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Preliminary Evaluation of an Adaptive Robotic Training Program of the Wrist for Persons with Multiple Sclerosis

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Abstract: Robotics can be used to describe wrist kinematics and assess sensorimotor impairments, while the implementation of training algorithms can be aimed at improving neuromuscular control. The purpose of this study was to use a robotic device to develop an adaptive and individualized training program of the distal upper extremity for individuals with multiple sclerosis (MS). This approach included an online assessment of performance aimed at changing the level of assistance/resistance provided during the task. Participants (N = 7) completed a robotic training program that occurred 3 times weekly for 4 weeks. The training protocol consisted of tracking a target moving along a figure by grasping the end-effector of the robotic device and moving it along the trajectory. Outcome measures were assessed pre- and post-intervention. Improvements in performance were quantified by average tracking ($p = 0.028$) and figural error ($p = 0.028$), which was significantly reduced by 26% and 43%, respectively. Isometric wrist strength significantly improved post-intervention (flexion: $p = 0.043$, radial and ulnar deviation: $p = 0.028$). The results of this work demonstrate that 4-weeks of adaptive robotic training is a feasible rehabilitative program that has the potential to improve distal upper extremity motor accuracy and muscular strength in a MS population.

Keywords: multiple sclerosis; neurorehabilitation; robotic rehabilitation; upper limb

1. Introduction

Multiple Sclerosis (MS) is a chronic, autoimmune and inflammatory disease affecting the central nervous and musculoskeletal systems. Presently, there is no existing cure. MS affects approximately 77,000 individuals in Canada and 2.5 million worldwide [1]. Specific causes of this disease remain unknown but are understood to be genetic or related to environmental factors [2]. It is the most common autoimmune disease affecting the central nervous system and is known as the most disabling chronic disease of young adults during their most productive years [3]. Inflammation can accumulate in the brain and spinal cord, eventually resulting in neurodegeneration and demyelination of the efferent/afferent pathways, which in turn, often affects the motor capabilities of the upper limb [3], resulting in upper limb disability in 66% of individuals diagnosed with MS [4]. Lack of hand function, lack of dexterity and declining grip strength hinders the individual's ability to perform activities of daily living (ADLs) such as bathing, dressing, and feeding. Individuals with MS can become dependent and require complete reliance on caregivers to help complete fine motor skills [5].

To promote motor learning and increased wrist function, manual motor therapy is required in high repetitions, multiple times daily [6]. This method is both costly for individuals with MS and time consuming for a physical or occupational therapist. Robotic rehabilitation can increase the amount of work per session compared to manual therapy and decrease the therapist's hands-on time. After injury, intensive task-specific therapy is needed to preserve wrist and hand function [6]. The repetitive, highly reproducible and high dose motor movements made possible with robotics often demonstrate positive results for motor learning and are promising for developing new motor pathways (or restoring) and increasing muscular strength, which should translate into improved function and control of the hand [7–9]. To date, there is a paucity of research on robotic neurorehabilitation for persons with MS, particularly for the upper limb [7], although, rehabilitation robotics have been highly researched and demonstrate positive adaptations in stroke patients [10–12]. Robotic rehabilitation does face challenges, as some suggest there are no further improvements than that of conventional therapy [13] however, a robotic approach ensures repeatable and controlled conditions, particularly relevant during intensive training over several days. Additionally, the accuracy of the imposed forces and the opportunity to measure real-time performance boosts the importance of developing robot-based solutions. Robotic devices could provide an online assessment of performance in terms of sensorimotor components and mechanical intrinsic properties of one's limb [14–16], thus enhancing the efficacy of therapeutic treatments through performance-based tailored programs [17].

The purpose of this work was to develop and evaluate a novel rehabilitation approach that exploited the advantages of robotics. The proposed training program aimed to improve wrist function for persons with MS and was based on the online *modulation* of torques imposed during a tracking task. Our algorithm provided real-time assistive torques until a minimum level of performance was reached. Performance was evaluated as a function of an indicator related to dexterity and eye-hand coordination. Here, the present study introduced a novelty with respect to the previous body of literature about the use of adaptive controllers for neurorehabilitation [18]. Indeed, during our robotic training, assistance switched to resistance, thus opposing user motion according to their online performance. This technique generated individualized progressive overload to create periodization and therapy progression, a therapy facet currently lacking in some robotic rehabilitation research. The neurorehabilitation mechanisms targeted by this study as outlined by [19], include the principles: use it or lose it, specificity and repetition. Study hypotheses included an improvement in tracking capabilities from pre- to post-intervention, and an increase in wrist strength that correlates with improved scores on functional tests and self-reported performance measures.

2. Materials and Methods

2.1. Participants

15 community-dwelling individuals with MS were recruited to participate in this study. In total, 7 participants with MS (mean age: 46.9 ± 15.9 years, see Table 1 for further details) completed a 4-week training program. Eight individuals were forced to prematurely terminate the training due to COVID-19 restrictions. Inclusion criteria consisted of individuals with any phenotype (3-relapsing remittent, 3-secondary progressive, 1-primary progressive) and severity of MS (Expanded Disability Status Scale (EDSS): 4.7 ± 1.8; years since diagnosis: 4.6 ± 10.3) who experience upper limb motor impairments. No participants were undergoing additional therapy interventions such as physical or occupational therapy at the time of the study. Participants were not taking any disease modifying drugs that would limit or enhance motor control of the upper limb. All experimental procedures were approved by the institutional Research Ethics Board (REB# 19-119) and written consent was obtained from all participants prior to participation.

Table 1. Participant Demographics.

	Age	MS Phenotype	Dominant Limb	Trained Limb	Years since Diagnosis	EDSS Score	Sex
S01	36	SPMS	R	L	14	7	Female
S02	60	PPMS	R	L	20	7	Female
S03	71	SPMS	R	L	20	3	Male
S04	43	RRMS	R	R	6	6.5	Female
S05	61	SPMS	L	R	34	6	Female
S06	27	RRMS	R	R	1 $\frac{1}{2}$	4	Male
S07	30	RRMS	R	L	7	2	Female

Note: SPMS = Secondary progressive, PPMS = primary progressive, RRMS = relapsing remittent, R = right hand, L = left hand.

