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Thank you.
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1. Research context

The present master thesis involves the domain of neurorehabilitation. Neurological disorders can lead to long-term disability, affecting multiple domains of human functioning. Worldwide, multiple sclerosis is the most common neurological disorder among young adults. Europe accounts for around half of the patients and women seem to be affected more frequently, with sex ratios in Europe ranging from 1.1 to 3 [1]. In Flanders, the prevalence of multiple sclerosis was given as 74/100.000 in 1994 [2], and overall the prevalence is increasing due to a longer survival and a true increase in incidence [3].
People with multiple sclerosis present with very individual patterns of symptoms depending on the location and severity of demyelination and neural atrophy. Typically, these patients suffer from a combination of sensorimotor impairments, cognitive malfunction, autonomous dysregulation and fatigue [4]. Concerning the physical rehabilitation, several therapy approaches are used by physical and occupational therapists to reduce impairments and to enhance the patient's activity and participation level. Besides training on skills such as mobility and transfers, upper limb rehabilitation is essential and it is known that upper limb function can be improved as a result of practice [5]. Here, task-oriented training (also called task-specific training, goal directed training, functional task practice etc.) is considered the 'contemporary' approach in neurological rehabilitation, in line with the paradigm shift from impairment-based training towards training of meaningful activities [6]. Recent studies have shown the effectiveness of task-oriented training, particularly in stroke rehabilitation [7, 8].

In the first year of our master's degree we have reviewed technology-supported task-oriented upper limb training in neurorehabilitation. We found that a diversity of rehabilitation technologies (robotic devices, a non-actuator device and sensor-based systems) were investigated in stroke (13 articles) and multiple sclerosis (one article), and concluded that technology-supported task-oriented upper limb training was feasible and resulted in improvements comparable to conventional task-oriented upper limb training.
In the second year of our master's degree we focused on the clinical effects of technology-supported task-oriented upper limb training in multiple sclerosis, and whether these effects are intensity-dependent (i.e. does more training elicit more improvements?). The current study was conducted at the Rehabilitation and MS centre Overpelt (January 2016 -

December 2016) and serves as the pilot within a larger research project called 'clinical and neural effects of task-oriented upper limb rehabilitation in multiple sclerosis'. The pilot study is still ongoing and to date 20 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. Peter Feys, who both have a great expertise in the assessment and rehabilitation of upper limb dysfunction, particularly in multiple sclerosis.

Both of us have contributed equally to this master thesis. The research protocol was largely developed by dr. Ilse Lamers before October 2015. Prior to the first baseline measurements (January 2016), we gave feedback and suggestions and helped with the practical set-up (e.g. the different difficulty levels and variations of the training tasks). We were not involved in participant recruitment at the Rehabilitation and MS centre Overpelt. Potential participants were screened regarding inclusion and exclusion criteria by the treating neurologist. During the training period (January 2016 - December 2016), we were able to supervise training sessions in one cohort of included participants (n=5) during an eight-week period (April 2016 - May 2016). In total, we supervised around 50 one-hour training sessions. Furthermore, we attended baseline and post measurements, which were conducted by a blinded assessor. After the data was collected, we converted all descriptive and experimental measures into Excel files and performed statistical analyses. We presented our work during a team meeting with, among others, our promotor and co-promotor, where we received feedback and suggestions. Hereafter, a meeting with a statistician (dr. Francesca Solmi, Department Mathematics and Statistics) was planned to discuss our analyses and ensure all procedures were performed/interpreted correctly. More specifically, she explained how to include the side (dominant and non-dominant upper limb) as random effects nested within the participants (see methods, data analysis) and gave advice on multiple comparison tests. She also explained the use of log transformations if data was not normally distributed. The academic writing was done independently, as well as the design of all tables and figures. During the writing process, feedback and suggestions were provided by the promotor and co-promotor, for which we would like to express our sincere gratitude again.

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2. Abstract

Background: People with multiple sclerosis (MS) often suffer from substantial sensorimotor impairments in the upper limb. Task-oriented training might be a valuable rehabilitation approach but the influence of training dosage on therapy outcomes is unknown.

Objectives: To compare the clinical effects of a task-oriented upper limb training program at two different training intensities and usual occupational therapy in MS.

Participants: People with MS (n=20, EDSS range 4-8) with different levels of upper limb disability (mild, moderate, severe) were divided into three groups: task-oriented training at a higher intensity (TOT100 group, n=7), a lower intensity (TOT50 group, n=8) and usual occupational therapy (UOT, n=5). Participants attended one-hour training sessions, five days/week, during eight weeks.

Measurements: Primary outcome measures were Action Research Arm Test (ARAT), Box and Block Test (BBT), Nine Hole Peg Test, Test d'Évaluation des Membres Supérieurs des Personnes Âgées and Manual Ability Measure-36 (MAM-36). Secondary outcome measures were maximal and sustained isometric hand strength, Motricity Index, Semmens-Weinstein Monofilaments Test, vibration tests and Symbol Digit Modalities Test.

Results: A mixed model analysis revealed significant improvements over time on upper limb capacity and perceived performance measures ($p<0.05$ on BBT; ARAT total score, subtest grasp, grip and pinch; MAM-36). Significant group*time interaction effects were only found for the BBT and sustained handgrip strength. The BBT improved in the TOT100 ($p<0.05$) and TOT50 group but not in UOT. Motor fatigability (sustained handgrip strength test) improved in the TOT100 group ($p<0.05$), but did not change in the TOT50 or UOT group.

Conclusion: Participants from all upper limb disability levels were able to perform high-intense one-hour sessions. We found several significant improvements over time, but no clear intensity-dependent effect during task-oriented training in MS. However, the results on the BBT and sustained handgrip strength may suggest a superiority of task-oriented training at a higher intensity.

3. Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system characterized by inflammation and neurodegeneration that results in sensorimotor, visual, cognitive and autonomous impairments [1]. According to Kister et al. (2013), 60% of people with MS (pwMS) report a diminished hand function in the first year after diagnosis. The amount of patients experiencing their hand function as moderately, severely or completely impaired increases considerably as the disease progresses, with less than 20% of pwMS reporting normal hand function after 14 years [2]. Sensorimotor deficits often present bilaterally. Bertoni et al. (2015) reported that even in patients with moderate impairment (Expanded Disability Status Scale (EDSS) 4-4.5) the scores on the Action Research Arm Test (ARAT) and Nine Hole Peg Test (NHPT) appeared abnormal bilaterally in 53% and 82% of pwMS, respectively [3]. In severely impaired patients (EDSS 7-9.5), 86% (ARAT) and 91% (NHPT) of pwMS had bilateral involvement. Given that manual dexterity acts as a predictor of overall activity limitations and participation restrictions [4], daily life can be hampered significantly.

Physical and occupational therapy are frequently used to treat MS related upper limb disabilities in daily practice. Here, interventions can be classified according to the levels of the International Classification of Functioning, Disability and Health (ICF): body functions and structures, activity and participation level [5, 6]. Even though a limited amount of research has been performed compared to stroke, several upper limb training approaches targeting different levels of the ICF were investigated (e.g. resistance training, robot-based training, task-oriented training). A recent systematic review on upper limb rehabilitation in MS revealed that multiple types of training could elicit improvements on body functions/structures and activity level [5]. No guidelines were formulated regarding preferred therapy modalities due to the large heterogeneity among studies. Interestingly, effects were more often found on the ICF level that training focused on. As such, based on current evidence the authors advocated to adapt the training program in function of the desired improvements and the patient's goals [5].

