Investigating cross-education in multiple sclerosis following upper limb robotic rehabilitation

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Abstract

The overall goal of this thesis was to develop an adaptive rehabilitation technique using a haptic wrist robotic device that would induce the phenomenon of cross-education to improve upper limb function. Following a literature review, Chapter 4 provides a scoping review of existing literature surrounding rehabilitation robots for MS. Chapter 5 reports the development and rationale of the rehabilitative approach, to develop an algorithm that is individualized and adaptive to the user. Once the algorithm was developed, an eight-week intervention for fourteen individuals with MS and eight non-affected adults was conducted. The purpose of the intervention was two-fold and presented in Chapter 6, to improve overall wrist and grip strength (assessed via maximal grip and isometric wrist strength) and Chapter 7, to improve overall motor control (assessed via robotic performance measures). Lastly, in both chapters, cross-over effects of strength and motor control to the untrained limb were evaluated. Results of this eight-week training reported increases in wrist strength for the MS group with an average percent change score across all muscle directions of 62.59% in the trained limb and 53.26% in the untrained limb. The control group also reported an average percent change of 31.31% in strength in the trained limb and 24.26% in the untrained limb. MS participants significantly decreased in tracking and figural error (degree of error) post-intervention suggesting evidence that motor control adaptations are possible following an adaptive and resistive robotic intervention of the upper limb. Following the results of the eight-week intervention, Chapter 9 was to investigate changes in strength and motor control following four-weeks of training in an additional subgroup of participants following the same rehabilitative protocol. Results demonstrate a clinically meaningful improvement in strength of the trained limb, but no significant improvements in figural or tracking error performance – suggestive that robotic rehabilitation of this kind needs to be longer in duration than four-weeks to elicit meaningful adaptations of motor control.

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List of Abbreviations

ADL – activity of daily living
AMT – active motor threshold
AUC – area under the curve
CE – cross-education
CNS – central nervous system
CSP – cortical silent period
DMD – disease modifying drug
E – extension
ED – excitatory drugs
EDSS – expanded disability status scale
EMG – electromyography
F – flexion
FCR – flexor carpi radialis
FU – follow-up
ID – inhibitory drugs
M1 – motor cortex
MEP – motor evoked potential
MS – multiple sclerosis
MVC – maximum voluntary contraction
PPMS – primary progressive multiple sclerosis
PwMS – persons with multiple sclerosis
RD – radial deviation
RMT – resting motor threshold
ROM – range of motion
RPMS – relapsing progressive multiple sclerosis
RRMS – relapsing remittent multiple sclerosis
SPMS – secondary progressive multiple sclerosis
TMS – transcranial magnetic stimulation
UD – ulnar deviation
WMFT – wolf motor function test

Chapter 1 – Introduction

1.1 Motivation for Research

For decades, research has been exploring rehabilitative, pharmaceutical, holistic, and therapeutic methods to delay disease progression of multiple sclerosis (MS). MS is currently an incurable and progressive disease of the central nervous system, affecting many motor functions including cognition, gait, and motor control (Burks & Johnson, 2000). For individuals with MS, basic activities of daily living become increasingly more difficult as the disease progresses. To date, rehabilitation research for MS mainly focuses on gait rehabilitation (Baird et al., 2018; Pau et al., 2020) and the upper limb is often a secondary thought in the therapy process (Alonso et al., 2021). However, loss of function in the upper limb creates more difficulty in even the most simplistic daily tasks such as bathing, eating, and propping oneself out of bed. There is a great need to focus on slowing the loss of motor function in the upper limb as well as maintaining upper limb strength, dexterity, and proprioception.

MS attacks motor capabilities bilaterally, but there are often laterality differences in the level of affliction (Kister et al., 2013). Individuals with MS typically rely solely on their more functional limb to execute daily tasks – leaving the contralateral limb to succumb to the "use it or lose it" principle, further degrading function. This more affected limb may be unable to resist gravity, move without spasticity or be directly rehabilitated. This leads to the unanswered question; does rehabilitating the less affected limb translate into improvements in the contralateral or untrained limb? There is a potential to rehabilitate the functional limb until there are sufficient improvements in the more affected limb such that it can be directly trained. This phenomenon is known as cross-education (CE), which has been proven in healthy individuals (Carroll et al., 2006) and post-stroke (Dragert & Zehr, 2013; Urbin et al., 2015), primarily following strength training.

However, the therapeutic/rehabilitative benefits for CE have yet to be fully known and explored for individuals with MS.

To elicit the CE effect, it is necessary to perform numerous repetitions under tension or force (Farthing & Zehr, 2014). One way to safely execute this for persons with minimal function is with the use of robotic devices. Robotic exoskeletons and end-effectors offer gravity assistance, external resistance, and assistance to move through efficient positions or tasks, all of which are facets of optimal rehabilitation. The intrinsically designed actuators and software allow for real-time adaptive programs that can achieve interventions beyond the scope of a human therapist and mobility training. Robots can quantify and record the executed movements, providing the clinician or researcher with an abundance of information for performance-based progressions (Iandolo et al., 2019). The same robotic devices are imperative for pre- and post quantitative assessments to assess the level of disability that expand beyond the typical subjective clinical scales used to date.

Using robotic rehabilitation to exploit the effects of CE on the upper limb for individuals with MS has yet to be explored. Very little research has focused on the neurophysiology of CE in MS and the site of neural adaptation in people with neurological impairments is currently unknown (Farthing et al., 2021). This dissertation aimed to provide a deeper investigation into CE using robotics and to explore its application to upper limb and wrist function. This fundamental knowledge could help transform current MS therapy approaches. The overall goals of this work were to evaluate a robotic technique that would induce the phenomenon of CE to benefit clinical outcomes and to investigate the mechanisms of CE in MS.

1.2 Global Scope and Aim of Research

The novelty of this dissertation is grounded in the use of a state-of-the-art rehabilitation robot to generate individualized training that leads to CE improved outcomes for the more affected limb in persons with MS (PwMS) and reduced asymmetry. Integrating cutting edge robotics into the rehabilitation process can be a beneficial adjunct strategy to unilateral treatment in neurological conditions whereby the affected limb is untrainable or becomes fatigued. While the underlying theme of the dissertation was to explore the effects of CE during robotic rehabilitation, it should be noted that there has been little research on the use of robotics in upper limb rehabilitation for PwMS. Our group previously demonstrated that a low resistive load with a highly repetitive upper limb robotic rehabilitation program was beneficial for individuals with MS (Mannella et al., 2021). At a fundamental level, this dissertation aims to provide further support and evidence for the benefits of robotic rehabilitation for PwMS. Mannella et al., 2021 was also the first to demonstrate that following an assistive/resistive robotic training program, significant increases in muscular strength and endurance were found in the untrained, less affected limb (measured as wrist strength and hand grip strength) in a small sample of PwMS. This important finding from our group hints at CE in MS and needed further investigation. Understanding the link between robotics, neural plasticity and CE in MS may be useful for clinicians to optimize the rehabilitation process and lead towards a better understanding of how to treat the upper limb with individualized care that will greatly impact one's quality of life. Therefore, the overall purpose was to examine the effects of an adaptive upper limb robotic training program on clinical and robotic sensorimotor outcomes in both the trained and untrained limbs in PwMS. It is anticipated that findings from this work will provide new knowledge and encourage robotics research in MS (which lacks research and previous literature compared to other neurological disorders). To our knowledge, this is the first investigation of CE in the upper limb following robotic rehabilitation in MS. This research design aims to provide knowledge for clinicians to help decide on optimal treatment using direct training of the more affected limb, or to focus treatment on the less-affected limb.