2.2. Experimental Set-Up and Protocol

The study protocol involved two sessions of assessment, prior to and following a 4-week training protocol. Both the assessment and training involved the use of a robotic device. Before starting the first session, participants completed a familiarization session where they became accustomed to the robotic apparatus, performing as many practice trials as needed until the tasks were fully understood. During robotic sessions, participants were seated in an upright neutral position in front of a monitor and rested their forearm (with a consistent elbow flexion of 135° ± 3.67°) on the robotic device, called WristBot (Istituto Italiano di Tecnologia, Genova, Italy) [13,15], grasping the handle with their hand (Figure 1). WristBot is a custom-built manipulandum with a Range Of Motion (ROM) that replicates typical human wrist motion in three Degrees of Freedom (DoF): flexion/extension, ±62°; radial/ulnar deviation, +40°/−45°; pronation/supination, ±60°. Wrist angular rotations on each DoF are measured by high-resolution incremental encoders. Additionally, four brushless motors deliver torques necessary to compensate for the weight and inertia of the device and to manipulate the wrist joint. This allows for force feedback to participants during sensorimotor training programs or therapy sessions. An integrated virtual reality environment provides visual feedback to participants and allows to perform eye-hand coordination tasks.

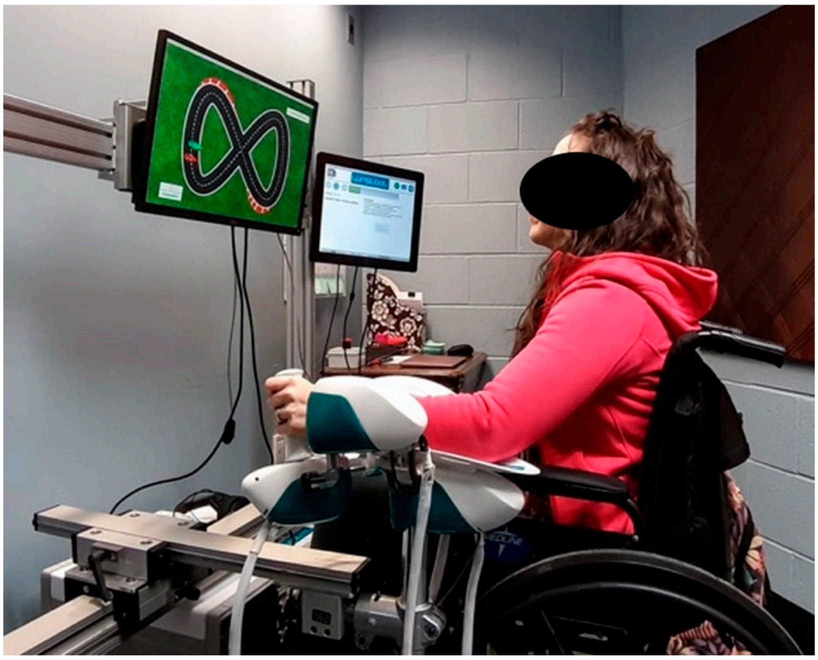

Figure 1. Experimental set-up with participant positioned at the WristBot, grasping its handle to perform the tracking task with visual feedback.

2.3. Assessment Sessions

Assessment sessions were performed at 2 time points, before starting (T0) and after completing (T1) the training program. Each session took approximately 1.5 h to complete and was performed on separate days from typical training sessions to avoid fatigue. The evaluation involved both upper extremities and included robotic and non-robotic measures, such as strength and clinical tests. For each limb, the robotic assessment evaluated:

1. Active and passive wrist ROM in flexion/extension and radial/ulnar deviation. Participants moved actively or were passively moved by the WristBot towards each direction until they reached maximal excursion. The outcome measure was maximal wrist rotation in degrees recorded by encoders along each direction.
2. The ability to track a target moving in the space identified by flexion/extension and radial/ulnar deviation. Without any assistive force, participants actively moved the handle of the robot to follow a target over a Lissajous figure (figure-eight shape) for 3 min. The pronation/supination plane was locked during the task. For each participant, the size of the figure never exceeded the 80% of the active ROM previously assessed. The trajectory was described by the following law of motion Equation (1):

$$\begin{cases} x = 80\% * \min(ROM) * \sin\left(\frac{2\pi t}{T}\right) \\ y = 80\% * \frac{1}{2}\min(ROM) * \sin\left(2 * \frac{2\pi t}{T}\right) \end{cases} \quad (1)$$

where min(ROM) is the minimum active ROM among the four directions assessed and T = 30 s (the duration of a complete lap). Outcome measures computed from these data were the Tracking Error (TE) and the Figural Error (FE). TE was defined as the mean angular distance in degrees between end-effector and target position at each time point. This outcome measure evaluated the performance, taking into account the difference in velocity between the end-effector and the target. TE was computed starting from the data recorded by the encoders along the flexion/extension (x [deg]) and radial/ulnar deviation (y [deg]) planes. Robot encoders recorded angular data, i.e., rotations along each degree of freedom. The measure is obtained through Equation (2):

$$TE = \frac{\sum_{i=1}^{N} \sqrt{(x_{T,i} - x_{H,i})^2 + (y_{T,i} - y_{H,i})^2}}{N} \quad (2)$$

where T,i and H,i are the target and the end-effector positions at each time sample and N is the total number of time samples. FE was measured to characterize performance as the trajectory of the participant from the ideal figure-eight shape (target trajectory), regardless of differences of speed between target and end-effector. FE was measured in degrees and computed as shown in Equation (3):

$$\begin{gathered} dist_{AB}(i) = \min_{j} \parallel A_i - B_j \parallel \;\; i = 1,2,\ldots n \\ dist_{BA}(j) = \min_{i} \parallel A_i - B_j \parallel \;\; j = 1,2,\ldots m \\ FE = \frac{\sum_{i=1}^{n} dist_{AB}(i) + \sum_{j=1}^{m} dist_{BA}(j)}{n+m} \end{gathered} \quad (3)$$

where A and n are the time series ($A[x(t),y(t)]$) and total samples of the target trajectory and B and m are the time series ($B[x(t),y(t)]$) and total samples of the end-effector trajectory [20].

Assessment of strength included:

1. Maximum grip force to measure overall grip strength. This was performed twice on each limb and the highest force in kg was recorded (Jamar Smart Digital Hand Dynamometer, Performance Health, Warrenville, IL, USA).
2. Grip force endurance test to measure muscular endurance on each limb. Participants gripped the dynamometer at 50% of their maximum grip force and the time to

fatigue in seconds (defined as when the participant could no longer hold 50% of their maximum for 2 consecutive seconds) was recorded.