To date, task-oriented training is used to effectively retrain motor skills in populations with neurological disorders, particularly after stroke [7-9]. Task-oriented training (also called task-specific training, goal directed training, functional task practice etc.) contains the repetitive

practice of movements and involves active problem solving towards the attainment of a functional and meaningful goal [10-12]. In MS, studies investigating task-oriented upper limb training remain scarce. A recent randomized controlled trial (RCT) compared a two-month task-oriented training program with passive mobilization in pwMS with mild-moderate upper limb dysfunction [13]. Clinical outcomes concerning unilateral arm-hand function improved over time but did not differ between groups, while a bimanual coordination task remained stable after task-oriented training but worsened after passive treatment. Furthermore, the authors demonstrated preserved white matter integrity in the corticospinal tract and corpus callosum after task-oriented training and not after passive mobilization.

While in stroke a small-to-moderate relationship between training dosage (defined as the time scheduled for therapy [14]) and therapy outcomes has been established, such data is lacking for the MS population. Training dosage is insufficiently reported in MS rehabilitation research [5, 6]. According to Page et al. (2012), training dosage is defined as the total amount of activity performed during a training period and covers different aspects such as intensity, frequency and duration [15]. Several studies investigating upper limb rehabilitation after stroke have used the number of repetitions performed of a given task or during a training period as indicators of training intensity [16-18].
Besides training intensity, the disease severity should be taken into account, as a dose-response relationship may differ across different disability levels in pwMS. For example, it is not known whether the response to training of severely impaired patients with less neural reserve differs from patients with more preserved brain and spinal cord tissue.

In summary, task-oriented training might be a valuable approach in MS upper limb rehabilitation and possible effects of training dosage remain unknown. In this pilot study a task-oriented upper limb training program was administered using two different training intensities and compared to a control group (usual occupational therapy). The aim was to explore the intensity-dependent clinical effects in a small sample of pwMS with different levels of upper limb disability.

4. Methods

Participants

Participants (n=20) were recruited at the Rehabilitation and MS centre Overpelt, Belgium. Both hospitalized and ambulatory pwMS referred for upper limb rehabilitation by the treating neurologist were allowed to participate in the study. Patients were diagnosed according to the McDonald criteria [19], aged >18y and had a minimal-to-severe self-reported upper limb dysfunction (six-point Likert scale). 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 upper limbs, (3) severe cognitive or visual deficits interfering with testing and training or (4) other medical conditions interfering with upper limb function (orthopaedic or rheumatoid impairment). All participants were informed about the study design and gave their written consent after a two-week reflection period. This pilot study was conducted from January 2016 until December 2016 and was registered at clinicaltrials.gov (NCT02688231). All procedures were approved by the Medical Ethics Committee of the University of Leuven, Hasselt University and 'Mariaziekenhuis Noord-Limburg' (17/12/2015).

Study protocol

Participants were stratified into three blocks of upper limb disability (mild, moderate, severe) according to the capability of raising the arms to 90° anteflexion for 20s and a cut-off score on the NHPT (33.3s [20]), see figure 1. Hereafter, they were randomized into two groups (a higher and a lower intensity task-oriented training group) by an independent staff member using a randomized complete block design to ensure homogeneous distribution of upper limb function. Participants were not aware that different treatment intensities were administered and, as such, were blinded.

Before the start of the interventions, participants were asked to choose three tasks from a list of 46 activities of daily living, based on the items of two questionnaires (ABILHAND and Manual Ability Measure-36 (MAM-36), table 1). 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

as described in the protocol (table 2). 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 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, during 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), particularly for the TOT100 group. Participants from both groups trained under constant supervision. The order in which the three tasks were practiced was randomly adapted before each training session. Task difficulty was progressed throughout the training period and new tasks could be introduced following pre-defined criteria (table 3).

During a period when no task-oriented training sessions were given, data from a third group was collected (not randomized), the *'Usual Occupational Therapy group'* (UOT). Participants received usual occupational therapy focusing on upper limb rehabilitation, with equal training frequency and duration as the TOT100 and TOT50 group (8 weeks, 5 sessions/week, 60 minutes). Furthermore, participants from all three groups received their usual physical therapy sessions at the rehabilitation and MS centre Overpelt (8 weeks, 5 sessions/week, 60 minutes), focusing on lower limb rehabilitation (gait and balance). A complete overview of the study design is given in figure 2.

To assist the task-oriented training with real-life objects in the TOT100 and TOT50 group, we used a technological device called the TagTrainer (figure 3) [21-23]. The TagTrainer is a sensor-based tabletop device placed in front of the participant and allows object manipulation on an interactive 24x24cm 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 provide 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 required assistance (anti-gravity support [24]) during the performance of different upper

limb tasks. The Diego can provide unilateral or bilateral support and does not impede the use of real-life objects.

Experimental 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 (TOT100 vs. TOT50, not UOT) and the sequence of the assessments was randomized to avoid order effects. Unilateral tests were completed with both upper limbs and hand dominance was established with the Edinburgh Handedness Inventory (ambidextrous pwMS were regarded as right handed) [25].

Primary outcome measures - ICF activity level

The NHPT, Box and Block Test (BBT), ARAT and the Test d'Évaluation des Membres Supérieurs des Personnes Âgées (TEMPA) were used as capacity measures, and the MAM-36 as perceived performance measure on the ICF activity level.

The **NHPT** is a unilateral assessment of manual dexterity measuring the time needed to insert and remove nine pegs as fast as possible [26]. The mean time was calculated based on two trials performed with each hand. For the **BBT** participants are asked to move as many blocks as possible from one side of a box to the other side (pick up - transport over a wall - release) within 60 seconds and the score reflects the total number of blocks transported by each hand [27]. The **ARAT** addresses unilateral arm-hand function with four subscales (grasp, grip, pinch, gross arm movements). Nineteen items are given a score (0, 1, 2, 3) with a maximum score of 57 [27]. The **TEMPA** measures the execution time and the amount of difficulty (score 0, -1, -2, -3) on nine standardized daily life tasks (four unilateral and five bilateral) [28]. In this study only the amount of difficulty score was used for statistical analysis. The **MAM-36** questionnaire measures the perceived arm-hand performance in daily life by scoring 36 unilateral and bilateral tasks using a four-point scale (1 to 4, score 0 indicates that the activity is not applicable) [29]. The sum score of each subject is subsequently Rasch-calibrated and converted into a 'manual ability measure' (0 indicating lowest and 100 indicating perfect manual ability).

Secondary outcome measures - ICF body functions and structures level

Maximal isometric hand strength tests and the Motricity Index were used to evaluate strength. A Static Fatigue Index (SFI) during a maximal sustained handgrip strength test was calculated to asses motor fatigability. Sensory function was assessed with the Semmens-Weinstein Monofilaments Test and a vibration test. The Symbol Digit Modalities Test (SDMT) was used to measure cognition.

Maximal isometric strength of handgrip, key grip, 3-jaw grip and thumb-index grip were measured as the average force produced during three trials of three seconds maximum voluntary contraction using the E-link (Biometrics Ltd.) [30]. A 30-second sustained maximal handgrip strength test was used to assess motor fatigability by calculating the **SFI** as described by Surakka et al. (2016) [31]. A higher SFI value (expressed as 0-100%) indicates a greater decline in grip strength over time, and thus more motor fatigability. The **Motricity Index** is a six-point ordinal scale assessing general muscle strength during shoulder abduction, elbow flexion and pinch grip, with a total score 0-100 [32]. The **Semmens-Weinstein Monofilaments Test** was performed to assess tactile sensitivity by stimulating the thumb and index finger with five monofilament diameters (each diameter corresponds with a clinical presentation, ranging from normal to absent sensibility) [33, 34]. The thumb and index finger were stimulated three times with each diameter during approximately 1.5 seconds in a random order. Participants were asked to give a verbal response if the pressure was felt. The thinnest filament which could be felt 3/3 times was regarded as the score for this finger. **Vibration sense** in the upper limb was assessed by placing a Rydel Seiffer Tuning Fork [35] at the distal interphalangeal articulation of the index finger (dorsal side) and on the ulnar styloid (dorsal side). When the sense of vibration was no longer felt by the participant, the assessor noted the score visible on the calibrated weights of the tuning fork (ranging between 0-8). The mean of three test trials was taken as the definitive score. The **SDMT** is designed to assess working memory, information processing speed and sustained attention. It consists of a key with nine numbers paired with symbols. The participant is asked to assign the corresponding numbers to a list of randomly ordered symbols, and the final score is the number of correct responses within 90 seconds [36].