A scoping review and one longitudinal data collection formed this dissertation, and results are divided into multiple manuscripts. Chapter 1 provides the global scope, aims and motivation behind the research. Chapter 2 presents a review of the literature and how this dissertation fills an important gap in knowledge. Chapters 3 specifically outlines the purpose of this work along with stated hypotheses. Chapter 4 includes a scoping review to critically examine the literature to gain insight into adaptations in muscular strength following robotic rehabilitation interventions for individuals with MS (objective 1). Chapters 5-8 includes the completed multiple manuscripts constructed from the one large database. Chapter 5 targets objective 2 and outlines the development of an adaptive algorithm. To address objectives 3 and 4 an 8-week robotic training intervention was conducted and the assessment of strength (Chapter 6), motor control (Chapter 7) and neurophysiology adaptations (Chapter 8) were assessed. Lastly, Chapter 9 addresses objective 5 and includes a completed manuscript constructed from a second longitudinal data set including a 4-week intervention focusing on strength and motor control changes.

Chapter 2 – Literature Review

2.1 Background of Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune and demyelinating disease of the central nervous system (CNS). MS affects the CNS via inflammatory demyelinating lesions and direct axonal injury (Zeller et al., 2010). In a healthy individual, T and B cells within the CNS are responsible for direct immune response allowing the immune system to respond quickly to unwanted or foreign bodies (Wu & Laufer, 2007). In MS, both T and B cells recognize the myelin sheath as an unwanted body and destroy the oligodendrocyte-derived myelin, and the loss of this myelin results in loss of nerve insulation and therefore conductivity. Formally defined as a strictly demyelinating disease, MS is now known to affect axons and myelin in the disease process (Weiner, 2012). There are three definitions of rehabilitation as it relates to MS: 1) halt progression of the disease, 2) reverse neurologic deficits and 3) develop a strategy to prevent MS (Weiner, 2012). However, there is no known cure or pharmaceutical treatment, but there are therapies and rehabilitation strategies that can help halt the progression of the disease and will be outlined in this literature review. MS affects every individual differently but there are common presenting symptoms. A few of these common symptoms include, fatigue, spasticity, tremor, bladder and bowel dysfunction, pain, decreased gait mobility and cognitive dysfunctions (Weiner & Stankiewicz, 2012). These symptoms can manifest independently or impact other symptoms, creating an interconnected cycle of symptoms (Figure 1) (Weiner & Stankiewicz, 2012).

There are 4 classifications of MS categorized by the way the disease acts upon the CNS. The first is relapsing remittent MS (RRMS). It is the most diagnosed classification as 85% of individuals diagnosed with MS are diagnosed with this phenotype and the remaining 15% are spread between the other phenotypes (MS Society of Canada, 2022). In this form there are clearly defined relapses with full recovery or with a residual deficit on recovery. The periods between disease relapses are characterized by a lack of disease progression and are known as periods of ‘remission’ (Burks & Johnson, 2000). RRMS typically has the earliest onset, averaging 25-29 years, compared with the other classifications. Primary progressive MS (PPMS) progresses from onset with occasional plateaus and temporary minor improvements but much fewer to no periods of remission. PPMS is not as commonly diagnosed as only about 10% of PwMS begin with primary progressive (Weiner, 2012). On average, PwMS progress from RRMS to PPMS around the age of 40-44 years. Primary progressive has a mean age onset of 35-39 years. Secondary progressive MS (SPMS) is an initial relapsing-remittent disease course followed by progression with or without occasional relapses, minor remissions, and plateaus. Finally, progressive-relapsing MS (PRMS) is the most severe type of MS and the most debilitating. Only 5% of PwMS are diagnosed with PRMS. The periods between relapses are characterized by continuing progression.

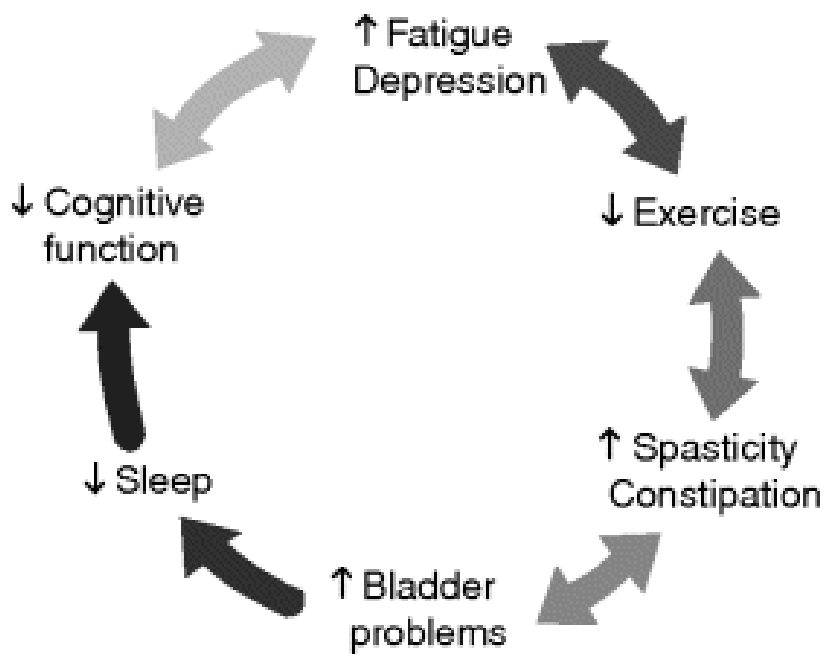

Figure 1. Presenting cycle symptoms of MS (Weiner & Stankiewicz, 2012)

2.1.1 Prevalence and Economic Cost of Disease

The prevalence of MS is the highest in Canada worldwide, as a Canadian is diagnosed with MS every 5 minutes (Amankwah et al., 2017). There is no current cure for this disease and MS cases are expected to rise 18% from 2011 to 2031 (Amankwah et al., 2017). The median age of onset (primarily RRMS) is 23.5 years (Weiner & Stankiewicz, 2012), affecting young adults in their most productive years and putting individuals at risk for facing challenges such as unemployment, underemployment, and long-term disability. Autoimmune diseases typically affect more women than men and as such, MS effects primarily women and the onset of disease is approximately 5 years earlier in women than in men (Weiner & Stankiewicz, 2012). Disease progression from RRMS to PPMS is approximately 40-44 years of age (Amankwah et al., 2017). The cause of MS remains unknown, but it is speculated that geography and specifically areas with lesser daylight have a role. High-risk areas for MS include Russia, southern Canada, the northern United States, New Zealand and south-eastern Australia (Amankwah et al., 2017). Along with geographical reasoning, genetics, and race may also be a determinant with Caucasians (specifically European) being at the highest risk.

Direct and indirect costs of living with MS can be financially debilitating for young adults. With the number of cases of MS being expected to rise, the total health sector costs of disease are also expected to rise upwards of 2 billion dollars (Amankwah et al., 2017). Direct costs include inpatient/outpatient care, drugs, diagnostics, nursing care, social services, and patient travel costs. Indirect costs include loss of work production, leave of absence from work, disability pension, and early old-age pension with health complications. Cost can also depend on the severity of disease. With a low level of MS severity, finances are primarily driven towards pharmaceuticals (further discussed in section 2.1.5) whereas in more severe cases, costs are more directed to patient care and loss of work. Costs can double or triple with increasing disease levels according to the severity of disease based on the Expanded Disability Status Scale (EDSS) (Wundes et al., 2010). In addition to direct and indirect costs associated with MS, intangible costs such as pain, anxiety and suffering should also be considered (Ernstsson et al., 2016). Regardless of the level of affliction, pain is experienced in 71% of individuals living with this disease (Piwko et al., 2007). Pain treatment is a subset of the direct cost of MS and averaged $3,197 over six months in 2007 (Piwko et al., 2007) and a total estimate of $79,444,888 was averaged for all Canadians in six months (Piwko et al., 2007). These costs can represent up to 50% of the total cost of MS (Ernstsson et al., 2016).

