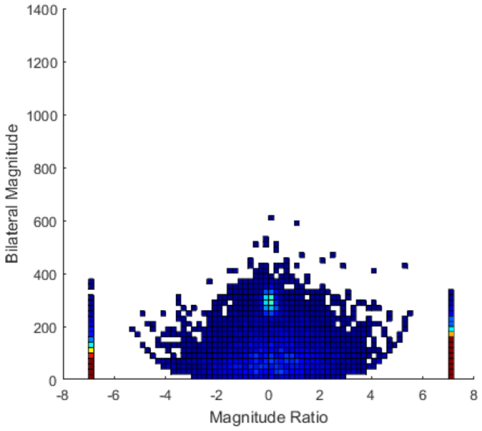
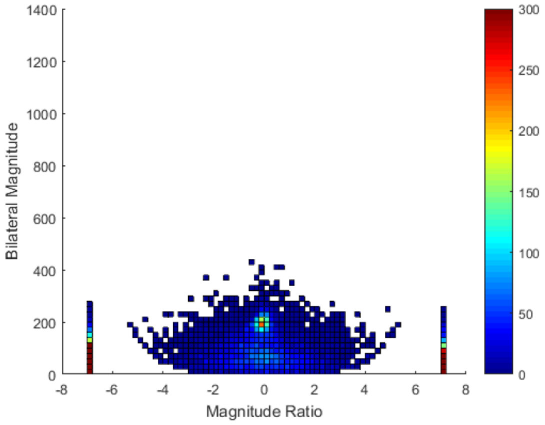
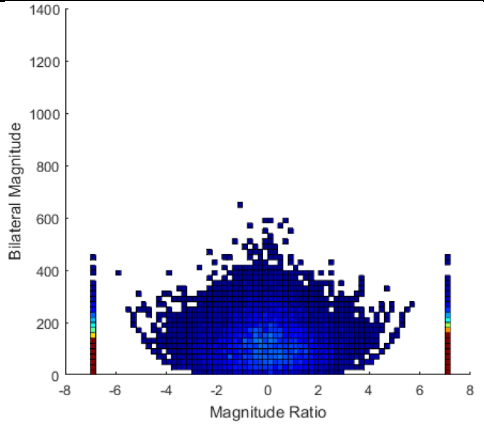
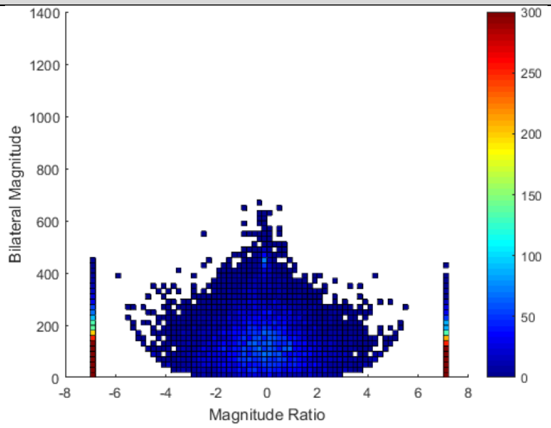


Figure 5: Boxplot represents median and IQR. Blue line indicates group mean scores between baseline and post measurement. Note two drop-out in the TOT50 group and UOT group, two participants with missing post-data in the TOT50 group.

8.1.6. **Figure 6:** Density plots from six representative participants with clinical scales

	PRE (week 1)	**POST (week 9)**
Participant 1		
Actigraph		
NHPT	35 sec	32.29 sec
ARAT	42	52.5
BBT	26.5	40
MAM-36	50.5	54.5
Participant 2		
Actigraph		
NHPT	24.16 sec	22.22 sec
ARAT	55	55.5
BBT	39.5	61
MAM-36	54.5	57.5
Participant 3		
Actigraph		
NHPT	61.76 sec	52.77 sec
ARAT	39	47
BBT	31.5	36
MAM-36	48	55