Data analysis

Statistical analyses were performed with SAS JMP Pro 12.2.0. The significance level was set at 0.05. The dominant and non-dominant test scores of unilateral tests were analyzed together in order to obtain a larger data set. Baseline characteristics of the three groups were compared using the Kruskal-Wallis test for continuous variables and the Fisher Exact test for categorical variables. For the experimental measures, a mixed model analysis was performed to investigate time, group and the group*time interaction as fixed effects. The participant was added as a random effect to account for repeated measurements. The side (dominant vs. non-dominant) was nested within the random participant effect to account for the existence of multiple scores on unilateral tests. Multiple comparisons (Tukey HSD) were performed on all outcome measures to test the evolution of scores within each group.

Before the analyses, the residuals were calculated and normality of the residuals was checked by visual inspection of the normal quantile plots. As this assumption was not met on the NHPT and the ARAT subtest grasp, a log transformation was performed after which normal distribution was achieved.

5. Results

Participants and training tasks

Baseline descriptive characteristics are given in table 4 and did not differ between TOT100 (n=7), TOT50 (n=8) and UOT (n=5). Overall, the included pwMS had an advanced disease progression (median EDSS 7 [IQR 5.6-7.4]). The experimental measures were comparable at baseline ($p>0.05$), except the key grip strength ($p=0.0225$), where post-hoc testing indicated significantly higher values in the UOT group compared to the TOT100 group.

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

The number of task repetitions performed during one training session varied considerably between different participants and different tasks and, on average, was higher in the TOT100 group (median 47 [IQR 38-87]) compared to the TOT50 group (median 32 [IQR 26-58]). The median total number of repetitions performed per participant after eight weeks was 1569 [IQR 1134-2353] for the TOT100 group and 1035 [IQR 588-1706] for the TOT50 group. Participants in the TOT50 group completed a larger percentage of their target number of repetitions compared to participants in the TOT100 group (median 88% [IQR 82-96] vs. 72% [IQR 69-76]).

Two participants (one from each group) initially needed antigravity support from the Diego (Tyromotion) but were able to train unassisted after two to seven weeks. One participant (TOT50 group, moderate upper limb disability) dropped out after seven weeks due to a relapse, unrelated to the intervention. Nineteen participants completed the post measurements. Available data from the drop-out was included to apply intention-to-treat analysis.

Primary outcome measures - ICF activity level

Results are displayed in table 5 and figures 4-6. Significant effects of time were found with regard to upper limb capacity (BBT, p=0.0012; ARAT total score, p=0.0008; ARAT subtest grasp, p=0.0148; ARAT subtest grip, p=0.0062; ARAT subtest pinch, p=0.0005) and perceived performance in daily life (MAM-36, p=0.0437). There were no changes on the NHPT and the changes observed on the TEMPA did not reach statistical significance. No main effect of group was found. There was a significant group*time interaction effect on the BBT (p=0.0255). Multiple comparisons revealed a significant improvement in the TOT100 group (mean change of 7.50 ± 1.82 blocks, p=0.0027), a non-significant improvement in the TOT50 group (mean change of 4.78 ± 1.81 blocks, p=0.1141) and no change in the UOT group (mean change of -0.50 ± 2.15 blocks, p=0.9999). Other group*time interactions indicated no significant differences in response to training between the three interventions. Multiple comparisons revealed that the ARAT subtest pinch improved significantly in the TOT100 group (mean change of 2.07 ± 0.61 points, p=0.0200), and not in the TOT50 group (mean change of 1.53 ± 0.61 points, p=0.1481) and UOT group (mean change of 0.70 ± 0.72 points, p=0.9250).

Considering the pilot nature of this study and the associated small sample size, we also did an observational analysis. For each participant, the percentage of change on a test was calculated as: %change = ((post score - pre score)/pre score)x100. The mean %changes on the ARAT were 12% (TOT100), 12% (TOT50) and 3% (UOT). On the BBT, the mean %changes were 26% (TOT100), 20% (TOT50) and -1% (UOT). Changes on the MAM-36 were smaller: 8% (TOT100), 6% (TOT50) and 2% (UOT). The mean time needed to complete the NHPT increased with 5% in the TOT100 group, reduced with 6% in the TOT50 group and increased with 12% in the UOT group.

Secondary outcome measures - ICF body functions and structures level

Results are displayed in table 6 and figure 7. No significant effects of time and group were found. There was only a significant group*time interaction for the SFI (p=0.0003). After the intervention, the TOT100 group demonstrated a significantly smaller decline in handgrip strength over the 30-second trial compared to baseline (mean change on SFI: -10.47 ± 2.83, p=0.0092), while most scores in the TOT50 and UOT group had worsened or remained stable (TOT50, mean change on SFI: 7.19 ± 3.02, p=0.1924; UOT, mean change on SFI: 4.32 ± 3.35, p=0.7877). Other group*time interactions indicated no significant differences in response to training between the three interventions.

6. Discussion

This pilot study aimed to explore the intensity-dependent clinical effects of a task-oriented upper limb training program using two different training intensities and a third control group (usual occupational therapy) in pwMS. In general, we found no indications for a clear intensity-dependent effect (i.e. dose-response relation), but several findings require a more comprehensive discussion.

Study findings

In this pilot study a wide range of clinical outcome measures were assessed on ICF activity and ICF body functions and structures level. Primary outcome measures addressed both upper limb capacity and perceived performance, as these assess different aspects and do not necessarily correlate in MS [37]. Overall, the participants' ability to grasp and replace objects

improved during the eight-week intervention period, as indicated by the significant time effects on the BBT and ARAT (total score, subtests grasp and grip). Furthermore, the ARAT subtest pinch showed a significant improvement in pinch grip performance in the whole sample and within the TOT100 group. This was not reflected in a faster execution of the NHPT, where a pinch grip is required in combination with speed of execution. Through the course of the training period, several participants reported improvements in their daily arm-hand use (e.g. one participant mentioned she had less difficulties and was more confident in doing the dishes), which was on a group level reflected in a significant improvement on the MAM-36 questionnaire.

The BBT was the only primary outcome revealing a significant difference in training response between the three groups, and a significant within-group improvement was reached in the TOT100 group. The change value in this group was higher than the Smallest Real Change (SRC) value found in the study of Lamers et al. investigating responsiveness of upper limb outcome measures in pwMS (a European RIMS multicenter study, *manuscript in preparation*): SRC of 1.80 blocks for the dominant side and 2.02 blocks for the non-dominant side. Interestingly, on the ICF body functions and structures level, there was a significant improvement on the SFI only in the TOT100 group. In general, participants in the current study demonstrated quite similar motor fatigability when compared to existing MS research on pwMS with EDSS $\geq$6 (SFI 52% vs. 47% [39]), but higher values when compared to the mean MS population (EDSS 1.5-8.5) and healthy controls (SFI 41% and 29% [39]). The underlying origin of this elevated motor fatigability in MS is not known and could be centrally and/or peripherally located. Some evidence suggests a central origin, i.e. insufficient cortical activation during sustained motor contraction [40]. Participants in the TOT100 group may thus have attenuated a cortical insufficiency but the exact mechanism is uncertain. As both the BBT and the SFI could be interpreted as endurance-related measures, this may suggest that a higher training intensity has an impact on endurance during movement and strength-related tasks.