2.1.2 Neurological Impairments

Sensory impairment and distortions are common in MS as a result of demyelinating lesions in the cerebral hemisphere and thalamus (Weiner & Stankiewicz, 2012). Loss of proprioception is an example of sensory impairment and is a more common symptom of MS than any other disease. Proprioception impairment is more visible in the hand and upper limb than in the foot. As sensory impairments are common on one side of the body, individuals with lesions in the dorsal columns of the spinal cord will demonstrate impairments on both sides (Weiner & Stankiewicz, 2012).

Joint position sense or somatosensory feedback is an essential and quantitative measurement in neurological disorders because improved and accelerated motor recovery has been associated with intact position sense (De Santis et al., 2014). Typically, in MS populations, proprioception is examined in balance and gait research; decreased proprioception in the absence of visual or auditory feedback increases postural sway and delay postural responses (Fling et al., 2014). Assessments of sensorimotor impairments and joint position sense are often subjectively measured by a clinician with poor sensitivity (Marini et al., 2016). Today, proprioception assessments can be conducted with the use of robotics to form validated and quantifiable performance measures. With MS there is a slowed conduction of processing and executing movements and difficulty in organizing a movement in the absence of appropriate sensation. Therefore, bodily spatial awareness defined as the body's ability to perceive and understand its own spatial orientation and position in relation to its surroundings is hindered. Proprioceptive feedback is principally supplied by proprioceptive receptors; however, these deficits are likely not a result of inactive mechanoreceptors (for example, muscle spindles) and are likely due to the damaged white matter pathways causing the lack of sensory feedback processing (Fling et al., 2014). With the use of robotics as a measurement tool, more than the accurate matching of the target can be quantified. Additional outcome measures such as absolute matching error (how accurately the user matched the target), variability error (overshooting or undershooting the target) and error bias (how consistently and similarly the participant matched the target) can also be measured from one repetition to name a few. Understanding the correlation between proprioceptive pathways and upper limb performance can help establish appropriate rehabilitative interventions to better one's performance of ADLs. A study using magnetic resonance imaging (MRI) following distal lower limb unilateral and bi-lateral active matching proprioception tasks inside a magnetic resonance environment at the ankle joint conducted by Iandolo et al., 2020, showed that parietal regions of the brain are involved in processing proprioceptive information as the parietal region includes the somatosensory cortex and is responsible for body orientation and sensory discrimination. Thus, lesions to the brain in the parietal areas could effectively damage proprioceptive sense. Likewise, performance in the absence of visual feedback was correlated with corpus callosum and damage to microstructural properties during bi-lateral proprioceptive tasks. Evoked potentials for individuals with MS are useful for detecting the site of lesions and anatomical sites in lesion tracts that cannot be seen in imaging (Weiner & Stankiewicz, 2012). Evoked potentials are electrical uptake from the CNS when peripherally stimulated.

2.1.3 Functional and Motor Impairments

Motor control is defined as "exploring how the central nervous system produces purposeful, coordinated movements in its interaction with the rest of body and with the environment (Latash et al., 2010). Motor control plays a role throughout one's daily life and is required for gross motor tasks (Latash et al., 2010) such as walking, picking up a glass of water or preparing meals. Motor control also plays a role in fine motor skills such as writing or typing on a keyboard. Either gross or fine motor, these are all voluntary movements and are executed and coordinated by the primary sensorimotor cortex, and motoneurons are responsible for evoking muscle contractions and are the final CNS functional element before muscle contraction (Bawa et al., 2000). Motor dysfunctions in MS are frequently due to muscle weakness, abnormal walking mechanics, balance problems, spasticity, and fatigue as a result of interrupted and deaccelerated signals from the motor cortex to the limbs (White et al., 2004). Joint motion is often limited because of spasticity and prolonged inactivity (Halabchi et al., 2017). Laczko et al., 2016, define spasticity as a "velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks" (Laczko & Latash, 2016). Spasticity affects 90% of individuals diagnosed with MS (Hobart et al., 2006). Similar to spasticity, tremors are involuntary movements affecting the physical movement of individuals living with MS. There are three common types of tremors. The most disabling type are intention tremors which occur during voluntary movements. This tremor occurs more often during reaching and grasping movements. Postural tremors occur when an individual is sitting or standing, but do not occur when the individual is lying down. Lastly, resting tremors occur when the individual is completely at rest and is generally diminished when the individual performs a voluntary movement (Bain et al., 2003).

Loss of coordination can severely impact the ability to successfully perform activities of daily living (ADLs). ADLs require both spatial and temporal mechanisms and they often involve reaching, grasping and upper limb obstacle avoidance (Laczko & Latash, 2016). Although lower limbs are frequently impaired and clinical scales of impairment refer to ambulation, 76% of PwMS have some incapacity in their upper limbs and 50% were considered ”moderate” disability (Johansson et al., 2007). Active range of motion (ROM), hand dexterity, and tactile sensitivity of the upper limb and hands are required to perform ADLs (Alonso et al., 2021). Lamers et al., 2014, found that general upper limb strength was the most important variable related to the capacity to perform ADLs (Lamers et al., 2015). Difficulties performing ADLs severely impact one's quality of life as Paltamaa et al., 2006, found that 47% of 240 individuals living with MS were not completely independent (Paltamaa et al., 2006).

2.1.4 Classifying Level of Disease

Over the decades there have been several methods developed for assessing and classifying the level of disease in PwMS. The predominant classification system is the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983)(See Appendix D). The EDSS is a scale ranging from 0-10. Level 0 is classified as non-symptomatic, whereas level 10 is classified as death by MS therefore, a higher score on the scale indicates a higher level of disease. It is based on a measure of impairments in eight categories of functional symptoms: pyramidal, cerebellar, brainstem, sensory, bowl/bladder function, visual function and cerebral functions. However, this test is not without its limitations. The scale is heavily related to the ability to walk a distance (meters) with or without a walking aid. Therefore, a person may have few symptoms affecting gait, appearing as a low level of disability but may suffer from upper limb motor impairments. Additionally, symptoms of MS vary day-to-day due to time of day due to triggers of fatigue, temperature, stress, etc. Therefore, an individual may vary above or below 0.5 units on the scale. The validity and reliability of the EDSS has been well tested. A systematic review by Meyer-Moock et al., 2014, confirmed that the literature has certified good validity of the assessment. Validity has been proven to have with strong correlations to functional clinical scales in diagnosing severity of disease such as the Functional Independence Measure (Brosseau & Wolfson, 1994). However, the EDSS has been proven to have a low inter and intra-rater reliability (Noseworthy et al., 1990; Meyer-Moock et al., 2014). Measures such as training users, and having the same investigator complete all assessments are methods to help strengthen the reliability of the scale. To improve these limitations, in 2001 the World Health Organization announced the International Classification of Functioning, Disability and Health (ICF) as the international standard to describe and measure health and disability (Figure 2).

The Multiple Sclerosis Functional Composite (MSFC) scale is a way to measure impairment in addition to the EDSS. The MSFC consists of three measures that examine ambulation, hand dexterity, and cognitive function and is given an overall score (Koch et al., 2014). Some less common classifications of disease or functional and motor impairment of the upper limb that have been used in research include ABILHAND (participant-reported outcome measure), Manual Ability Measurement (MAM), Disabilities of the Arm Shoulder and Hand Outcome Measure (DASH) and Motor Activity Log (MAL) (Kahraman, 2018).