Participant 4		
Actigraph		
NHPT ARAT BBT MAM-36	250.31 sec 37 13 38	219.63 sec 44 16.5 43
Participant 5		
Actigraph		
NHPT ARAT BBT MAM-36	53.8 sec 42 20.5 48	66.5 sec 41.5 23 47.5
Participant 6		
Actigraph		
NHPT ARAT BBT MAM-36	68.2 sec 41.5 22 49.5	81.3 sec 45 24 54.5

Time points are from baseline (top) to post-intervention assessments (bottom). The y-axis (Bilateral magnitude) represents the intensity of movement, with higher values indicating larger, more intense movements. The x-axis (Magnitude ratio) represents the contribution of each limb to an activity, with 0 indicating equal UL contribution. The color scale shows overall frequency of UL movement, with warmer colors indicating more UL movement. The small bars on each side of the plot indicate non-paretic (negative) and paretic (positive) unilateral movement.

NHPT = Nine Hole Peg test; ARAT = Action Research Arm test; BBT = Box and Block test; MAM-36 = Manual Ability Measure-36

8.2.1. **Table 1:** List of training tasks, based on items of the ABILHAND and MAM-36

#	**Task**	**Unimanual – bimanual**
1	Eating a slice of bread	Unimanual
2	Drinking a glass of water **(1)**	Unimanual
3	Picking-up a half-full can **(2)**	Unimanual
4	Using a spoon or fork **(3)**	Unimanual
5	Spreading butter/jam on a slice of bread **(2)**	Bimanual
6	Cutting meat with a fork and a knife **(8)**	Bimanual
7	Squeezing toothpaste on a toothbrush **(1)**	Bimanual
8	Brushing teeth	Unimanual
9	Brushing, combing or drying your hair	Bimanual
10	Washing your hands	Bimanual
11	Wringing a towel	Bimanual
12	Zipping pants	Bimanual
13	Zipping a jacket	Bimanual
14	Buttoning clothes **(10)**	Bimanual
15	Fastening a snap (jacket, bag)	Bimanual
16	Cutting nails **(5)**	Bimanual
17	Tying shoes **(1)**	Bimanual
18	Using a remote control **(1)**	Unimanual
19	Dialing in telephone numbers	Bimanual
20	Turning a door knob	Unimanual
21	Turning a key in a keyhole	Unimanual
22	Loading and carrying a shopping bag **(3)**	Bimanual
23	Opening a jar (jam, mayonnaise) **(7)**	Bimanual
24	Opening a carton (milk, cereals) **(1)**	Bimanual
25	Pouring liquid from a bottle in a glass **(4)**	Bimanual
26	Opening a bottle with a child-proof top **(1)**	Bimanual
27	Opening an envelop **(1)**	Bimanual
28	Peeling fruits or vegetables	Bimanual
29	Handling money **(4)**	Bimanual
30	Taking things out of a wallet	Bimanual
31	Writing sentences **(9)**	Bimanual
32	Turning pages **(3)**	Unimanual
33	Shuffling cards **(4)**	Bimanual
34	Using a screwdriver	Bimanual
35	Hammering a nail	Bimanual
36	Folding clothes	Bimanual
37	Opening a CD/DVD	Bimanual
38	Peeling onions	Bimanual
39	Sharpening a pencil	Bimanual
40	Taking the cap of a bottle **(3)**	Bimanual
41	Filing one's nails	Bimanual
42	Tearing open a pack of chips **(1)**	Bimanual
43	Unwrapping a chocolate bar	Bimanual
44	Threading a needle **(2)**	Bimanual
45	Wrapping up gifts **(1)**	Bimanual
46	Shelling hazel nuts	Bimanual

Values in parentheses are the number of participants, that trained the task

8.2.2. **Table 2:** Determination of the individual maximum number of repetitions