All other outcome measures did not show significant group*time interaction effects. One may conclude that there is no difference between usual occupational therapy and task-oriented training, as well as no intensity-dependent effect during task-oriented training in MS regarding manual dexterity, self-reported upper limb use, maximal strength, sensory function or cognition.

Even though the mixed model analysis did not show consistent statistical differences between groups, it seems plausible that the significant 'time' effects on the primary outcome measures were mainly due to the TOT100 and TOT50 group, with less contribution from the UOT group for the following reasons: (1) the overall larger observable changes in the TOT100 and TOT50 groups (%changes); (2) the significant multiple comparison tests in the TOT100 group (BBT, ARAT subtest pinch); (3) the lower number of participants in the UOT group (n=5).

It should be noted that not every participant showed improvements and most outcome measures included a mix of responders and non-responders. One possible explanation is that rehabilitation was adapted towards the individual's training preferences and the training program differed for every participant. According to the specificity of training principle, we believe that participants are most likely to improve on these aspects that were trained and not on other, unrelated, skills. Even though it is difficult to draw conclusions based on individual cases it was remarkable that, for example, the two participants who practiced the task 'threading a needle' improved noticeably with both the dominant and the non-dominant side on tests using the pinch grip (NHPT, ARAT subtest pinch).

One previous study described task-oriented upper limb training in MS [13]. In this study of Bonzano et al. (2014), task-oriented training (two months, 20 sessions) was compared to passive mobilization and the authors found a significant time effect but no significant group*time interaction effect on the ARAT and NHPT. In the present study we did not find an improvement on the NHPT and the group*time effects cannot be compared as we did not include a passive intervention as control therapy. Furthermore, white matter integrity (diffusion tensor imaging) in the corticospinal tract and corpus callosum was only preserved in the group receiving task-oriented training and not in the passive mobilization group. Training intensity was not described in this study.

In stroke, two recent RCTs have investigated dose-response relationships during task-oriented upper limb training. The ICARE trial compared a task-oriented training program (mean 27 hours total training time) with dose-equivalent occupational therapy (mean 27 hours total training time) and usual occupational therapy (without specification of dose, mean 11.2 hours total training time) in subacute stroke patients (mean 46 days) with moderate upper limb impairment [9]. No differences between groups were found after ten

weeks of training (Wolf Motor Function Test and Stroke Impact Scale). Lang et al. (2016) compared four different therapy doses in chronic stroke patients [17]. Doses were defined by the number of repetitions: 100 repetitions/session (total median 3200), 200 repetitions/session (total median 6398), 300 repetitions/session (total median 9582) and an individual maximum (total median 10808). The authors were surprised to conclude that higher doses were no more beneficial than lower doses to improve arm-hand capacity (ARAT). The findings of these RCTs do not support the conclusions of an earlier meta-analysis demonstrating a dose-response relationship in stroke rehabilitation [14]. This meta-analysis did however not specifically target the upper limb. Although our research involved a different disease population, we also did not find a clear dose-response relationship in measures for upper limb capacity such as the ARAT. However, the results on the SFI and BBT might offer new insights in possible intensity-dependent effects for endurance-related tasks.

Methodological considerations

Training program and rehabilitation technology

The present study aimed to implement several motor learning components deemed important in motor rehabilitation [6, 41]. Training was 'client centered', difficulty was progressed and variability was added to stimulate learning and transfer effects. Most tasks were performed bilaterally, in contrast to the majority of MS upper limb research to date [5]. The training components 'random' and 'distributed' practice, both considered beneficial to motor learning, were not implemented due to practical concerns. Earlier research did implement these components in technology-supported task-oriented upper limb training in stroke [8, 42].

The addition of technology to support upper limb training is an upcoming approach in neurological rehabilitation and might add several advantages such as increasing total therapy time and enabling independent and quantifiable training [45]. Research has primarily focused on robot-assisted stroke rehabilitation, particularly targeting the ICF body functions and structures level [43-46]. However, the TagTrainer allows training of functional tasks on ICF activity level using real-life objects. This device can also facilitate the implementation of the motor learning component 'knowledge of results feedback' (counting number of repetitions, LED lights displaying correct object placement or removal), which can be important to guide the training and maintain patient motivation and involvement [45].

The clinical usability of the TagTrainer was already investigated among therapists treating patients with stroke and tetraplegia [21]. The present study is, to the best of our knowledge, the first clinical trial to integrate the TagTrainer in an upper limb training program.

Upper limb disability levels

Participants were classified into three different upper limb disability levels for two reasons. First, this has ensured balanced distribution among groups (TOT100 and TOT50) through blocked randomization even while the sample was small. Second, we aimed to explore whether the response to task-oriented upper limb training differed for pwMS with varying levels of upper limb disability. However, due to the small sample size no statistical analyses were performed to answer this research objective.

The EDSS is often used to classify pwMS, but is weighted towards the lower limbs. Although pwMS with higher EDSS scores demonstrate significantly more upper limb abnormalities [3], this scale cannot be used to classify a patient sample with EDSS scores ranging 4 to 8 into distinct upper limb disability levels. Upper limb tests appear more suitable to separate such patient subgroups. However, there is currently no gold standard test or procedure available. We aimed to classify the participants considering both their distal (hand, fingers) as well as their proximal (shoulder) function based on a cut-off value described in existing MS literature (33.3s on NHPT [20]) and a self-selected criterion (90° anteflexion, 20s). Using these criteria, most participants were classified as having mild (n=6) or moderate (n=11) upper limb disability. Observational analysis did not reveal clear differences in training response between these participants. Each intervention group also included one participant with severe upper limb disability, which was too few to draw conclusions.

We note that other methodologies might have yielded a different classification and/or outcome. For example, Bonzano et al. (2014) distinguished between mild and moderate motor deficits by manual muscle testing around the shoulder, elbow, wrist and fingers [13]. Here, only one participant was regarded as ‘moderate’ and 29 as ‘mild’.

Training intensity

Training intensity acts as one determinant of training dosage [15]. Previous research concerning stroke rehabilitation concluded that the time scheduled for therapy may not accurately reflect the actual practice time nor the number of movement repetitions

performed [14] and as such does not reflect dosage optimally. Recently, several studies in stroke rehabilitation incorporated a fixed number of repetitions as indicators of training intensity during task-oriented training [16-18]. To date, there are no studies investigating the effects of upper limb training at different training intensities in the MS population.

In the present study we introduced a protocol to establish training intensity using an individualized maximum number of repetitions as reference instead of imposing a fixed number of repetitions, in order to account for differences between participants and between training tasks. All other parameters influencing the dosage, such as training duration and frequency, were matched between groups. No adverse effects occurred and pwMS from all upper limb disability levels were capable to perform task-oriented training during high-intense one-hour training sessions.

We found that participants from the TOT100 group performed more repetitions per session and had more difficulties to reach their target number of repetitions compared to the TOT50 group. However, considering that on average the participants in the TOT50 group did not reach their target number of repetitions either, there may have been insufficient differentiation between the two groups. More differentiation in intensity might yield different results and reveal additional intensity-dependent effects. In contrast, presuming that a higher number of repetitions does not influence the results compared to a lower number of repetitions, one could state that it is not necessary to request the patient to perform a task as many times as possible in clinical practice.