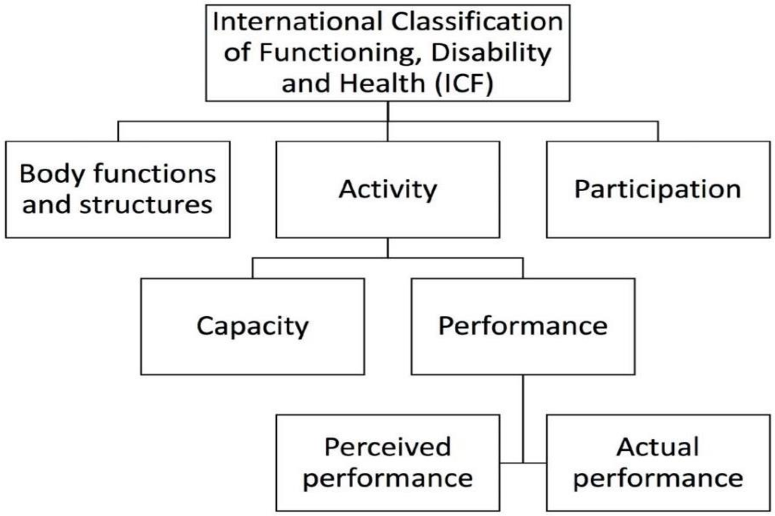

Figure 2. International Classification of Functioning, Disability and Health (ICF) levels (Lamers and Feys, 2008)

When assessing health-related outcomes in MS, stroke, or other neurological conditions, it is important to also evaluate the minimal clinically important difference (MCID). The definition of MCID is "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management" (Jaeschke et al., 1989). The MCID helps in deciding if a treatment effect is large enough to be considered beneficial in a clinical setting and is used to assess the practical, real-world impact of a treatment. Whereas statistical significance is objective and data-centered, focusing on the likelihood that the observed effect is due to chance. An intervention effect can be clinically important without being statistically significant if the study is underpowered due to a small sample size (i.e., too small to detect a statistically significant difference even if one exists). There are two-ways to assess MCID; 1) distribution based, 2) anchor-based (Beaton et al., 2002). For the distribution-based method, MCID is based on change scores within a sample. A limitation of this method is that the power or importance of the percent change score is unknown. For the anchor-based method, change scores are compared with a clinician or participant reference value (Beaton et al., 2002; Lang et al., 2008). For either method, the MCID only refers to the specific outcome measures that have been established. For example, comparing the MCID of the speed of gait is not comparable to the MCID of an upper limb arm function task, as the arm function task would have its own MCID score. Many factors such as severity of disease, duration of disease, or years of age can influence the MCID and for this should not replace statistical significance, but used in adjunct with to strengthen outcome results (Beaton et al., 2002). In MS, MCID scores have been established primarily for functional tests (such as the Wolf Motor Function Test, 9-hole peg test), gait speed and balance with little focus on upper limb strength. However, the MCID of grip strength and upper limb isometric force has been tested in stroke. Using the distribution-based method, Lang et al., 2008, reported MCID values of grip strength, and upper extremity strength of the wrist flexors and extensors in 52 stroke survivors. Results showed that a minimum of a 16-30% change score would be needed to be considered clinically meaningful for the strength measures. Additionally, Lang et al., 2008, investigated the MCID for the Wolf Motor Function Test (WMFT) of stroke survivors and determined an overall change score of 1.0 for the dominant (17% change score) and 1.2 points (20% change score) for the non-dominant limb on the WMFT can determine clinically important changes (Shirley Ryan Ability Lab, 2016). Overall, there is a need to establish MCID of relevant assessments for MS specifically and MCID should not be a stand-alone measure but can provide insight for clinicians and researchers of functional changes in outcomes.

2.1.5 Pharmaceutical Interventions

Although MS is an incurable disease, it is a treatable disease. Disease control is defined as decreasing relapses, decreased lesions visible on functional magnetic resonance imaging (fMRI) and lessening or preventing symptoms before and after a relapse (Robertson & Moreo, 2016). The use of Disease modifying drugs (DMDs) have been well established for RRMS or early diagnosed MS (Weiner, 2012). DMDs include immunosuppressants and/or immunomodulators. The main purpose of DMDs is to lessen the inflammatory response from the CNS with the goal to reduce disease activity (Robertson & Moreo, 2016). There are seven self-injecting therapies, three oral and three infusion therapy that are currently FDA-approved. DMDs are expected to protect against 20-60% of relapses (Robertson & Moreo, 2016). Along with few adverse effects, DMDs can cost the user tens of thousands of dollars per year. DMDs have been shown to not directly predict severity of disease (EDSS) (Chaves, Snow, et al., 2021) indicating that DMDs do not have a direct effect on motor performance.

Additional pharmaceuticals are neurotransmitters. Neurotransmitters play a critical role in sending and amplifying nerve-to-nerve signaling and transmission through the CNS (Teleanu et al., 2022). MS is a considered a neurotransmitter disorder of the CNS. Pharmaceuticals that effect neurotransmitters are categorized by inhibitory drugs (ID) or excitatory drugs (ED) and are used to treat symptoms associated with MS. IDs or inhibitory neurotransmitters prevent neurons from firing and are considered beta-adrenergic blockers, anticholinergics, dopamine receptor antagonists, anticonvulsants, GABA-ergic medications (Chaves, Snow, et al., 2021). Excitatory drugs or excitatory neurotransmitters increase the activity of neurons. Excitatory drugs are considered dopamine agonists, serotonin receptor agonists, and noradrenergic receptor agonists. ID or ED neurotransmitters can influence coordination and motor capabilities.

Lastly, the role of medicinal cannabis in treatment of symptoms has also become a popular option of PwMS. THC (tetrahydrocannabinol) and CBD (cannabidiol) interacts with the endocannabinoid system in the human body. Cannabinoids have the possibility to reduce neuroinflammation and have neuroprotective effects on the CNS (Zeine & Teasdale, 2023). Research suggests that cannabis may modulate inflammation with its anti-inflammatory properties by activating cannabinoid receptors in the immune system to reduce the release of pro-inflammatory molecules (Guy et al., 2004). Cannabis is used to treat neuropathic pain or overall pain management with its analgesic properties (ability to relieve the perception of pain) that restrain pain signaling pathways of the nervous system (Zeine & Teasdale, 2023). The safety and low cost of cannabis comparative to previous mentioned pharmaceuticals are two advantages to using cannabis. PwMS have reported using cannabis to treat a variety of symptoms including, but limited to: pain, spasticity, and sleep issues (Zeine & Teasdale, 2023).

2.2 Forearm and Wrist Anatomy

Understanding the anatomy of the forearm and wrist is crucial when studying training interventions because it provides insight into the specific muscles, tendons, and joints involved in movement and strength (Figure 3). This knowledge allows for targeted exercises that can effectively strengthen these muscles, enhance flexibility, and improve overall performance. Additionally, understanding the anatomy helps prevent injury by ensuring that training programs are designed to promote balanced muscle development and proper joint function.