Steps	**Description of the protocol**
Step 1.	Determination of initial task difficulty Can the participant perform the basic task ≥3x without compensations, assistance or aids? ➢ YES → Increase difficulty (see table 4) ↓ Can he/she perform this training task ≥3x without compensations, assistance or aids? ➢ YES → Increase difficulty level (see table 4) ➢ NO → Go to step 2 and use the initial task difficulty. ➢ NO → Decrease difficulty (see table 4) ↓ Can he/she perform this training task ≥3x without compensations, assistance or aids? ➢ YES → Go to step 2. ➢ NO → Decrease difficulty (divide whole task into parts). Go to step 2.
Step 2.	Determination of the individual maximum number of repetitions ➢ Participant performs the Box and Block Test with both sides. ➢ Participant performs the chosen training task as many times as possible. After every 25 repetitions, the participant fills in the BORG score (perceived exertion, scale 6-20) and performs the Box and Block Test. The individual maximum number of repetitions is reached if at least one of the following criteria is met: - BORG score = 20. - A decrease ≥25% of the number of blocks transported in 1 minute (BBT). - Participant cannot perform the task without compensations, and compensations cannot be corrected (therapist judgement). - Participant performs the training task for 20 minutes without rest and without meeting the first three criteria.
Step 3.	Group allocation and training intensity. ➢ TOT100 group → training at 100% of the individual maximum number of repetitions. ➢ TOT50 group → training at 50% of the individual maximum number of repetitions.

8.2.3. Table 3: Principles of motor learning applied during the training sessions

Principles of motor learning
Demonstration: The first time the patient performed a task or a progression of a task, the supervising therapist showed the action as it should be performed (modeling) to create a reference of correctness
Guiding: Providing physical assistance to the patient in learning the task, is mainly applied through the rehabilitation technology. The Diego from Tyromotion gives support of the impaired UL against gravity. No further hands-on guiding was implemented
Distribution of practice: Massed practice; three tasks were trained for 20 min without any predetermined rest intervals, thus the amount of active practice is larger than rest time
Variability of practice: Variable practice; patient chooses to train three specific tasks in each session. Characteristics of a task varied within one session, e.g. the weight and size of an object, the speed of movement execution, the workspace, the position of the tagboards, etc. (within-task variability)
Practice order: Blocked practice; each task was trained for 20 min repetitively, before moving on to the next task. Each task was practiced consecutively
Part-whole practice: Whole practice was encouraged as much as possible, but might be preceded by part practice. If a task cannot be performed in total, part practice was applied. Part practice is a task broken down into different skill components, and one or more of these components are practiced separately (see progression levels)
Content of practice: Client-centered practice; patients choose from 46 tasks with a clear functional goal, which resembles an activity of daily living. Most of the tasks were performed bilaterally
Extrinsic feedback: Knowledge of results (KR); TagTrainer provides Knowledge of results (KR) by visual, colored LED lights, with additional written text on the computer screen reflecting summary feedback on the task completion and number of repetitions
Intrinsic feedback*:* Extrinsic feedback was given immediately after the task execution. Empty slot time was not applied to give an opportunity for intrinsic feedback
Multiple movement planes: There are no restrictions in freedom of movement at any joint in the UL (shoulder, elbow, forearm) and the hand (wrist, fingers)
Dual tasks: Dual tasks are present in some tasks, but are not systematically implemented.

8.2.4. Table 4: Progression within and between training tasks

Criteria	**Possible changes (principles of progression)**
The participant reaches his/her individual maximum number of repetitions of a training task without compensations and adverse effects in 2 consecutive training sessions	The difficulty level of the task is upgraded: - Whole practice: combine the different skill components - Object characteristics (weight, size, material, etc.) - Variability within the task (alternate different object characteristics in subsequent repetitions) - Workspace (place targets further away) - Increase load/resistance (0.5 or 1.0 kg at the distal forearm) with Diego (Tyromotion) - Patient positioning (standing)
The participant is not able to perform his/her individual maximum number of repetitions of a training task without compensations or adverse effects in 2 consecutive training sessions.	The difficulty level of the task is downgraded: - Part practice: divide a task in different skill components - Object characteristics (weight, size, material, etc.) - Variability within the task (alternate different object characteristics in subsequent repetitions) - Workspace (place targets nearby) - Antigravity support with Diego (Tyromotion) - Patient positioning (sitting)
After at least one progression is made and the participant can perform the training task without any compensations or adverse effects in 2 consecutive training sessions.	The participant is asked to select a new task out of the pre-defined list of training tasks (table 1)
The participant is not able to make progression for 4 weeks.	The participant is asked to select a new task out of the pre-defined list of training tasks (table 1)