3. Maximum isometric wrist force measured in kg was determined for flexion/extension and radial/ulnar deviation using a stationary load cell (Model: BG 500, Mark-10 Corporation, New York, NY, USA).

Finally, clinical outcome measures included:

1. 19-Hole Peg Test (9-HPT) was performed twice on each limb. 9HPT is used in clinics to evaluate finger dexterity [21] accordingly to the time taken to accomplish the required tasks. One participant was physically unable to complete the test with the trained limb at T0 due to a disabling tremor and was eliminated from the mean values.
2. The Patient Rated Wrist Evaluation (PRWE) was administered, and participants had to answer 15 questions that pertained to pain, ADLs in the affected limb and activities that require the use of both limbs [22]. Higher final scores point out higher levels of wrist disability.

2.4. Training Sessions

The training program lasted 4 weeks and included 3 training sessions per week. Each session took 40 min and training days were scheduled on the same weekdays and time each week. The robotic training program was based on a high dose, high frequency [23], and task-oriented basis. During each training session, participants performed two 20 min work blocks of a tracking task separated by a 5 min rest period. Each block included 4 sets made up of 4 min of tracking, separated by a 1 min break. Only the participant's self-reported most affected limb was trained; the other limb was considered an untrained control limb.

Using the WristBot, participants followed a Lissajous curve (figure-eight) by tracking a moving target on the computer screen. Participants were asked to follow the target to the best of their abilities. The tracking law of motion was the same as described in Equation (1) and both the size and the duration of the tracking were kept the same among training sessions. The tracking required movements in the space identified by flexion/extension and radial/ulnar deviation planes. Motors locked the supination and pronation plane in the neutral position. Since the size of the tracking figure was not meant to challenge the participant, it was scaled to a maximum of 80% of the individual's active ROM collected in T0 [24]. The active ROM was evaluated in 2 planes (flexion/extension, radial/ulnar deviation) and the smallest value was chosen to scale the figure. A greater ROM figure was not implemented for safety and to avoid end ROM while actively following a target trajectory. Given that the training protocol did not aim specifically at increasing ROM, the size of the figure did not change throughout the protocol and was only used as a safety standard before beginning the allotted training. However, before each session, participants underwent an active ROM test performed using the robot. This procedure was implemented for participant safety to ensure that ROM did not decrease with respect to T0 due to the unpredictable nature of MS symptoms (spasticity/rigidity) restricting joint motion [21].

Differently from the tracking performed during the assessment, the training task included assistive or resistive torques, accordingly to the online performance recorded. Figural error (FE, Equation (3)) was measured to characterize performance as the trajectory of the participant from the ideal figure-eight shape, regardless of speed. The training force was implemented as a virtual spring ($modulation * k * \Delta\theta$, see Equation (5)). The end-effector was pulled towards the moving target according to instantaneous distance ($\Delta\theta$) and the selected spring stiffness. The stiffness of the spring determined the level of active muscle work required to perform the task more accurately. Opposingly, in the presence of resistive torques, the virtual spring would push the hand away from the target, effectively adding resistance to task completion.

The evaluation of average figural error was completed every 3 laps/repetitions and was used to modify the level of assistance/resistance (*modulation*) according to the magnitude of deviation from the previous performance. The first three laps were performed without training force and used to assess the starting level of performance in terms of FE, required to compute *modulation* for the following laps. The first 3 laps were excluded from the training analysis. Later, *modulation* was adjusted for the following three laps as a computation of the mean FE and the assistance/resistance level of the previous laps, and was computed with Equation (4):

$$modulation_{new} = modulation_{old} + a * \ (FE_{last3} \ - \ FE_{old}) + b \tag{4}$$

where $modulation_{new}$ is the level of assistance to be adjusted to for the next 3 laps and $modulation_{old}$ is the level of assistance from the previous 3 laps. FE_{last3} represents the participant's figural error from the prior 3 laps performed with the old value of *modulation*. FE_{old} is the error from the previous 3 laps, preceding the laps performed with $modulation_{old}$ just finished. a and b are experimental parameters (a = 5 rad^{-1} and b = −0.1) that managed the changes of *modulation* in its range of variability. Since *modulation* changes linearly with the changes in FE, a and b represented the slope and the intercept of the line, respectively. Because of empirically tested safety conditions, positive values of $modulation_{new}$ reached saturation when greater than 1, negative values when lower than −0.2. These values were chosen to avoid resulting torques too high in both the resistive and the assistive mode. In the first case, we wanted to avoid severe fatigue during the training, for these reasons we choose to saturate τ_{DoF} values based on previously performed experiments, in which presence of fatigue at similar levels of forces (i.e., less than τ_{max}) was checked using EMG techniques [16]. Instead, during the assistive modality, when $modulation_{new}$ was close to 1, movements were not completely passive and small muscle forces were still required to move the end-effector, in order to avoid the slacking effect [25] and to still promote active voluntary contribution. The computed assistance/resistance level (*modulation*) was a pure number and was used to implement the assistive/resistive torque for the following three tracking laps, modifying the initial stiffness of the spring (k). Specifically, the instantaneous amount of exerted torque on each DoF was determined by both the spring stiffness ($modulation*k$) and the real-time distance between the target and end-effector ($\Delta\theta$). When *modulation* was positive the actual modality was assistive, while the robot switched to resistive mode when *modulation* resulted to be negative. Equation (5) presents the formula used for torques (τ_{DoF}) computation in both modalities:

$$\begin{cases} \tau_{DoF} = modulation * k * \Delta\theta - d\,\dot{\theta} & ; modulation \geq 0 \\ \tau_{DoF} = -sign\ (\Delta\theta) * \ [\tau_{max} - |(0.2 + modulation\ ) * k * \Delta\theta|] - d\,\dot{\theta} & ; modulation < 0 \end{cases} \tag{5}$$

where τ_{DoF} is the exerted torque (assistive or resistive) modelled as a spring, k = 0.5 Nm/rad initial stiffness of the spring, and $\Delta\theta$ represents the instantaneous distance between the target and end-effector on that specific DoF. Because of the high back-drivability of the robot, a small viscous field ($-d\dot{\theta}$, d = 0.02 Nms/rad, $\dot{\theta}$ the velocity of the end-effector) was added to provide a minimal damping to the inertia of the hand, without affecting the torque direction and thus producing unsafe conditions. τ_{max} was a fixed value (τ_{max} = 0.5 Nm) evaluated to allow participants to move even with the highest resistance. Once the assistance/resistance *modulation* transitioned from positive to negative, the exerted torques moved from pulling the participant towards the target (assistance) to pushing the participant away from the target (resistance).