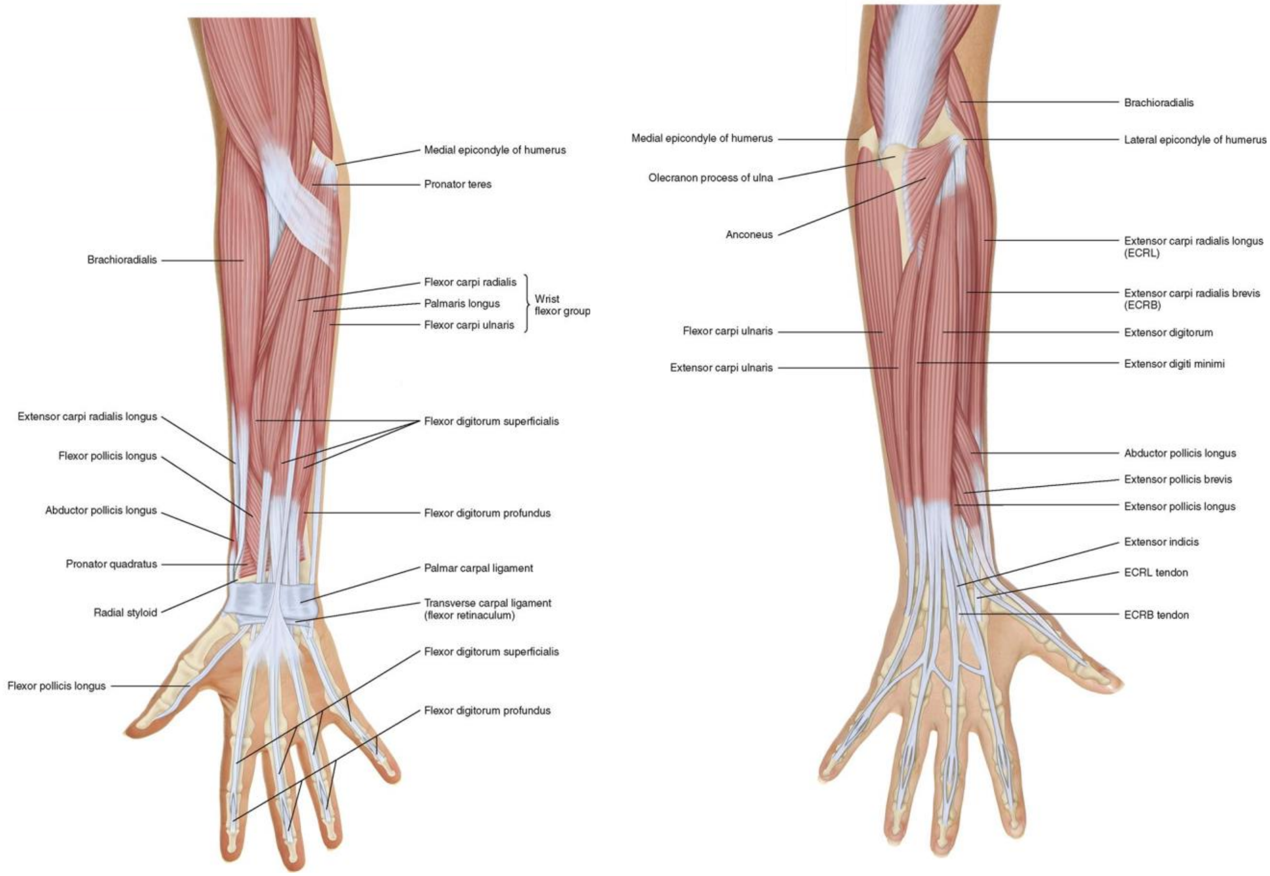

Figure 3. Anatomy of the muscles of the forearm that cross the wrist joint in an anterior view (left) and a posterior view (right). (Image courtesy of Musculoskeletal Key)

2.2.1 Anatomy of the Forearm

The bone framework of the forearm consists of the radius and the ulna. When in anatomical position, the radius is lateral in position and distally forms the wrist joint with eight carpal bones; scaphoid, lunate, triquetrum, pisiform, trapezium, trapezoid, capitate and hamate (Drake et al., 2015). The ulna is medial in the forearm and is the “load-bearing” bone. The ulna supports the radius as the radius rotates around the ulna (Lees, 2016). Pronation and supination of the hand are generated by the radius rotating over the adjacent end of the ulna as rotation about the proximal radioulnar joint (near the elbow) and distal radioulnar joint occurs (near the wrist) (Drake et al., 2015, Lees, 2016). The interosseous membrane is a strong connective tissue that holds the radius and ulna together (Kehr & Graftiaux, 2017). The function of the interosseous membrane is to decelerate pronation and supination of the wrist and forearm (Kehr & Graftiaux, 2017). The dorsal radioulnar ligament helps stabilize the distal radioulnar joint during pronation and supination and the palmer radioulnar ligament, situated on the paler side of the distal radioulnar joint, contributes to stability during weight-bearing at the hand/wrist (Kehr & Graftiaux, 2017).

2.2.2 Anatomy of the Wrist and Hand

The wrist joint/radiocarpal joint is a condylar synovial joint formed between the radius and carpal bones and distal to the ulna and the articular disc (Drake et al., 2015). The wrist joint is possible of moments about flexion/extension (F/E) and radial/ulnar (R/U) deviation. Movement along the pronation/supination (P/S) axis and a combination of these movements (circumduction) occur at the proximal radio-ulnar joint (Drake et al., 2015).

Fifteen muscles cross the wrist, contributing to movement about flexion/extension and radial/ulnar deviation (Bawa et al., 2000). Six of the 15 muscles that cross at the wrist joint with the primary function of producing wrist movement: flexor carpi radialis, flexor capri ulnaris, extensor carpi radialis longus, extensor carpi radialis brevis, extensor carpi ulnaris. The remaining muscles that cross the wrist joint contribute to various movements of the hand, fingers, and thumb as well as stabilizing the wrist during these actions (Bawa et al., 2000). The hand is highly dependent on the biomechanical activation of the muscles that cross the wrist joint for movement (Bawa et al., 2000). These muscles can be sectioned into the anterior and posterior compartments in respect to anatomical positioning. Muscles of the anterior compartment of the forearm are typically associated with flexion at the wrist, flexion of the fingers and pronation of the forearm. There are four muscles in the superficial layer, flexor carpi ulnaris, palmaris longus, flexor carpi radialis, and pronator teres. One muscle in the intermediate layer: flexor digitorum superficialis.

Lastly, three muscles in the deep layer: flexor digitorum profundus, flexor pollicis longus, pronator quadratus (Drake et al., 2015). Extensor carpi radialis longus and brevis, extensor carpi ulnaris, extensor digitorum, extensor indicis and extensors pollicis longus and brevis are muscles of the posterior compartment are associated with extension of the wrist, extension of the finger and thumbs, and supination.

The superficial layer includes brachioradialis, extensor carpi radialis longus, extensor carpi radialis brevis, extensor digitorum, extensor digiti minimi and extensor carpi ulnaris. The deep layer consisting of supinator, abductor pollicis longus, extensor pollicis brevis, extensor pollicis longus and extensor indicis. These muscles combined allow the hand to be radial and ulnar deviated, flexed and extended at the wrist. As the radial styloid process extends further distally relative to the ulnar styloid process, the hand can perform ulnar deviation to a greater degree than radial deviation (Drake et al., 2015).

2.2.3 Forearm and Wrist Function and Mechanics

The wrist joint is important for many ADLs (Majors & Wayne, 2011). Healthy range of motion (ROM) is 65-80º of flexion and 55-75º of extension. Due to slight palmar tilt of the distal radius surface, flexion ROM normally exceeds extension by an average of 10º (Mohd Nazri Bajuri & Mohammed Rafiq Abdul Kadir, 2013). Kinematics of the wrist joint consists of two axes; flexion/extension and radial/ulnar deviation and require substantial motor programming to coordinate multiple muscles that cross the wrist joint.