Study limitations

Several limitations need to be addressed. First, the number of participants was small and our data showed large variability given the broad inclusion criteria which were deliberately chosen for this pilot study. This cautions against generalization of the study results and hinders the evaluation of outliers and their possible influence on the small data set. Second, group composition was not completely balanced. The blocked randomization resulted in an equal distribution of upper limb disability between the TOT100 and TOT50 group. However, the UOT group was recruited separately, was not randomized and counted only five participants, none of which were classified in the mild upper limb disability subgroup. The pilot study is still ongoing and the aim is to collect data of ten participants in each group. Third, the content and intensity of the UOT training sessions were not registered. Fourth,

therapists were not blinded for group allocation. The assessor was only blinded with respect to the TOT100 and TOT50 group but not to the UOT group, inducing a possible detection bias. Fifth, the TEMPA (unilateral and bilateral score) and ARAT (gross movement subtest) exhibited a ceiling effect as >20% of participants reached the maximum score at baseline. Sixth, participants in the TOT100 and TOT50 group performed the BBT during the determination of the individual maximum number of repetitions. Intervention results on the BBT should be interpreted with some caution because a learning effect may have augmented a true improvement in grasp/transport capability in these two groups.

Future research

This pilot study is still ongoing and was conducted to get more insights in order to design a larger RCT investigating the clinical and neural effects of upper limb rehabilitation in pwMS. Based on the complete pilot data, power calculations for the larger RCT will be made. Regarding training intensity, the protocol to determine the individual maximum number of repetitions can be implemented to enhance the standardization of research on task-oriented training. The optimal dosage of task-oriented training for pwMS should be explored, and possibly more differentiation in training intensity is needed (e.g. using the present study protocol: 30% vs. 100%). It is also not known whether a 'minimal threshold' and/or a 'ceiling' exists with regard to training intensity and its effect on therapy outcome.

As most outcomes on ICF body functions and structures level remained stable after training, measures such as vibration sense can be omitted. The training effects on motor fatigability (SFI) during the sustained handgrip strength test need further exploration. As earlier research has shown that diffusion tensor imaging can yield distinct outcomes from clinical tests after upper limb rehabilitation in MS [13], neuroimaging techniques can be added in a larger RCT.

Follow-up measurements should be performed to investigate retention and long term effects. Lastly, future research can explore the benefits of technology-supported upper limb rehabilitation in MS. For example, the use and the effectiveness of the TagTrainer with limited supervision or as a tool during group sessions can be evaluated.

7. Conclusion

PwMS from all upper limb disability levels were able to perform high-intense one-hour sessions. We found several significant improvements over time, but no clear intensity-dependent effect during task-oriented training in MS. However, the results on the BBT and SFI may suggest a superiority of task-oriented training at a higher intensity.

8. Reference list

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9. Figures and tables

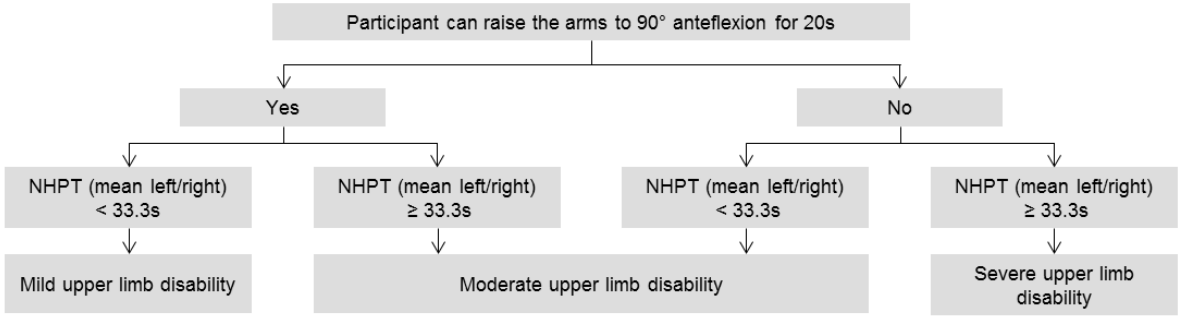

Figure 1. Determination of the participant's upper limb disability level.

NHPT: Nine Hole Peg Test.

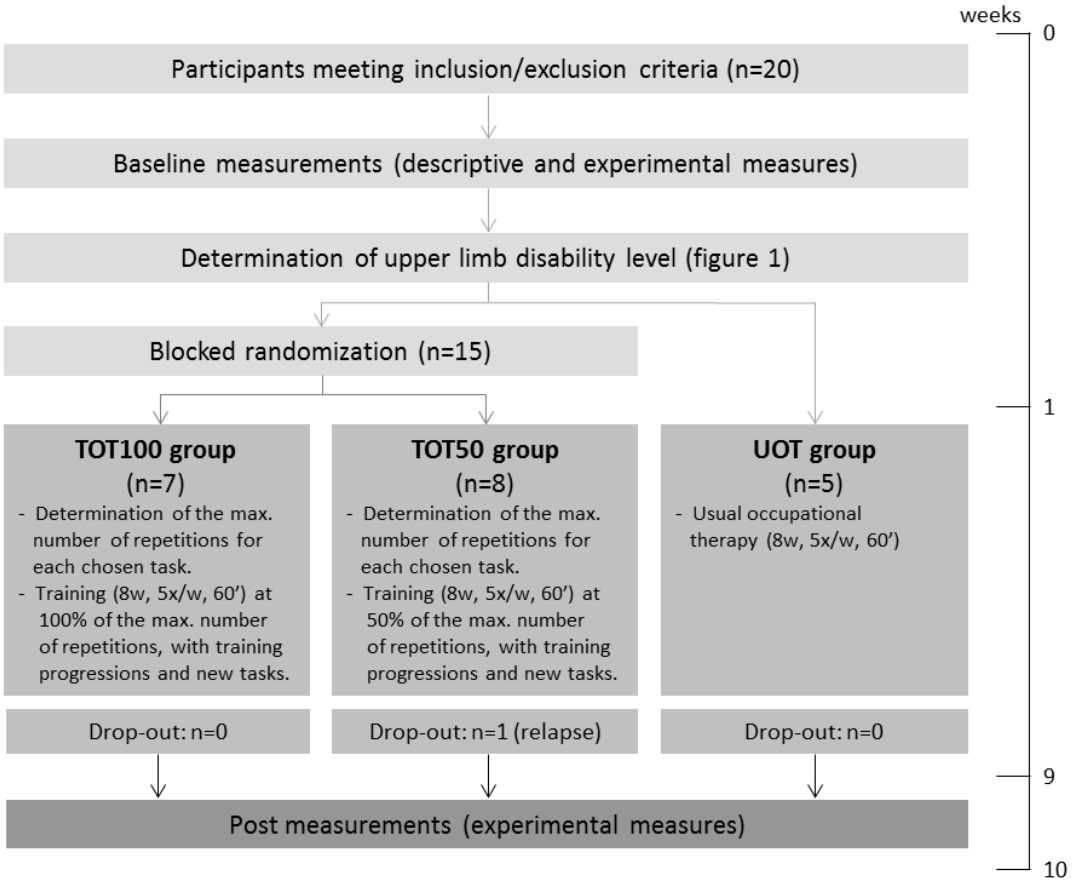

Figure 2. Study design.

Figure 3. Training set-up and technological 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.