3. Data and Statistical Analysis

All outcome measures were collected at baseline (T0) and at the end of the training program (T1). Robotic outcome measures were computed from data of joint rotation recorded at a 100 Hz sampling rate and filtered with a sixth order Savitzky-Golay low-pass filter (8 Hz cut-off frequency). Data were analyzed off-line (MATLAB 2019a, Mathworks Inc., Natick, MS, USA). Wilcoxon Matched Pairs Tests were conducted to compare all outcome measures at T0 and T1 within each limb. Wilcoxon Matched Pairs Tests were conducted also to compare the differences in the outcome measures at T1 between the trained and control limb. Significance was set to $p < 0.05$. Correlations were analyzed using linear regression models and goodness-of-fit measures were computed to compare experimental and regression results (SPSS Statistics for Windows, Version 26.0. IBM Corp.: Armonk, NY, USA).

4. Results

4.1. Training

On average, training data revealed that participants performed in the resistive modality (*modulation* < 0) for 90% percent of the entire training protocol. There was no significant change in FE as the average decrease in FE from the first to the last training session was 37% ($p = 0.58$), while TE increased 13% ($p = 0.02$). Figure 2 shows a representative example (S03) of performance across training sessions. Panel A presents the resulting performance across laps and sessions, in terms of TE. Panel B shows how *modulation* of the same lap changed across sessions. Notably, the chosen lap (7th) corresponded to the second time *modulation* changed during each training session.

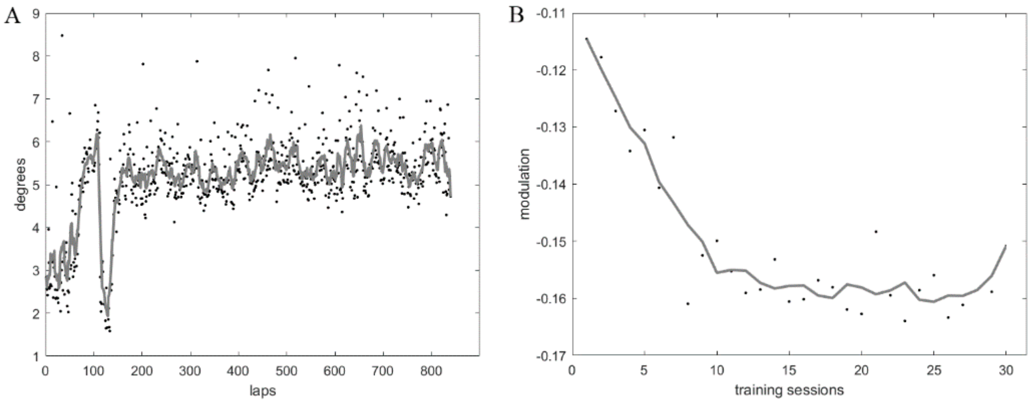

Figure 2. Performance in the training task from a single participant (S03). Black dots in (**A**) present the computed TE in each lap. (**B**) presents how *modulation* changed across training sessions in S03, considering the same lap (7th). Higher absolute values of *modulation* stay for higher resistance toques exerted. Grey lines represent the same data smoothed with a moving average window (width 1% of the total number of data points).

4.2. Assessment: Wrist Kinematics

Wrist kinematics were extracted from the robotic device and tracking performance was determined by comparing the end-effector to the target icon. Tracking error in the trained limb improved significantly for each participant from T0 to T1 (Figure 3). There was a significant reduction in tracking error, with an average decrease of $0.97 \pm 0.13°$ ($p = 0.03$; $3.77 \pm 2.12°$ at T0, $2.79 \pm 1.99°$ at T1). No significant improvements were found in the control limb ($p = 0.87$; $2.91 \pm 2.12°$ at T0, $3.45 \pm 2.51°$ at T1). No significant differences were found when comparing group averages of the trained vs. control limb ($p = 0.38$) at T1. Participant 01 and Participant 03 suffered from intention tremors, hindering motor accuracy with volitional movements and can speculate why there were no improvements in tracking errors.

Figural error was calculated from each of the unassisted laps performed of the tracking task. All participants significantly improved (less figural error) from T0 to T1 ($p < 0.03$; $1.06 \pm 0.07°$ at T0, $0.57 \pm 0.03°$ at T1). Although both limbs significantly improved, there were significant differences found between trained and control limbs, as trained limbs had less figural error at T1 (T0: $p = 0.05$, T1: $p = 0.02$). Figure 4 demonstrates representative tracking data from an individual participant from T0 to T1.

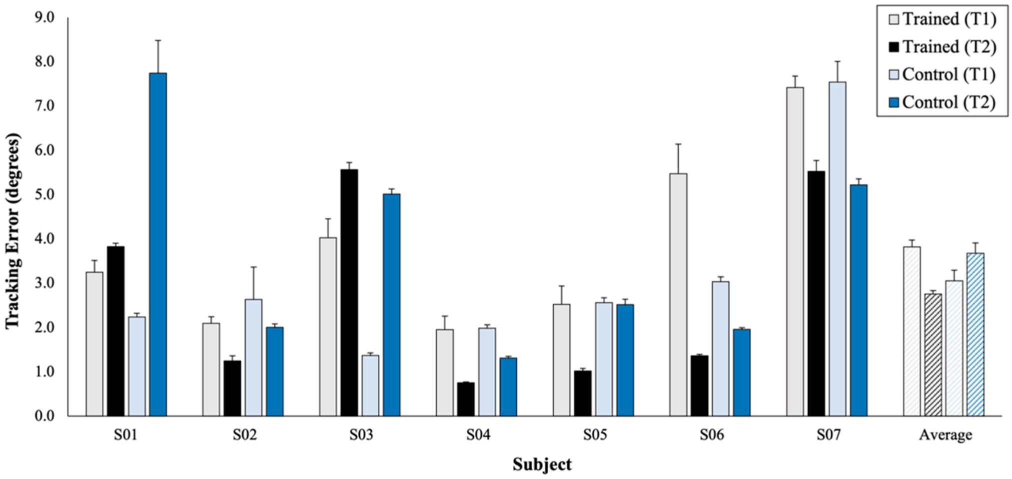

Figure 3. Median tracking error (degrees) comparing the trained (black/grey) and control (colors) limbs at T0 and T1. The amount of tracking error significantly decreased from T0 to T1 ($p = 0.03$).