2.3 Motor Control and Motor Learning

2.3.1 Motor Learning in MS

Motor learning has been described as a "set of the processes associated with practice or experience leading to a relatively permanent change in the capability for skilled behaviour" (Schmidt et al., 2019). Motor learning is quantified by the acquisition, retention, and transfer of skills. 71% of individuals with MS have been reported to experience limitations in activities and participation related to hand and arm use (Kahraman, 2018). 56% of individuals experience interrupted and distorted afferent signals, requiring constant relearning of motor skills. Individuals with neurological conditions that affect the motor function of the upper limb need to relearn the motor skill with an altered number of sensory channels available and quality of sensory feedback available (Muratori et al., 2013). As evidenced from a study by Perez & Cohen, 2008, using fMRI, motor learning occurs in three main regions of the brain including the primary motor cortex (M1), the supplementary motor area, and the premotor cortex. Of the three regions, the primary motor cortex has been noted as the most involved in the motor learning process. There is evidence of M1 activity in the contralateral and ipsilateral to an active limb (Farthing, 2009).

To relearn a motor skill, task specificity, intensity and frequency are important principals to incorporate in any rehabilitation therapy (Langhorne et al., 2011). Additional system complexity occurs with the degrees of freedom available to the system and its relationship with movement efficiency (Bernstein, 1969). There are vast movement options and redundancy of the CNS and peripheral nervous system (PNS) available to perform the same action, and the resolution to this problem will vary depending on the characteristics of the learner as well as the components of the task and environment (Bernstein, 1969). There are three distinct ways to promote skill acquisition, and they are described below.

1. Amount and Intensity of Practice – In rehabilitation, more practice is better. This concept has been proven effective with constraint-induced movement therapy. Results from this type of rehabilitation program have shown that intense, repetitive practice leads to improvements in function, quality of movement, timing, and even changes in the neurosubstrates of the brain which correspond to improved movement capabilities (Muratori et al., 2013; Holper et al., 2010).
2. Whole vs Part Practice – Dependent on the acquired motor skill, it is essential to consider if the practice should be performed at once (whole) or whether rest breaks (part) are necessary.
3. Feedback – Feedback includes sensory, visual, and auditory. Augmented feedback (knowledge of results/performance). Feedback can also be considered as applied feedback such as online and offline feedback (i.e., instantaneous vs. delayed feedback).

2.3.2 Neuroplasticity

The term neuroplasticity refers to the ability of the brain to modify its structure and function in response to learning (Muratori et al., 2013). The phenomenon of neural plasticity regards the brain's ability to adapt in response to external stimuli or lesions (Zeller & Classen, 2014) and may represent compensation and recovery from MS-induced neuronal damage (Zeller et al., 2010). Overall, neuroplasticity may be the brain's attempt to recover following injury via neural reorganization. Existing literature provides proof that motor learning is capable of inducing neuroplastic adaptations across ages and disease states (Muratori et al., 2013). Neural plasticity is adaptable from changes in the strength of a single synapse or from rapid-onset plasticity to chronic spatial reorganization, whereby the strength of a synapse refers to its ability to transmit signals from one neuron to another. Neural plasticity can be visually observed by imaging of the brain with fMRI. An increase in neural activity results in an increased cerebral blood flow and an increased oxygen utilization (Zeller & Classen, 2014). Neuroplasticity also depends on experience as outlined by, Kleim & Jones, 2008 (Table 1). To induce neural plastic changes, motor training is often effective and chronic reorganization is functionally important for MS-related CNS injuries. The chronic reorganization is often associated with learning and adaptation and refers to the change in structure and function of neural circuits (Tomassini et al., 2011). Chronic reorganization as well as structural changes (e.g. dendritic growth and neurogenesis) and functional changes (e.g. recruitment and excitability of additional neurons) all play a role in regaining function for PwMS.

Table 1. Principles of experience-dependent plasticity (Kleim & Jones, 2008)

Principle	**Description**
1. Use It or Lose It	Failure to drive specific brain functions can lead to functional degradation
2. Use It and Improve It	Training that drives a specific brain function can lead to an enhancement of that function
3. Specificity	The nature of the training experience dictates the nature of the plasticity
4. Repetition Matters	Induction of plasticity requires sufficient repetition
5. Intensity Matters	Induction of plasticity requires sufficient training intensity
6. Time Matters	Different forms of plasticity occur at different times during training
7. Salience Matters	The training experience must be sufficiently salient to induce plasticity
8. Age Matters	Training-induced plasticity occurs more readily in younger brains
9. Transference	Plasticity in response to one training experience can enhance the acquisition of similar behaviours
10. Interference	Plasticity in response to one experience can interfere with the acquisition of other behaviours

2.4 Resistance Training with MS

Strength/resistance training is defined as "the person's use of muscle contractions against a load for increasing muscle strength" (Halabchi et al., 2017a). Whereas muscle weakness is defined as "reduced ability to generate maximal force" and muscle fatigue as "decline in motor performance during sustained muscle activity" (Taylor et al., 2006). Muscle weakness and fatigue can be a result of incomplete motor unit recruitment and motor unit discharge rates but can also be caused by disuse atrophy as those with MS are typically inactive (Taylor et al., 2006). Resistance training in individuals with MS is typically limited due to several factors. Mainly, the MS population experiences overall fatigue and an elevated body temperature, both of which can exacerbate fatigue symptoms (Petajan et al., 1996). As a result, individuals tend to avoid or limit resistance training and physical activity to utilize that energy for everyday tasks. This cycle repeats as a sedentary lifestyle over time can lead to muscle weakness, greater fatigue and increased health risks such as osteoporosis and pathological fractures, particularly when combined with the use of therapeutic corticosteroids. Although resistance training cannot reverse impairments caused by the disease, it can reverse deconditioning effects and can slow the loss of muscle and bone mass in PwMS (White et al., 2004).

Resistance training for the MS population comes needs to be performed with caution to avoid injury or exercise-related fatigue. The individualized exercise program should be designed to address an individual's chief complaint or goal (improve strength, endurance, balance, coordination, fatigue) (Halabchi et al., 2017a). Closed kinetic chain exercises such as weight training machines are preferred (Halabchi et al., 2017a). It is recommended that the training frequency be 2-3 sessions per week, consisting of 8-15 repetitions exerting an effort at 60-80% of 1 repetition maximum. There are key principles to resistance training in an MS population as outlined by Taylor et al (2006). The participant should perform a small number of repetitions with relatively high loads until muscle fatigue is reached, allow sufficient rest between exercises for recovery and increase the load as the ability to generate muscle force develops (Taylor et al., 2006).

Progressions are an important concept in resistance training. It is recommended that resistance be added by 2-5% once the individual reaches 15 repetitions in each exercise successfully. Exercises should be performed in 1-3 sets to begin with and can further increase to 3-4 sets to add volume to the training session (Taylor et al., 2006). For basic knowledge of progressions, the exercise staircase model (Figure 4) has been developed to outline the stages of progression (Halabchi et al., 2017a). It is always important to note that day-to-day variability in fatigue will likely justify flexibility in the resistance program and alter the need for progressions. Day-to-day fatigue and disease symptoms such as spasticity, neurological, or cognitive decline should be monitored daily before beginning training sessions.