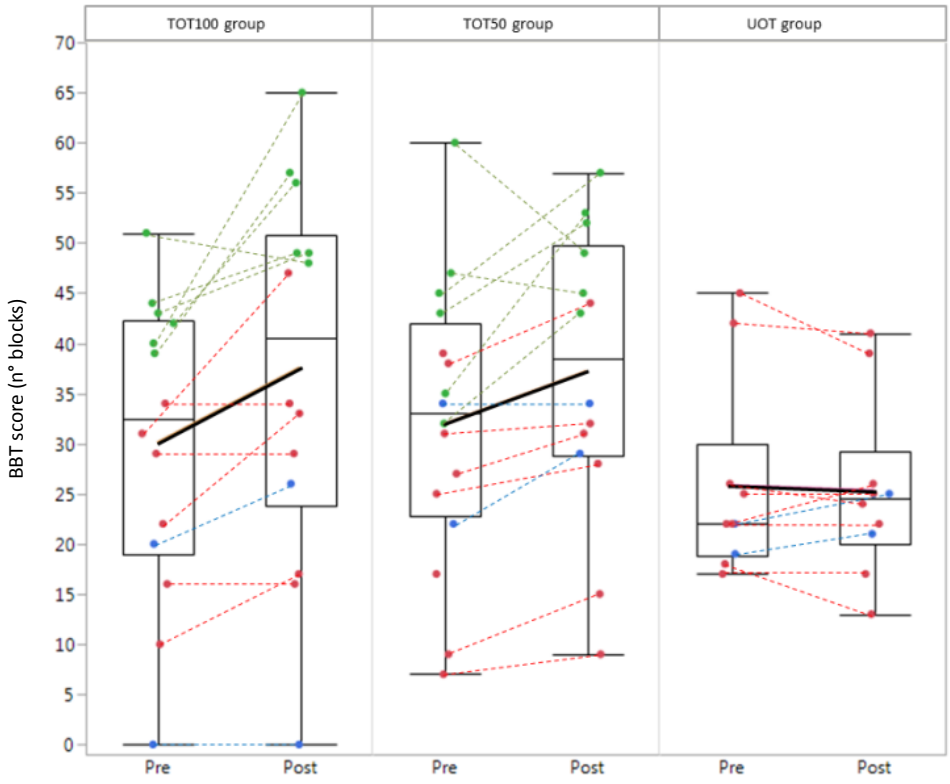

Figure 4. Results on the Box and Block Test.

Boxplots represent median and IQR. Solid black lines indicate the group mean score. Dots and dashed lines represent individual participant scores. Green: mild upper limb disability, Red: moderate upper limb disability, Blue: severe upper limb disability.
Note one drop-out in the TOT50 group.

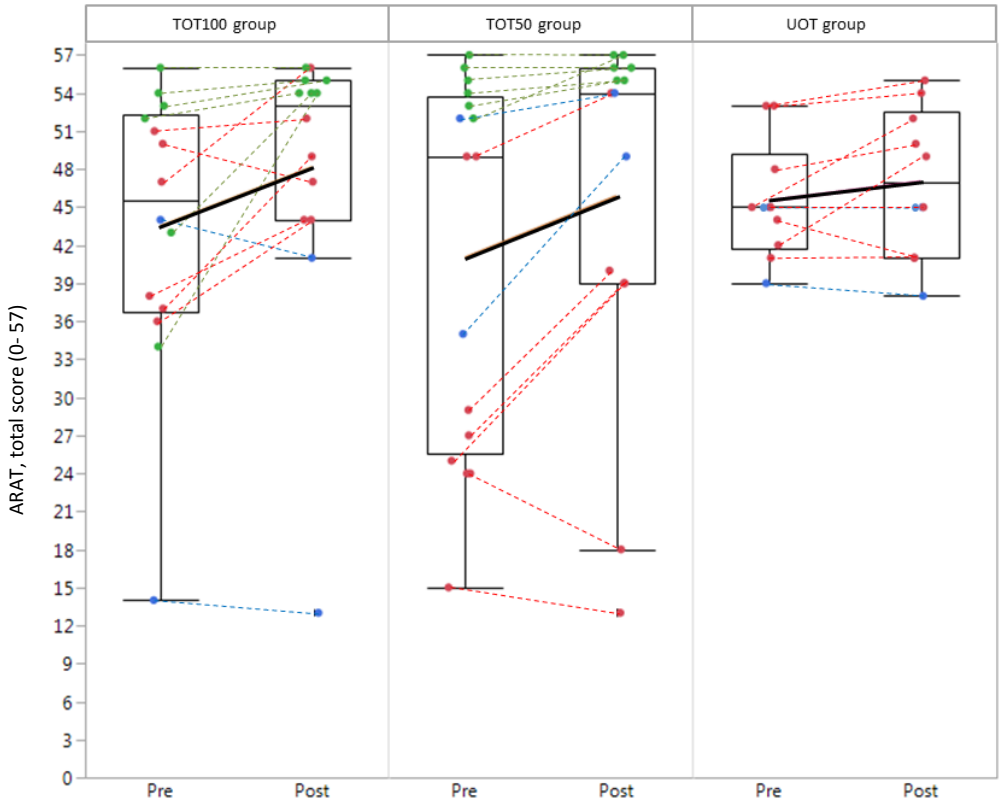

Figure 5. Results on the Action Research Arm Test.

Boxplots represent median and IQR. Solid black lines indicate the group mean score. Dots and dashed lines represent individual participant scores. Green: mild upper limb disability, Red: moderate upper limb disability, Blue: severe upper limb disability.
Note one drop-out in the TOT50 group.

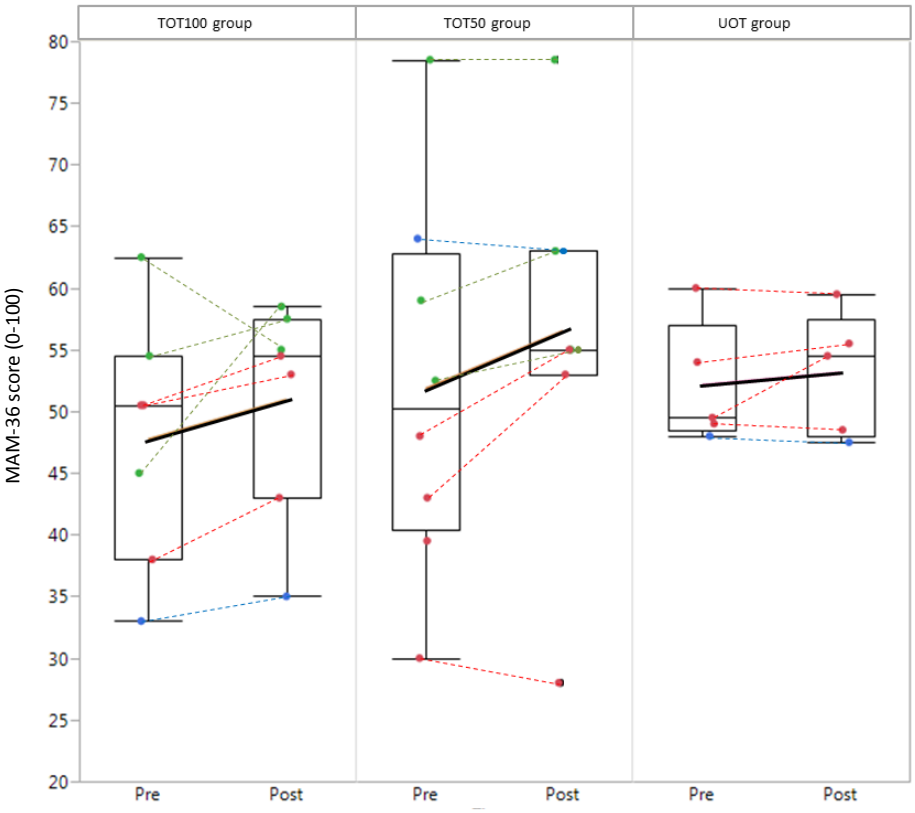

Figure 6. Results on the Manual Ability Measure-36.

Boxplots represent median and IQR. Solid black lines indicate the group mean score. Dots and dashed lines represent individual participant scores. Green: mild upper limb disability, Red: moderate upper limb disability, Blue: severe upper limb disability.
Note one drop-out in the TOT50 group.