8.2.5. Table 5: Description of 6 accelerometer variables from the MATLAB script (C.Lang)[37]

Variables derived from Actigraph data using MATLAB script	
Duration of use	*Definition:* Total amount of time, in hours, that UL was active. This is measured by summing the seconds, when the activity count > 2 This can reflect both the most and less impaired UL. This is a broad measure of UL activity over the recording period.
	Interpretation: Mean hours of dominant UL activity was 9.1 ± 1.9 hours in healthy adults, while hours of non-dominant UL activity was 8.6 ± 2.0 hours. Decreased hours of dominant UL activity are associated with increased time spent in sedentary activity [58]
Use ratio	*Definition:* The hours of most impaired UL use, divided by the hours of less impaired UL use. It quantifies the contribution of the most impaired relative to the less impaired UL to activity.
	Interpretation: Use ratio value close or equal to 1 indicates nearly equal durations of activity from both ULs, while value less than 1 indicates greater activity of the less impaired UL, and values greater than 1 indicate more activity of the most impaired UL. Use ratio between non-dominant and dominant UL is 0.95 ± 0.06 in healthy adults [58]
Magnitude ratio	*Definition:* Natural log of vector magnitude of the most impaired UL, divided by the vector magnitude of the less impaired UL. This describes the contribution of both ULs to activity for each second.
	Interpretation: MR value of 0 indicates both UL contributed equally to the activity. Negative MR value indicates greater less impaired UL activity, and positive MR value indicates greater most impaired UL activity. In healthy adults, median MR value averages -0.1 (0.3) [38]
Bilateral magnitude	*Definition:* This measures the intensity of UL activity, by summing the vector magnitude of the most and less impaired UL. This variable distinguishes between high and low intensity movements for every second.
	Interpretation: BM value of 0 indicate no movement, increasing values are indicative for more intense UL movement. Referent median value of 136.2 (36.6) is established in healthy adults [38]. Higher values are associated with activities requiring larger and faster movements (e.g. placing boxes on a overhead shelf), while lower values indicate more smaller, less intense movements (e.g. chopping vegetables) [57]
Median acceleration	*Definition:* This variable examined only the most impaired UL. It captures the individual's median acceleration value over the recording period [21]
	Interpretation: A higher value indicates more overall movement of most impaired UL.
Acceleration variability	*Definition:* This variable examined only the most impaired UL. This is the variance of the mean acceleration value over the recording period, and explains the average distance of the most impaired acceleration from the mean acceleration [21]
	Interpretation: A higher value indicates greater variability of most impaired UL activity