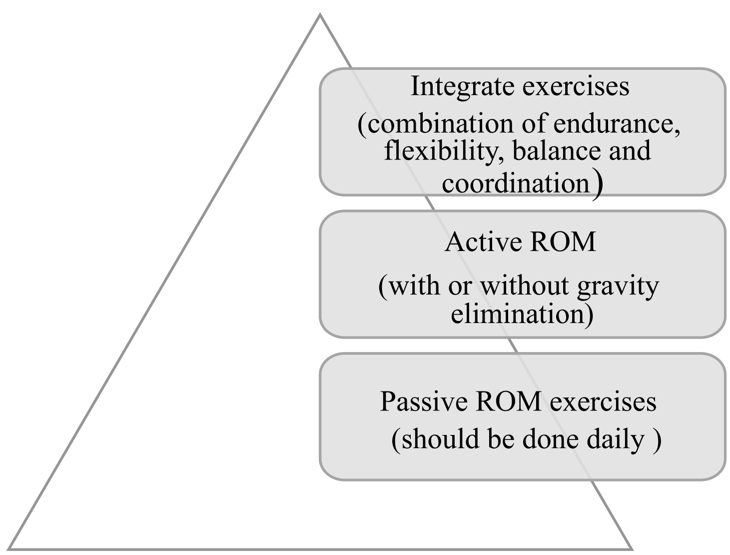

Figure 4. Progression exercise staircase model (Halabchi et al., 2017a)

2.5 Rehabilitative Robotics

Robotics for the use of neurorehabilitation are an innovative therapy based on human-robot interaction. Rehabilitative robotics have been studied for over two decades, and enable a revolutionary repetitive task practice, gravity-assisted and gravity-eliminated rehabilitation, or a combination of the above, potentially addressing the needs of individuals with severe motor impairment (Livengood et al., 2011). Human-robot interaction is an important instrument in motor recovery. In addition, robotic devices provide standardization of movement, precise measurement of discrete movement (joint angles, acceleration, force), and interactive multisensory feedback through computer interfaces and thus, allows for more opportunities to induce neuroplastic changes. The overall goal of a robotic device is to allow the limb to move naturally for specificity of learning so that practiced motor tasks can be translated into functional tasks. There are several key components to a robotic device used for rehabilitation and a main consideration is the mechanical design. Described below are three categories of robotic devices along with their unique characteristics and functionalities:

1. End-effectors – End-effectors are the last dividing factor between the robot and the user; they attach to the end of the device and manoeuvre distal extremities (Lo & Xie, 2012). End-effectors do not control the whole kinematic chain, allowing the upper limb to respond or adapt to external forces. Typically, end-effectors are accompanied by impedance control strategies and use positional feedback to regulate the mechanical impedance.
2. Exoskeletons – The opposite of end-effectors, exoskeletons encompass the whole kinematic chain and are designed to control the position of the joint. Exoskeletons can encompass more than one joint and multiple actuators, co-ordinating movements, and

control position across multiple joints (e.g., shoulder, elbow, wrist robots). Exoskeletons are typically accompanied by admittance control strategies, as the robot measures the controller's force feedback to regulate position.

3. Planar robots – typically only move in one plane of motion. These robots are more cost effective and are commonly a type of end-effector-based robot. Examples of planar robots include the KINARM, MEMOs and PLEMO.

Actuation is an important aspect in the mechanism design and control of wrist rehabilitation robots as they are the main powering elements. The common types of actuators are listed below.

1. Electric motors – electric motors are the backbone of the device (DC brushed, DC brushless, PMSM, steppers, servos, etc.). Electric motors are the most common because they easily provide relatively high power and can store energy; however, some are too heavy and/or their impedance is too high for rehabilitation settings.
2. Hydraulic motors – can generate high forces. Their system is relatively complex considering the maintenance of pressurized oil under pressure to prevent leakage.

   However, they are also heavy; only well spatially designed hydraulic actuators are used.
3. Pneumatic – they have lower impedance and weigh less than electric actuators.
4. Series Elastic Actuators – An elastic element placed in series with an actuator. It decreases the inertia and intrinsic impedance to allow a more accurate and stable force control and increase safety
5. Functional Electrical Stimulation or electromyography – Uses natural actuators. However, it is difficult to achieve precise and repeatable movement using this technique and it may be painful for the participant

6. Backdrivability – is the ability for interactive transmission of force between input axis and output axis. To get high backdrivability, friction of power transmission must be reduced considerably. Backdrivability provides actuators with high force sensitivity and high impact resistance which adapts to quick external force mechanically.

Another important component of robotic design is choosing the correct Control Paradigms (Hussain et al., 2020). There are both high-level and low-level control strategies. Each of the strategies have been outlined in Table 2.

Table 2. Control strategies of rehabilitation robots

High-level control	A control strategy with control algorithms explicitly designed to induce motor plasticity
Assistive control	In which the device provides physical assistance to aid the user in accomplishing an intended movement
Challenge-based control	Challenges the user to accomplish an intended movement (resistive, amplifying error or constraint-induced)
Haptic stimulation	Haptic interface is used to perform activities, often in a VR environment
Coaching control	Neither assistive nor resistive only provides feedback
Low-level control	Considered in the implementation of the “high-level” control strategy in a device by appropriate control of the force, position, impedance, or admittance
Admittance control	Force exerted by the user is measured, and the device generates the corresponding displacement
Impedance control	The motion of the limbs is measured, and the robot provides corresponding force feedback. Measures the human-induced joint torque by using force sensors and increases or decreases the robot applied torques based on that

Assist-as-needed control paradigms have been the most used strategies in robotic rehabilitation. Assist-as-needed can estimate the user’s intent and can modify the robot applied forces to enhance active participation in the rehabilitation process. A well-known example of this is the MIT-Manus end-effector-based wrist robotic device (Krebs et al., 2007).

2.5.1 Robotic Rehabilitation Terminology

It is important to clarify and define common exercise prescription terminology used in robotic rehabilitation. The first term of importance to be defined is ‘dosage’ or also known as ‘therapy dosage’. Dosage is a collective term that encompasses various parameters such as frequency of training, duration of a single training session, duration of an intervention, and training intensity (Lamers et al., 2014). Finding the optimal dose for robotic rehabilitation involves balancing factors such as the user's goals, severity of their condition and tolerance for the training. Frequency of the training refers to the number of training days per week or total training days in an intervention that is prescribed to the user. Frequency of the therapy directly influences the total amount of therapy received by the user. The term 'load' refers to the amount of resistance or force delivered from the robotic device. Resistance is the level provided by the robotic device against the user whereas force is the force exerted by the muscles or effort of the user. The goal of the applied load can be to promote strength and/or endurance. 'Duration' of training refers to the time of a single therapy session or total time of the therapy across an intervention, regardless, duration is commonly reported in minutes. Lastly, the term 'intensity' refers to the repetitions and sets prescribed to a protocol or intervention. In combination with 'load', the number of repetitions and sets performed has an influence on the overall workload.

2.5.2 Robotic Rehabilitation in Clinical Settings

Robotics have been increasingly popular in clinics because they can produce a more highly consistent, standardized, and measurable program than other interventions. Livengood et al., 2011, interviewed several clinicians on the effectiveness of robotics in their programs. Results showed that therapists value robotic devices for several reasons: ease and replication of setup and adjustment, portability, types of interactive activities provided through computer interfaces, timing (real-time, delayed) and mechanisms (visual, auditory, haptic) of feedback, memory capacity for client specific settings and performance data, display and storage of performance data for analyses, planes of movement and amount of assistance provided (passive versus active) (Livengood et al., 2011). During upper limb therapy training, greater interaction resulted in greater opportunities for the nervous system to experience ADLs related to sensorimotor input (Masiero et al., 2014).

2.5.3 Robotic Training Translation (Functional Improvements)

There are considerations when using robotics for rehabilitation to induce functional improvements. Systematic reviews of therapy interventions with robotics for stroke survivors suggest that users benefit from therapy programs in which they practice tasks directly rather than from interventions that focus on impairments (Rodgers et al., 2019). A key function of the CNS is to control redundancy, and reducing the degrees of freedom can help the learner resolve a given task (Muratori et al., 2013). The intensity of therapy is also important; a Cochrane overview of systematic reviews found moderate quality Grading of Recommendations, Assessment, Development and Evaluations evidence that arm function after a stroke can be improved by the provision of at least 20 hours of additional repetitive task training (Rodgers et al., 2019). Robots can quantify sessions/progressions of the exercise to allow clinicians to adjust as necessary (Washabaugh et al., 2018). Robotic devices can predict torques required to perform a directed movement and correct for inaccuracies during the movement, allowing the CNS to feedback control from the robotic device to learn a movement (Laczko & Latash, 2016).