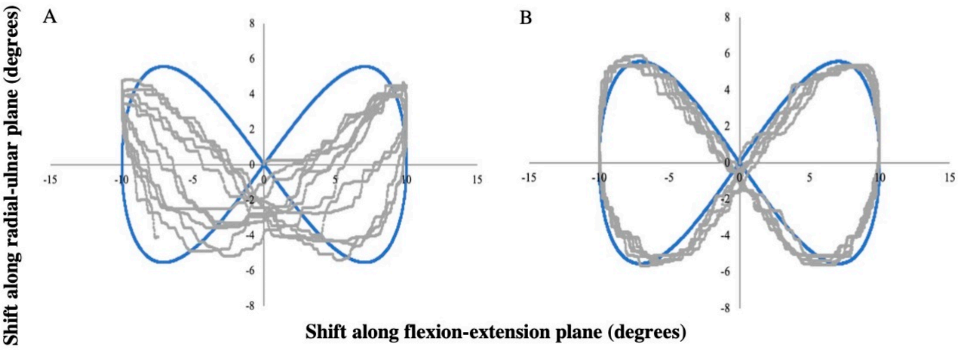

Figure 4. Figural error displayed for S06 at T0 (**A**) compared to T1 (**B**) for the trained limb. Significant reduction in figural error from pre-post intervention ($p = 0.03$). Blue line represents target trajectory, and the grey line represents the participant's trace attempt for each of the 6 laps.

In our sample of participants, median active and passive ROM was almost unimpaired at T0 (active: flexion, 54.6 ± 3.1°, extension: 53.4 ± 7.4°, radial: 34.7 ± 4.3°, ulnar: 30.5 ± 2.3°; passive: flexion, 54.7 ± 1.8°, extension: 53.4 ± 3.1°, radial: 34.7 ± 2.0°, ulnar: 30.0 ± 0.8°). There were no significant improvements in mean active ROM from T0–T1 across all directions in the trained limb (flexion: $p = 0.61$, extension: $p = 0.74$, radial: $p = 0.09$, ulnar: $p = 0.74$), control limb (flexion: $p = 0.87$, extension: $p = 0.60$, radial: $p = 0.31$, ulnar: $p = 0.74$), or between the trained and control limbs at T1 (flexion: $p = 0.81$, extension: $p = 0.38$, radial: $p = 0.58$, ulnar: $p = 0.48$). Similarly, there were no significant improvements in mean passive ROM from T0–T1 in the trained limb (flexion: $p = 0.72$, extension: $p = 0.74$, radial: $p = 0.46$, ulnar: $p = 0.074$), or between the trained and control limbs (flexion: $p = 1.00$, extension: 0.40, radial: $p = 0.42$, ulnar: $p = 0.37$).

4.3. Assessment: Wrist Strength

Mean isometric wrist strength for the trained limb significantly increased from pre (T0) to post-intervention (T1) for flexion ($p = 0.04$) and radial and ulnar deviation ($p = 0.03$ for both). Mean isometric wrist strength significantly increased by 2.77 kg, 1.08 kg and 2.51 kg for flexion, radial and ulnar deviation, respectively. There was significant improvement in the control limb from T0–T1 in radial deviation, increasing by 3.84 kg ($p = 0.03$; 9.14 ± 3.96 kg at T0, 12.98 ± 2.95 kg at T1). Although not significant (flexion: $p = 0.13$, extension: $p = 0.13$, ulnar: $p = 0.06$), the control limb showed improvements in wrist strength for flexion, extension, and ulnar deviation, increasing on average by 2.15 kg, 1.89 kg and 3.04 kg, respectively. No significant differences were found between the trained and control limbs at T1 as both limbs showed almost equal improvements (flexion: $p = 0.14$, extension: $p = 0.94$, radial: $p = 0.44$, ulnar: $p = 0.23$).

There were no significant differences for maximum grip force in the trained limb ($p = 0.93$; 29.81 ± 10.23 kg at T0, 29.46 ± 9.58 kg at T1) or control limb ($p = 0.25$; 31.67 ± 11.16 kg at T0, 32.49 ± 11.11 kg at T1), indicative that grip strength did not increase post-intervention. There were no significant differences for the submaximal grip force endurance test for the trained limbs ($p = 0.13$). However, group averages showed a 60.12% and 78.0% increase from baseline after the 4-week intervention for the trained ($p = 0.13$; 34.28 ± 43.86 s at T0, 54.89 ± 40.08 s at T1) and control limbs ($p = 0.06$; 32.86 ± 11.16 s at T0, 58.50 ± 45.79 s at T1), respectively. No significant differences were found when comparing the trained limb to the control limb at T1 ($p = 0.29$).

4.4. Assessment: Clinical Outcome Measures

For the 9-HPT, no significant differences were found between trained vs. control limbs (T0: $p = 0.49$, T1: 0.16). No significant improvements were found for the trained limb at T0–T1 ($p = 0.12$; 30.48 ± 5.34 s at T0, 27.64 ± 4.18 s at T1) or for the control limb from T0–T1 ($p = 0.25$; 28.99 ± 2.79 s at T0, 25.47 ± 2.66 s at T1). No significant differences ($p = 0.84$) were found between the responses for T0 and T1 in the PRWE.

4.5. Correlations

There was a significant correlation between decreased tracking error and increased maximum isometric wrist strength from T0–T1 (Table 2). This correlation occurred in flexion/extension and radial deviation where r^2 represents how much variation of the dependent variable (wrist force) is explained by the independent variable (tracking error).

Table 2. Linear regression correlation between isometric wrist force and tracking error of the trained limb at T1 (mean values).

Direction	*p*-Value	r^2
Flexion	0.03 *	0.64
Extension	0.02 *	0.68
Radial Deviation	0.04 *	0.59
Ulnar Deviation	0.08	0.49

* Denotes significant differences, $p < 0.05$.