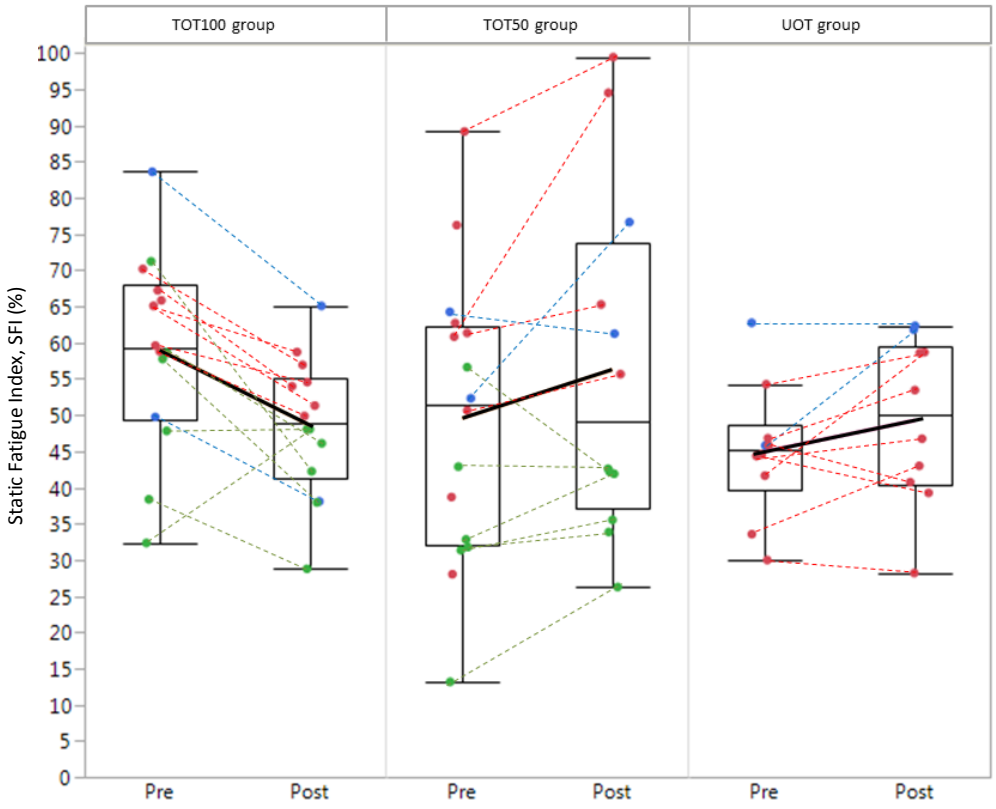

Figure 7. Results on the Static Fatigue Index (SFI) during a sustained maximal handgrip strength test.

Boxplots represent median and IQR. Solid black lines indicate the group mean score. Dots and dashed lines represent individual participant scores. Green: mild upper limb disability, Red: moderate upper limb disability, Blue: severe upper limb disability.
Note one drop-out and one participant with missing post data in the TOT50 group.

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

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

Values in parentheses: number of participants training the task.

Table 2. Determination of the individual maximum number of repetitions.

Steps	**Description of 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 3) → Can the participant perform this training task ≥3x without compensations, assistance or aids? - Yes: Increase difficulty level (see table 3). - No: Go to step 2 and use the initial task difficulty. - No: Decrease difficulty (see table 3) → Can the participant 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.	1) Participant performs the Box and Block Test with both sides. 2) 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 (Box and Block Test). - 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.

Table 3. Progressions within training tasks and choosing new tasks.

Criteria	**Possible changes (progression, downgrading, new task)**
The participant reaches his/her individual maximum number of repetitions of a training task without compensations and adverse effects in 2 consecutive training sessions.	Principles of progression: - Part practice: divide a task in different skill components or combine these parts to reach the whole task. - Object characteristics (weight, size, material, etc). - Variability within the task (alternate different object characteristics in subsequent repetitions). - Workspace (place targets further away, etc). - Antigravity support (Diego, Tyromotion). - Increase load/resistance (0.5 or 1.0 kg at the distal forearm). - Patient positioning (sitting, 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 using the same principles as for task progression.
After at least one progression is made and the participant is able to 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).

Table 4. Overview of participant descriptive characteristics at baseline.

Measurement	TOT100 group (n=7)	TOT50 group (n=8)	UOT group (n=5)	p-value
Upper limb disability level				0.5832
Mild	3	3	0	
Moderate	3	4	4	
Severe	1	1	1	
Gender				0.8483
Male	3	2	2	
Female	4	6	3	
Age (years)	57 [42-69]	55 [43-62]	64 [47-78]	0.5006
Type of MS				0.6004
RRMS	4	3	3	
SPMS	1	4	2	
PPMS	2	1	0	
Time since diagnosis (years)	19 [7-29]	10.5 [6.5-20.5]	21 [10-40]	0.3886
EDSS (0-10)	7 [5-7]	7 [5.6-7.9]	6.5 [6-7.5]	0.6589
Hand dominance, EHI				0.3376
Right	5	6	4	
Left	0	2	0	
Ambidextrous	2	0	1	
Most impaired hand, self-reported				0.7833
Right	4	6	3	
Left	3	1	1	
Both	0	1	0	
Finger-to-nose test: intention tremor (Fahn's rating) ‡				0.3801
Score 0, none	9	12	5	
Score 1, slight	3	4	2	
Score 2, mild	0	0	1	
Score 3, marked	1	0	2	
Score 4, severe	1	0	0	
MAS ‡ †				0.4549
Score 0	11	13	10	
Score 1	2	3	0	
Score 2	1	0	0	
Score 3	0	0	0	
Score 4	0	0	0	
Score 5	0	0	0	
MFIS				
Physical subscale (0-36)	26 [19-31]	25 [17-28]	20 [14.5-29.5]	0.7933
Cognitive subscale (0-40)	25 [13-29]	19 [8-26]	22 [16-30]	0.7642
Psychological subscale (0-8)	6 [3-6]	3.5 [0.3-5.5]	4 [2-6.5]	0.3764
Total score (0-84)	51 [36-62]	46 [30.8-58.5]	47 [32.5- 65.5]	0.7564

Continuous data are presented as Median [IQR]. Continuous variables were compared with the Kruskal-Wallis test, categorical variables with the Fisher Exact test.
EDSS: Expanded Disability Status Scale, EHI: Edinburgh Handedness Inventory, MAS: Modified Ashworth Scale, MFIS: Modified Fatigue Impact Scale, PPMS: primary progressive multiple sclerosis, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary progressive multiple sclerosis.
‡ conducted with both upper limbs, † mean score of shoulder adductors, elbow flexors and wrist flexors (rounded).

Table 5. Primary outcome measures - ICF activity level.