8.2.6. Table 6: Participant descriptive characteristics at baseline

Measurement	**Total (n=20)**	**TOT100 (n=7)**	**TOT50 (n=7)**	**UOT (n=6)**	**p-values***
UL dysfunction level					**0.35**
Mild	3 (15%)	1 (14%)	1 (14%)	1 (17%)	
Moderate	11 (55%)	3 (43%)	3 (43%)	5 (83%)	
Severe	6 (30%)	3 (43%)	3 (43%)	0	
Age (y)	55.5 [42; 64.75]	57 [42; 69]	54 [42; 63]	59.5 [38.5; 74]	**0.73**
Gender/sex					**0.8**
Male	8 (40%)	3 (43%)	2 (29%)	3 (50%)	
Female	12 (60%)	4 (57%)	5 (71%)	3 (50%)	
Type of MS					**0.62**
RRMS	10 (50%)	4 (57%)	3 (43%)	3 (50%)	
SPMS	7 (35%)	1 (14%)	3 (43%)	3 (50%)	
PPMS	3 (15%)	2 (29%)	1 (14%)	0	
Time since diagnosis (y)	19 [8.5; 26.25]	19 [7; 29]	11 [8; 21]	19.5 [12; 38.5]	**0.61**
EDSS (0 – 10)	7 [5.5; 7.5]	7 [5; 7]	7 [5.5; 8]	6.5 [6; 7.5]	**0.69**
Hand dominance, EHI					**0.74**
Right	16 (80%)	5 (71%)	6 (86%)	5 (83%)	
Left	1 (5%)	0	1 (14%)	0	
Ambidextrous	3 (15%)	2 (29%)	0	1 (17%)	
Most impaired hand, self-reported					**0.83**
Right	13 (65%)	4 (57%)	5 (71%)	4 (67%)	
Left	6 (30%)	3 (43%)	1 (14%)	2 (33%)	
Both	1 (5%)	0	1 (14%)	0	
Fahn’s TRS Intention tremor (0 – 4)					**0.47**
Score 0	24 (60%)	9 (64%)	10 (71%)	5 (42%)	
Score 1	11 (27.5%)	3 (22%)	4 (29%)	4 (33%)	
Score 2	1 (2.5%)	0	0	1 (8%)	
Score 3	3 (7.5%)	1 (7%)	0	2 (17%)	
Score 4	1 (2.5%)	1 (7%)	0	0	
Fahn’s TRS Dysmetria (0 – 4)					**0.07**
Score 0	21 (52.5%)	4 (29%)	7 (50%)	10 (83%)	
Score 1	15 (37.5%)	7 (50%)	6 (43%)	2 (17%)	
Score 2	2 (5%)	1 (7%)	1 (7%)	0	
Score 3	2 (5%)	2 (14%)	0	0	
Fahn’s TRS Postural tremor (0 – 4)					**0.32**
Score 0	31 (79%)	11 (85%)	9 (64.3%)	11 (92%)	
Score 1	5 (13%)	2 (15%)	2 (14.3%)	1 (8%)	
Score 2	3 (8%)	0	3 (21.4%)	0	
MAS (0 – 5)					**0.01**
Score 0	15 (75%)	7 (50%)	11 (79%)	12 (100%)	
Score 1	1 (5%)	4 (29%)	0	0	
Score 2	3 (15%)	2 (14%)	1 (7%)	0	
Score 3	0	0	0	0	
Score 4	1 (5%)	0	2 (14%)	0	
Score 5	0	1 (7%)	0	0	
MFIS					**0.65**
Physical (0 – 36)	23 [17.5; 28]	26 [19; 31]	23 [16; 28]	21,5 [15.3; 28.7]	
Cognitive (0 – 40)	19 [13.25; 26.5]	25 [13; 29]	18 [6; 23]	20 [16.25; 26.5]	
Psychological (0 – 8)	3,5 [2; 6]	6 [3; 6]	6 [0; 6]	3,5 [2; 6.25]	
Total (0 – 84)	47 [33.75; 60.5]	51 [36; 62]	45 [30; 54]	45 [34.25; 62.25]	

Continuous data are presented as median [IQR]. Continuous variables were compared with Kruskal-Wallis test, categorical variables with Fisher Exact test.

RRMS = Relapse-Remitting multiple sclerosis; SPMS = Secondary progressive multiple sclerosis; PPMS = Primary progressive multiple sclerosis; EDSS = Expanded Disability Status Scale; EHI = Edinburgh Handedness Inventory; Fahn’s TRS = Fahn’s tremor rating scale for intention and postural tremor; MAS = modified Ashworth Scale; MFIS = modified Fatigue Impact Scale

Fahn’s TRS and MAS were conducted with both upper limbs. MAS is mean total score of should adductors, elbow flecors and wrist flexors.