There was no significant correlation between tracking error and EDSS score ($p = 0.09$, $r^2 = 0.47$). Participants with a higher EDSS score (greater severity of disease) did not have a higher degree of tracking error (worse performance) than participants with a lower EDSS score for the trained limbs at T1.

5. Discussion

In this work we presented a robotic rehabilitation program that has the potential to improve wrist motor control in individuals with MS. Significant decreases in tracking and figural error occurred from pre to post intervention in the trained limb, supporting our first hypothesis related to improvements in wrist motor accuracy. To our knowledge, this was the first study to deliver an adaptive training program to the upper limb in an MS population, offering resistive torques as well as assistance. This adaptive, repetitive, and participant tailored approach has proved beneficial for various types of MS, severity of disease and years since diagnosis. Additionally, results of increased muscular strength at the wrist joint partially supports our second hypothesis. However, no correlations between wrist strength and clinical outcome measures were found.

The results of this study identified significant improvements in tracking performance (defined by decreases in tracking and figural error) in the trained limb. The adaptive and repetitive protocol was designed to improve the neuromechanical control of the hand during the tracking task, as indicated by error decreases, improved accuracy, and control of the trajectory without assistance. Training results (Section 4.1) showed that participants improved their performance across sessions in terms of spatial accuracy (FE), while TE tended to get worse. FE considered only the spatial component of tracking, i.e., the accuracy in replicating the target trajectory, conversely TE considered the differences in speed between target and end-effector. These trends should be investigated further, since they could be either a marker of fatigue or a sign of changed motor strategy, that turned to prefer spatial accuracy. In particular, the latter could have been the successful choice that made participants improve both TE and FE in the last assessment, without forces. Comparing the performance during the assessment sessions (Section 4.2), in absence of assistive/resistive torques, FE reduced by 46%, while TE decreased by 26%. These significant reductions in both figural and tracking error demonstrate improvements in task performance, with a significant reduction in error between the target and the end-effector. This could result from an increase in motor control of the distal upper limb to correctly perform the task without the assistance of the robot. These results align with existing work on robotic rehabilitation of the upper limb for stroke and MS populations that report improvements or demonstrated a reduction in errors from pre–post intervention of reaching and tracing tasks [7,17,19]. Movement accuracy is typically quantified by smoothness of the curvature or the decreasing measure of end-point trajectory post-intervention, as was also demonstrated in our results; these findings indicate that the repetitive and high-dose tracking task improved overall performance of the skill. The combination of wrist movements necessary to complete the figure-eight tracking task were a combination of wrist flexion/extension and radial/ulnar deviation. These movements are a fundamental component in performing many ADLs such as turning a doorknob or twisting a lid off a jar. Improving muscular strength and movement accuracy when performing these basic daily tasks may enhance one's quality of life [26].

Although only the most affected limb underwent the adaptive training protocol, both limbs showed improvements. Interestingly, significant differences were found pre–post intervention for both the trained limb and control limb for figural error, maximum isometric wrist strength and submaximal grip force endurance. This could partly be attributed to a neurophysiological concept known as cross-education, where one limb is trained, and the control or untrained limb also shows improvements in strength measures following unilateral resistance training [22]. While not a facet of the study hypotheses, this finding generates interesting research questions. A systematic review demonstrated an overall 17% increase in strength for the untrained limb and a 30% increase in strength for the trained limb following ipsilateral strength training [27]. After a 5-week maximal wrist extension intervention in stroke recovery, a 42% increase in extension strength was found in the trained arm and a 35% increase in the control arm [28]. Although literature on cross-education in an MS population is lacking, it is known that MS affects the CNS, causing damage to structure and function via afferent and efferent pathways and rehabilitation of one limb helps overall CNS conduction [6]. Positive changes in neuroplasticity helps counter declines in CNS conductivity by relaying information to both upper limbs. An additional hypothesis as to how cross-education occurs suggests that unilateral training can cause a "spill over" of neural drive to the untrained side to induce changes in the control system. Unilateral strength training allows these changes to the control system to be accessed by the opposite limb [22]. Further research is necessary to fully understand the neurophysiology mechanisms behind cross-education for the MS population. Regardless, the high repetitions of our training task, supports the theory that, in presence of CNS damage, repetitive, resistance exercises with the affected limb causes the brain to develop new neural pathways controlling motor functions [28]. The development of new neural pathways leads to functional restoration in overall motor functions (i.e., both limbs) and is foundational to robotic rehabilitation. Even though comparing traditional and robotic rehabilitation was not the purpose of this study, we acknowledge that the efficacy of robotic rehabilitation compared to the standard of care has been long debated [13,25]. However, many studies demonstrated that robotics ensure those advantages already presented in Section 1: repeatable and controlled conditions even in long lasting trainings, increased spatial and temporal accuracy, and the resultant possibility to develop high-reliable performance-based tailored programs.

The adaptive program focused on reducing tracking error/increasing motor accuracy rather than increasing muscular strength. However, in the beginning, the level of upper-limb impairment of our specific sample was unknown. Consequently, our underestimation of MS individuals' performance took the algorithm to converge quickly towards the resistive modality. Because of this limitation, the assistive phase was not deeply exploited, and the training was mainly resistive for all participants. Even in the resistive modality, the exerted repulsive torques were modulated by participants' online performance. The resistive progressions used in this research could have acted as a strength training model, requiring the muscles of the forearm to increase activation to complete each lap. Over the 4-week duration of the training, there was an increase in isometric wrist strength in each of the 4 planes, with an average increase in the trained limb of 28% for flexion, 11% for extension, 44% for radial and ulnar deviation. Only radial deviation showed statistically significant improvements in the control limb. Although not significant, the other directions demonstrated an average increase of 22%, 19%, 56%, for flexion, extension and ulnar deviation, respectively, which could have clinical or functional significance. While our protocol was not designed with considerations of inducing strength adaptations, it can be speculated that as training progressed, performance improved and the tracking was made more challenging, this likely increased muscular demand and forearm muscle activation. Increases in muscular strength are typically observed after high intensity training and the resistance provided in the tracking task was a low percentage of the participant's maximum wrist strength. However, low loads at a high dosage can elicit strength gains. This has been demonstrated in work by [26], that low loads can promote increases in muscle growth especially for untrained participants. These gains may be both functionally and metabolically meaningful; it has been shown that resistance training in persons with MS is often attributed to neural adaptations rather than an increase in muscle mass [28]. It can be assumed that the strength gains observed in this study can be applied to improvements in motor control of the distal upper limb. Future studies should focus on this area of research, particularly with the use of quantitative assessment tools.