Outcome measure	TOT100 group (n=7)			TOT50 group (n=8)			UOT group (n=5)			Mixed model analysis		
	Pre	Post	Change	Pre	Post	Change	Pre	Post	Change	Time	Group	Group*Time
NHPT, time (s)	35.61 [26.58-155.36]	40.93 [23.51-213.03]	0.22 [-4.16-10.64]	37.47 [29.42-136.89]	41.61 [23.80-97.55]	-1.2 [-10.69-2.24]	60.35 [51.68-77.36]	70.02 [55.15-87.95]	6.54 [2.10-11.87]	0.7666	0.8990	0.1037
ARAT, subtest grasp (0-18)	16 [13.5-18]	18 [16.75-18]	0 [0-4]	16 [8.25-18]	17.5 [15-18]	0 [0-3.5]	16 [13-18]	17 [14.75-18]	0 [0-2.25]	**0.0148**	0.4756	0.6003
ARAT, subtest grip (0-12)	9 [7.5-11.25]	10.5 [7.5-12]	0 [-0.25-1.25]	10 [6.25-11]	11 [9-11.25]	0 [0-2.25]	8.5 [8-10]	9.5 [8-10]	0 [-0.25-1.25]	**0.0062**	0.9728	0.4821
ARAT, subtest pinch (0-18)	13.5 [9.75-15]	15 [12-18]	2 [0-4]	14.5 [4.25-15.75]	17 [6-17.25]	1 [0-3]	12 [11-13.5]	12.5 [11-15.25]	1 [-1-2]	**0.0005**	0.5796	0.3608
ARAT, subtest gross movement (0-9)	8 [7-9]	9 [8-9]	0 [0-1.25]	8.5 [8-9]	9 [8-9]	0 [-0.25-0]	9 [8.75-9]	9 [7-9]	0 [-1.25-0]	0.9195	0.4642	0.0977
ARAT, total score (0-57)	45.5 [36.75-52.25]	53 [44-55]	2 [-0.25-9.5]	49 [25.5-53.75]	54 [39-56]	2 [0-11.25]	45 [41.75-49.25]	47 [41-52.5]	0.5 [-0.25-3.25]	**0.0008**	0.7377	0.3861
BBT (n° blocks)	32.5 [19-42.25]	40.5 [23.75-50.75]	6 [0-14.5]	33 [22.75-42]	38.5 [28.75-49.75]	5 [0.75-9.5]	22 [18.75-30]	24.5 [20-29.25]	0 [-2.75-2.25]	**0.0012**	0.2450	**0.0255**
TEMPA, unilateral score (-12 - 0)	-1 [-4.75-0]	0 [-1-0]	0.5 [0-2.25]	-1.5 [-5-0]	0 [-1.75-0]	0.5 [0-2]	-3 [-7- -0.75]	-4 [-5.25- -1.5]	0 [-3-2.25]	0.0649	0.4723	0.4704
TEMPA, bilateral score (-15 - 0)	0 [-6-0]	0 [-3-0]	0 [-1-1]	-1.5 [-2.75-0]	0 [0-0]	1 [0-2]	-4 [-10- -3]	-7 [-8.5- -4]	-1 [-3.5-3]	0.4714	0.0959	0.4271
TEMPA, total score (-39 - 0)	-2 [-20- -1]	0 [-4-0]	2 [1-2]	-5.5 [-10.5- -2]	0 [-5-0]	2 [2-2]	-9 [-23.5- -4.5]	-16 [-19.5- -6.5]	0 [-9.5-8]	0.2257	0.4088	0.5492
MAM-36 (0-100)	50.5 [38-54.5]	54.5 [43-57.5]	3 [2-5]	50.25 [40.38-62.75]	55 [53-63]	2.5 [-1-7]	49.5 [48.5-57]	54.5 [48-57.5]	-0.5 [-0.5-3.25]	**0.0437**	0.7731	0.6944

Data are continuous and presented as Median [IQR].
ARAT: Action Research Arm Test, BBT: Box and Block Test, ICF: International Classification of Functioning, Disability and Health, MAM-36: Manual Ability Measure-36, NHPT: Nine Hole Peg Test, TEMPA: Test d'Évaluation des Membres Supérieurs des Personnes Âgées.

Table 6. Secondary outcome measures - ICF body functions and structures level.

Outcome measure	TOT100 group (n=7)			TOT50 group (n=8)			UOT group (n=5)			Mixed model analysis		
	Pre	Post	Change	Pre	Post	Change	Pre	Post	Change	Time	Group	Group*Time
Handgrip strength (kg)	15.3 [9.38-21.5]	16.65 [11.58-19.45]	1.4 [-0.93-5.18]	15.5 [8.95-26.8]	21.25 [9.95-23.18]	0.65 [-1.88-2.45]	22.55 [14.45-31.1]	22.4 [15.53-33.45]	-0.45 [-1.3-1.93]	0.1656	0.1530	0.5565
Key grip strength (kg)	3.65 [2.33-4.43]	3.9 [2.4-4.95]	-0.2 [-0.6-0.93]	4.2 [1.9-5.38]	4.25 [3.23-6.38]	0.1 [-0.28-1.2]	5.85 [4.73-6.93]	5.5 [4.35-7.03]	-0.15 [-0.93-0.68]	0.6952	0.1971	0.3542
3-jaw grip strength (kg)	3.8 [1.65-5.33]	3.25 [1.95-5.4]	-0.15 [-0.95-1.5]	3.45 [0.98-4.8]	3.85 [1.98-5.75]	0.6 [-0.25-1.78]	4.5 [2-5.25]	4.35 [2.48-6.03]	0.6 [-0.75-1.38]	0.0596	0.8254	0.1369
Thumb-index grip strength (kg)	2.85 [1.53-3.98]	2.5 [1.53-4.03]	-0.1 [-1.25-1]	2.5 [0.83-3.25]	2.5 [1.68-3.88]	0.25 [-0.35-1.45]	3.3 [2.6-4.7]	3.15 [2.78-4.35]	0.05 [-0.45-0.43]	0.4248	0.2848	0.2267
Motricity Index (0-100)	80.5 [63-88.75]	76.5 [68.5-85]	-1.5 [-6.75-1.5]	88 [67-91]	83 [70-91]	0 [-9.5-6.25]	79.5 [73.5-91.25]	76 [70.5-84]	-2.5 [-8.5-0]	0.1355	0.5450	0.9224
Monofilament, thumb (1-6)	3 [2-3.25]	3 [1-3]	0 [-1-0]	3 [2-3]	2 [1.75-3]	0 [0-0]	2 [1-4]	2.5 [2-3]	0 [-1-1]	0.1628	0.9866	0.3542
Monofilament, index finger (1-6)	2 [2-3]	2.5 [1.75-3]	0 [-1-1]	3 [2-4]	2 [1.75-3]	-0.5 [-1-0]	2 [1-4]	2.5 [1.75-3.25]	0 [-1-0.25]	0.4134	0.8907	0.4861
Vibration, DIP (0-8)	7 [6-7.63]	7 [5-8]	0 [-0.25-0.63]	7 [5.13-8]	7.5 [5-8]	0 [-0.25-1]	6.5 [5.75-8]	7.25 [6-8]	0.5 [0-1]	0.2705	0.5368	0.5041
Vibration, ulna (0-8)	6.75 [4.75-8]	6.75 [5.5-8]	0 [-0.13-2]	6.5 [5-7.75]	6.25 [4.88-8]	0 [-0.75-0.25]	5.5 [5-7.25]	6.25 [5-7.13]	0.25 [-0.5-1]	0.2327	0.8929	0.2749
SDMT (n° correct responses)	28 [26-35]	32 [29-55]	4 [-6-8]	37 [21.5-49.5]	34 [23-52]	2 [-3-7]	16.5 [10.75-40.25]	19 [11-42.75]	3 [-4.75-7]	0.3224	0.3778	0.7442
SFI (0-100%)	59.22 [49.27-67.98]	48.99 [41.2-55.17]	-12.09 [-14.97--6.62]	51.5 [32.04-62.37]	49.14 [37.12-73.82]	4.59 [0.31-12.38]	45.20 [39.62-48.68]	50.1 [40.37-59.47]	3.35 [-2.63-11.08]	0.8462	0.5219	**0.0003**

Data are continuous and presented as Median [IQR].
DIP: distal interphalangeal articulation of the index finger, ICF: International Classification of Functioning, Disability and Health, SDMT: Symbol Digit Modalities Test, SFI: Static Fatigue Index (sustained handgrip strength test).

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