8.2.7. **Table 7:** Primary outcome measures – accelerometer variables of 24h (Friday)

	TOT100 group (n=7)			**TOT50 group (n=5)**			**UOT group (n=6)**			**Mixed model analysis**		
	PRE	POST	CHANGE	PRE	POST	CHANGE	PRE	POST	CHANGE	TIME	GROUP	TIME*GROUP
Hours of use, time (h)[1]	6.5 [5.44; 8.17]	5.25 [4.44; 7.23]	-0.96 [-1.55; -0.47]	5.6 [4.09; 6.96]	5.44 [3.04; 6.36]	-0.21 [-1.37; 0.26]	5.47 [3.96; 6.49]	5.82 [4.09; 7.25]	0.31 [-0.36; 1.65]	p=0.13	p=0.71	p=0.85
Use ratio[2]	0.98 [0.69; 1.2]	0.99 [0.63; 1.12]	-0.003 [-0.07; 0.01]	0.95 [0.75; 1.1]	1.01 [0.9; 1.74]	-0.01 [-0.08; 0.94]	0.97 [0.78; 1.14]	0.91 [0.82; 1.01]	-0.09 [-0.26; 0.26]	p=0.30	p=0.44	p=0.18
Magnitude ratio[3]	-0.08 [-1.41; 0.35]	-0.023 [-2.07; 0.27]	0 [-0.31; 0.01]	-0.1 [-1.01; 0.12]	-0.033 [-0.59; 3.91]	0.06 [-0.37; 4.6]	-0.04 [-0.78; 0.52]	-0.28 [-0.45; 0.07]	-0.26 [-0.92; 1.05]	p=0.04	p=0.06	p<0.001
Bilateral magnitude[4]	86.09 [71.3; 99.26]	87.17 [68.3; 100.7]	-3.54 [-8.67; 1.08]	74.87 [62.1; 104.7]	76.71 [61.1; 102.5]	1.85 [-12.6; 9.45]	78.83 [65.67; 85.7]	77.04 [62.1; 107.2]	0.04 [-10.5; 24.2]	p=0.98	p=0.92	p=0.47
Median acceleration[5]	22.02 [10.4; 51.66]	25 [6; 45.82]	-0.93 [-5.85; 1.22]	16 [11.5; 39.94]	39 [16.64; 44.8]	5 [-0.9; 19.9]	25.06 [21.19; 28]	25.44 [15.74; 35.4]	0.38 [-12.3; 14.2]	p=0.38	p=0.91	p=0.31
Acceleration variability[6]	69.91 [56.25; 75.4]	67.94 [53.34; 76.2]	-1.96 [-4.48; 1.22]	57.9 [50.97; 74.7]	56.97 [52; 76.26]	0.33 [-1.37; 3.35]	67.15 [56.9; 70.27]	67.53 [53.5; 77.83]	1.01 [-7.28; 7.49]	p=0.74	p=0.95	p=0.73

Continue variables are presented as Median [IQR].

[1] Hours of use: dominant UL activity was 9.1 ± 1.9 hours in healthy adults, while hours of non-dominant UL activity was 8.6 ± 2.0 hours.

[2] Use ratio: value close or equal to 1 indicates nearly equal durations of activity from both ULs, reference value of 0.95 ± 0.06 in healthy adults

[3] Magnitude ratio: value of 0 indicates both UL contributed equally to the activity [-7;7], reference value of -0.1 in healthy adults

[4] Bilateral magnitude: increasing values are indicative for more intense UL movement, reference value of 136.2 in healthy adults

[5] Median acceleration: higher value indicates more overall movement of most impaired UL

[6] Acceleration variability: higher value indicates greater variability of most impaired UL activity

8.2.8. **Table 8:** Primary outcome measures – MAM-36

	TOT100 group (n=7)			**TOT50 group (n=5)**			**UOT group (n=6)**			**Mixed model analysis**		
	PRE	POST	CHANGE	PRE	POST	CHANGE	PRE	POST	CHANGE	TIME	GROUP	TIME*GROUP
MAM-36	50.5 [38; 54.5]	54.5 [43; 57.5]	3 [2; 5]	52.5 [45.5; 61.5]	55 [54; 63]	4 [0.75; 8.5]	51.75 [48.75; 58.5]	54.75 [48.25; 56.5]	-0.5 [-1.13; 2.38]	p=0.02	p=0.32	p=0.43

Continue variables are presented as Median [IQR].
MAM-36 = Manual Ability Measure-36.