Group averages in grip force endurance showed 60–78% increases from baseline to post intervention in the trained and control limb, respectively, indicating augmented muscular endurance post-intervention. There was a trend towards significance and a 60% increase in grip endurance is likely clinically significant and is a meaningful improvement that could translate to improved functionality in ADL. It is likely that our noted endurance changes may relate to improvements in ADLs, and this should be investigated further.

The findings from this study suggested a correlation between wrist strength and hand motor control. Resistive training targeted both eccentric and concentric movements of the muscles of the forearm and significant correlations were found between wrist strength and tracking errors; as isometric wrist strength increased, tracking errors decreased. Interestingly, there was no correlation found between EDSS score and tracking error. A higher score on the EDSS is representative of an increase in severity/disability of disease. It could be expected that those with a greater level of disease would have poorer tracking performance. Tracking error could be linked to functional performance or ability to perform ADLs. This finding could suggest that EDSS is not an appropriate indicator of upper limb disability and additional quantitative measures should be taken by the clinician or the researcher when investigating the upper limb in MS. This poor correlation in our population suggests that further work is needed in this area, particularly in the development of objective robotic assessment tools for the upper limb to reduce reliance on subjective questionnaire assessments.

Despite improvements in tracking error and wrist strength, this work also demonstrates that our progressive robotic rehabilitation program for this specific population may not promote the transfer of learned skills. In our work, it appears that this population benefits from task-specific or goal directed exercises, rejecting our original hypothesis. This is shown in grip force, ROM and 9-HPT. The PRWE was a questionnaire pertaining to how the participant was feeling based upon pain and daily functioning at home on a 0–10 scale. No significant group differences were observed. As the participants were to respond to the difficulty of performing a task on a scale of 1–10, the large rating scale may have been insensitive to capturing anecdotal responses. Participants in this study were not undergoing additional therapy for training programs and were mostly inactive; for a population such as this it is important to engage in any active rehabilitation programs to promote improvements in mental and physical well-being.

6. Limitations

Results from this study demonstrated the feasibility and the potential benefits of an adaptive robotic rehabilitation program for MS. While additional studies with a larger sample size are needed to confirm the benefits of such an adaptive program, this work is in line with sample sizes of other MS focused work [7,17,27,29]. To our knowledge, this was the first study to deliver an adaptive training program to the upper limb in a MS population, offering resistive torques as well as assistance. From this preliminary validation, further consideration should be taken to develop a protocol better tailored to the individualized performance of persons with MS to establish the optimal dosage of therapy. Furthermore, additional measures of performance should be considered to improve the assessment of wrist function in this population, such as related to smoothness of movement, rigidity, or proprioception. If the focus is on strength outcomes, the training protocol could be modified in intensity. This can be done by modulating the magnitude of exerted torques, increasing frequency of the training (days per week) as well as the duration of an individual session. Differently, other sensorimotor improvements could emerge with a training task that presented a different adaptive modality. To corroborate the applicability of the proposed method, future studies will address a comparison between this protocol of robotic training and standard of care targeting muscle strength and motor control. Nonetheless, our 4-week (3x/week), adaptive tracking task, evoked motor learning effects leading to improved neuromechanical control of the hand and an overall improvement of task performance for our given task.

7. Conclusions

This study highlights a novel adaptive and individualized robotic rehabilitation program providing both assistance and resistance to the distal upper extremity for persons with MS. Results of this work demonstrated that this 4-week robotic training program has the potential to improve wrist motor control and muscular strength. The adaptive training approach used in this work has demonstrated effective individualization of the therapy process with assistance levels and progressions for various types of MS, severity of disease and age levels. This work provides insight that rehabilitation robotics of the upper limb for a MS population can yield beneficial results and combined with conventional therapy might promote increased motor control and function.