8.2.9. Table 9: Correlation between changes in actual UL performance and changes in perceived UL performance and UL capacity

	Hours of use		***Use ratio***	***Magnitude ratio***	***Bilateral magnitude***	***Median acceleration***	***Acceleration variability***
	Dominant	**Non-dominant**					
Capacity measures							
NHPT dom	-0.16	/	-0.38	-0.37	-0.06	-0.31	0.02
NHPT non-dom	/	0.15	0.15	0.18	0.13	0.16	0.06
BBT dom	-0.52*	/	-0.13	-0.18	-0.31	-0.38	-0.17
BBT non-dom	/	-0.31	-0.23	-0.21	-0.27	-0.37	-0.34
TEMPA dom	-0.11	/	0.17	0.05	0.04	-0.009	-0.02
TEMPA non-dom	/	0.33	-0.17	-0.16	-0.02	-0.35	-0.18
TEMPA bilateral	-0.14	0.28	-0.04	0.01	0.05	-0.17	-0.13
TEMPA total score	-0.23	0.16	0.001	-0.06	0.004	-0.17	-0.14
ARAT dom	-0.16	/	0.06	-0.003	0.30	0.20	-0.11
ARAT non-dom	/	0.11	-0.16	-0.19	0.42	-0.02	-0.14
Perceived performance							
MAM-36	-0.145	-0.07	0.05	-0.01	-0.06	-0.05	-0.07

Spearman rho correlation coefficients; a positive value indicates a proportional relation between outcome measures; a negative value indicates a disproportional relation between outcome measures
p<0.05*; p<0.01†
NHPT = Nine Hole Peg Test; BBT = Box and Block test; TEMPA = Test d'Évaluation des Membres supérieurs des Personnes Âgées; ARAT = Action Reach Arm test; MAM-36 = Manual Ability Measure-36.
dom = dominant UL; non-dom = non-dominant UL; mean = mean score of dominant and non-dominant UL.

Auteursrechtelijke overeenkomst

Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
Actual and perceived upper limb performance after a task-oriented training in people with MS

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij neurologische aandoeningen**
Jaar: **2017**

in alle mogelijke mediaformaten, - bestaande en in de toekomst te ontwikkelen - , aan de Universiteit Hasselt.

Niet tegenstaand deze toekenning van het auteursrecht aan de Universiteit Hasselt behoud ik als auteur het recht om de eindverhandeling, - in zijn geheel of gedeeltelijk -, vrij te reproduceren, (her)publiceren of distribueren zonder de toelating te moeten verkrijgen van de Universiteit Hasselt.

Ik bevestig dat de eindverhandeling mijn origineel werk is, en dat ik het recht heb om de rechten te verlenen die in deze overeenkomst worden beschreven. Ik verklaar tevens dat de eindverhandeling, naar mijn weten, het auteursrecht van anderen niet overtreedt.

Ik verklaar tevens dat ik voor het materiaal in de eindverhandeling dat beschermd wordt door het auteursrecht, de nodige toelatingen heb verkregen zodat ik deze ook aan de Universiteit Hasselt kan overdragen en dat dit duidelijk in de tekst en inhoud van de eindverhandeling werd genotificeerd.

Universiteit Hasselt zal mij als auteur(s) van de eindverhandeling identificeren en zal geen wijzigingen aanbrengen aan de eindverhandeling, uitgezonderd deze toegelaten door deze overeenkomst.

Voor akkoord,

Hollandts, Jessie