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References

1. Walton, C.; King, R.; Rechtman, L.; Kaye, W.; Leray, E.; Marrie, R.A.; Robertson, N.; La Rocca, N.; Uitdehaag, B.; van der Mei, I.; et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. *Mult. Scler. J.* **2020**, *26*, 1816–1821. [CrossRef] [PubMed]
2. Weiner, H.L.; Stankiewicz, J.M. *Multiple Sclerosis: Diagnosis and Therapy*; John Wiley & Sons: Hoboken, NJ, USA, 2012.
3. Burks, J.S.; Johnson, K.P. *Multiple Sclerosis: Diagnosis, Medical Management, and Rehabilitation*; Demos Medical Publishing Inc.: New York, NY, USA, 2000.
4. Zhong, J.; Nantes, J.C.; Holmes, S.A.; Gallant, S.; Narayanan, S.; Koski, L. Abnormal functional connectivity and cortical integrity influence dominant hand motor disability in multiple sclerosis: A multimodal analysis: FC, Structural and Behavioural Changes in MS. *Hum. Brain Mapp.* **2016**, *37*, 4262–4275. [CrossRef] [PubMed]
5. Mekki, M.; Delgado, A.D.; Fry, A.; Putrino, D.; Huang, V. Robotic Rehabilitation and Spinal Cord Injury: A Narrative Review. *Neurotherapeutics* **2018**, *15*, 604–617. [CrossRef] [PubMed]
6. Olek, M.J. *Multiple Sclerosis: Etiology, Diagnosis, and New Treatment Strategies*; Humana Press: Totowa, NJ, USA, 2005.
7. Vergaro, E.; Squeri, V.; Brichetto, G.; Casadio, M.; Morasso, P.; Solaro, C.; Sanguineti, V. Adaptive robot training for the treatment of incoordination in Multiple Sclerosis. *J. Neuroeng. Rehabil.* **2010**, *7*. [CrossRef] [PubMed]
8. Krebs, H.I.; Volpe, B.T.; Williams, D.; Celestino, J.; Charles, S.K.; Lynch, D.; Hogan, N. Robot-Aided Neurorehabilitation: A Robot for Wrist Rehabilitation. *IEEE Trans. Neural Syst. Rehabil. Eng.* **2007**, *15*, 327–335. [CrossRef] [PubMed]
9. Lo, H.S.; Xie, S.Q. Exoskeleton robots for upper-limb rehabilitation: State of the art and future prospects. *Med. Eng. Phys.* **2012**, *34*, 261–268. [CrossRef]
10. Vergaro, E.; Casadio, M.; Squeri, V.; Giannoni, P.; Morasso, P.; Sanguineti, V. Self-adaptive robot training of stroke survivors for continuous tracking movements. *J. Neuroeng. Rehabil.* **2010**, *7*. [CrossRef]
11. Colombo, R.; Pisano, F.; Micera, S.; Mazzone, A.; Delconte, C.; Carrozza, M.C.; Dario, P.; Minuco, G. Robotic Techniques for Upper Limb Evaluation and Rehabilitation of Stroke Patients. *IEEE Trans. Neural Syst. Rehabil. Eng.* **2005**, *13*, 311–324. [CrossRef] [PubMed]
12. Carpinella, I.; Cattaneo, D.; Abuarqub, S.; Ferrarin, M. Robot-based rehabilitation of the upper limbs in multiple sclerosis: Feasibility and preliminary results. *J. Rehabil. Med.* **2009**, *41*, 966–970. [CrossRef]
13. Rodgers, H.; Bosomworth, H.; Krebs, H.I.; van Wijck, F.; Howel, D.; Wilson, N.; Aird, L.; Alvarado, N.; Andole, S.; Cohen, D.L.; et al. Robot assisted training for the upper limb after stroke (RATULS): A multicentre randomised controlled trial. *Lancet* **2019**, *394*, 51–62. [CrossRef]
14. Albanese, G.A.; Holmes, M.W.R.; Marini, F.; Morasso, P.; Zenzeri, J. Wrist Position Sense in Two Dimensions: Between-Hand Symmetry and Anisotropic Accuracy Across the Space. *Front. Hum. Neurosci.* **2021**, *15*, 662768. [CrossRef]
15. Albanese, G.A.; Marini, F.; Taglione, E.; Gasparini, C.; Grandi, S.; Pettinelli, F.; Sardelli, C.; Catitti, P.; Sandini, G.; Masia, L.; et al. Assessment of human wrist rigidity and pain in post-traumatic patients. In Proceedings of the 2019 IEEE 16th International Conference on Rehabilitation Robotics (ICORR), Toronto, ON, Canada, 24–28 June 2019; pp. 89–94.
16. Mugnosso, M.; Marini, F.; Holmes, M.; Morasso, P.; Zenzeri, J. Muscle fatigue assessment during robot-mediated movements. *J. Neuroeng. Rehabil.* **2018**, *15*. [CrossRef] [PubMed]
17. Iandolo, R.; Marini, F.; Semprini, M.; Laffranchi, M.; Mugnosso, M.; Cherif, A.; De Michieli, L.; Chiappalone, M.; Zenzeri, J. Perspectives and Challenges in Robotic Neurorehabilitation. *Appl. Sci.* **2019**, *9*, 3183. [CrossRef]
18. Blank, A.A.; French, J.A.; Pehlivan, A.U.; O'Malley, M.K. Current Trends in Robot-Assisted Upper-Limb Stroke Rehabilitation: Promoting Patient Engagement in Therapy. *Curr. Phys. Med. Rehabil. Rep.* **2014**, *2*, 184–195. [CrossRef]
19. Kleim, J.A.; Jones, T.A. Principles of Experience-Dependent Neural Plasticity: Implications for Rehabilitation After Brain Damage. *J. Speech Lang. Hear. Res.* **2008**, *51*. [CrossRef]
20. Conditt, M.A.; Gandolfo, F.; Mussa-Ivaldi, F.A. The Motor System Does Not Learn the Dynamics of the Arm by Rote Memorization of Past Experience. *J. Neurophysiol.* **1997**, *78*, 554–560. [CrossRef]
21. Halabchi, F.; Alizadeh, Z.; Sahraian, M.A.; Abolhasani, M. Exercise prescription for patients with multiple sclerosis; potential benefits and practical recommendations. *BMC Neurol.* **2017**, *17*. [CrossRef] [PubMed]
22. Carroll, T.J.; Herbert, R.D.; Munn, J.; Lee, M.; Gandevia, S.C. Contralateral effects of unilateral strength training: Evidence and possible mechanisms. *J. Appl. Physiol.* **2006**, *101*, 1514–1522. [CrossRef]
23. Lamers, I.; Maris, A.; Severijns, D.; Dielkens, W.; Geurts, S.; Van Wijmeersch, B.; Feys, P. Upper Limb Rehabilitation in People With Multiple Sclerosis: A Systematic Review. *Neurorehabil. Neural Repair* **2016**, *30*, 773–793. [CrossRef]
24. Albanese, G.A.; Taglione, E.; Gasparini, C.; Grandi, S.; Pettinelli, F.; Sardelli, C.; Catitti, P.; Sandini, G.; Masia, L.; Zenzeri, J. Efficacy of wrist robot-aided orthopedic rehabilitation: A randomized controlled trial. *J. Neuroeng. Rehabil.* **2021**, *18*, 130. [CrossRef]

25. Casadio, M.; Sanguineti, V. Learning, Retention, and Slacking: A Model of the Dynamics of Recovery in Robot Therapy. *IEEE Trans. Neural Syst. Rehabil. Eng.* **2012**, *20*, 286–296. [CrossRef]
26. Schoenfeld, B.J.; Grgic, J.; Ogborn, D.; Krieger, J.W. Strength and Hypertrophy Adaptations Between Low- vs. High-Load Resistance Training: A Systematic Review and Meta-analysis. *J. Strength Cond. Res.* **2017**, *31*, 3508–3523. [CrossRef]
27. Green, L.A.; Gabriel, D.A. The effect of unilateral training on contralateral limb strength in young, older, and patient populations: A meta-analysis of cross education. *Phys. Ther. Rev.* **2018**, *23*, 238–249. [CrossRef]
28. Carlos, M.-P.; Fernanda, d.S.-T.; Rodrigo, F.-G.; Antonio, d.P.-F.J. Effects of a resistance training program and subsequent detraining on muscle strength and muscle power in multiple sclerosis patients. *NeuroRehabilitation* **2014**, 523–530. [CrossRef]
29. Sun, Y.; Ledwell, N.M.H.; Boyd, L.A.; Zehr, E.P. Unilateral wrist extension training after stroke improves strength and neural plasticity in both arms. *Exp. Brain Res.* **2018**, *236*, 2009–2021. [CrossRef] [PubMed]