2.5.4 Robotic Assessments

A large gap between neurological assessment and rehabilitation is the ability to accurately measure the level of impairment and disability (Scott & Dukelow, 2011). Many clinical assessments of motor and sensory impairment are subjective with low inter-rater reliability. Subjective clinical scales can be the difference between inaccurately quantifying abnormal motor patterns or severity of disease. Understanding sensory, motor, and cognitive functions rely heavily on research-oriented diagnostic tools and assessments to quantify these activities. This issue can be solved by replacing tests that are more subjective in nature, with quantifiable robotic assessments. Exoskeletons can provide information regarding whole limb motion and joint behaviour whereas end-effectors provide a more robust measure of limb motion as the robot is grasped by the participant's hand (Scott & Dukelow, 2011). Although end-effectors supply less joint motion information than exoskeletons, end-effectors are typically less expensive and easier to implement and use. Robotic devices can elicit discrete perturbations whereby muscle-stretch reflexes can be assessed beyond a typical hammer tap test. Another highlight of using robotics for typical assessments is the ability to eliminate gravity or weight-support the testing limb. While eliminating the force of gravity, a user may move their limb through a greater range of motion (Ellis et al., 2008). The KINARM is a well-established end-effector robotic device that has been used for assessments that measure upper limb motor, sensory and cognitive function (Krebs et al., 2007). In a recent study, quantitative robotic measures were compared to subjective clinical scales and the results demonstrate strong correlations between the two, providing evidence of efficiency and validity of robotic assessments while in addition, demonstrating a broad range of cognitive, motor and sensory assessments that may complement the clinical scales (Simmatis et al., 2020).

2.6 TMS and Assessing Neurological Adaptations

Transcranial magnetic stimulation (TMS) is a non-invasive and painless way to assess the integrity of one's central motor pathways. The corticospinal tract is the main descending pathway from the cerebral cortex to the spinal cord and can be activated by TMS (Zewdie & Kirton, 2016). While electromyography (EMG) provides insight into muscle activation during movement, evaluating the corticospinal tract can provide a window into the neural control of movement. Changes in corticospinal excitability can occur at cortical or spinal levels (McNeil et al., 2013). TMS and electrical stimulation techniques can be used to evaluate corticospinal, spinal and supraspinal excitability in both healthy and those with neurological impairments (Rossini & Rossi, 1998). It has been suggested that TMS findings can be useful for an early diagnosis or prognostic prediction of MS (Kobayashi & Alvaro, 2003). An electrical current is passed through copper coils, creating a magnetic field (Zewdie & Kirton, 2016). When placed over the scalp, this magnetic field stimulates cortical neurons, resulting in their depolarization, and the generation of action potentials. EMG electrodes placed over muscles of interest, records the electrical activity of the motor unit action potential along depolarizing sarcolemma. This represents the excitability of corticospinal neurons and the response recorded in the contralateral muscles following cortical stimulation is known as a motor evoked potential (MEP) (Zewdie & Kirton, 2016). When TMS is used on individuals with MS it can be an indicator of axonal damage represented by a decrease in MEP amplitude and prolonged central motor conduction time (time taken for neural impulses to travel through the CNS to the targeted muscle) (Stampanoni Bassi et al., 2017). Therefore, TMS can be used as a quantitative assessment tool for evaluating any neurophysiological adaptations for this specific group. Single pulse TMS can assess simple cortical excitability measures and paired-pulse TMS can assess inhibitory and excitatory circuits in the motor cortex (Stampanoni

Bassi et al., 2017). MS causes demyelination in conduction blocks and axonal damage; it is expected at baseline that there would be an increase in latency and a decrease in MEP amplitude compared to healthy controls resulting from either attenuation of amplitude or prolongation of the central motor conduction time (Neva et al., 2016). Many outcome measures can be investigated with the use of TMS. Below are commonly used measures when exploring corticospinal excitability changes or disease progression.

- TMS generates descending volleys, which activate motoneurons (at the spinal level). The action potential of the motoneuron descends to the muscle resulting in depolarization and muscle contraction (Zewdie & Kirton, 2016). Using EMG electrodes, we can measure the sum of this action potential, which is called a MEP. Following exercise, it can be expected that neurophysiological adaptations will occur, resulting in synaptic plasticity/reorganization of the corticospinal motor pathway (Valero-Cabré et al., 2017). MEP amplitudes are calculated offline and are recorded as the difference in voltage from the maximal peak (positive) to the lowest peak (negative) of the MEP waveform and is known as the peak-to-peak amplitude (Chaves, Snow, et al., 2021). Changes in MEP amplitude after acute or chronic exercise are often associated with increased corticospinal excitability. In a study investigating MEP amplitude changes for persons with progressive MS, MEP amplitudes were recorded from the first dorsal interosseous muscle, pre- to post cardiovascular exercise (body-weight supported treadmill training). Results demonstrated an increase in peak-to-peak amplitude, in which authors deemed to indicate enhanced excitability and contributed this to the enhanced neuroplasticity (Chaves, Devasahayam, Kelly, et al., 2020). Contrary, a systematic review investigating neurophysiological changes in healthy resistance trained individuals reported generally unchanged MEP amplitudes following acute resistance training (Santos et al., 2023). These findings could suggest that the MEP amplitude changes can depend on type of exercise, length of treatment and participant pool.

- Resting motor threshold (RMT) is defined as the lowest stimulus intensity to elicit a clearly discernable MEP in at least 50% of conducted trials while the participant is completely at rest. Whereas active motor threshold (AMT) is the lowest stimulus intensity to elicit a clear MEP during a submaximal muscle contraction (10-20% of maximum) (Zewdie & Kirton, 2016). Both RMT and AMT are recorded using single-pulse TMS resulting in MEPs from the contracting muscle. Resting motor threshold (RMT) and active motor threshold (AMT) can be increased in diseases that affect the corticospinal tract, such as MS (Zewdie & Kirton, 2016). For stroke survivors, a low RMT is typically associated with a high cortical excitability (Veldema et al., 2021). Therefore, a decrease in RMT or AMT and an increase in MEP amplitude following exercise would be indicative of increased corticospinal excitability (Valero-Cabré et al., 2017).
- MEP onset, also referred to as MEP latency is defined as the time from the TMS trigger to the onset of the MEP. MEP onset can be influenced by location and intensity of stimulus and individual neurophysiological characteristics (Valero-Cabré et al., 2017). Strength or skill training that results in training-induced adaptations in the CNS can affect the time it takes for the electrical signal generated by TMS to propagate along the corticospinal tract and reach the muscle of the upper limb (Latella et al., 2017).
- Cortical silent period (CSP) is representative of intracortical inhibition and is displayed as a suppression of EMG or muscle activation following a MEP (Zewdie & Kirton, 2016). A decrease in CSP is indicative of inhibitory circuit activity within M1 (Boyd et al., 2014) and has been observed to decrease in the trained limb following unilateral resistance training in stroke (Lim & Madhavan, 2023; Sun et al., 2018a). CSP are clearly discernable

for healthy populations, neurological conditions can alter or produce an undetectable silent period (Zewdie & Kirton, 2016).

Ultimately, TMS is a quantifiable measure of neurophysiological adaptations and can be a useful tool to investigate corticospinal excitability, corticospinal inhibition and disease progression in neurological disorders such as MS.

2.7 Cross-Education

2.7.1 Phenomenon and Mechanisms of Cross-Education

Cross-education (CE) is a neurophysiological phenomenon whereby one limb is trained, and the opposing (contralateral) limb also demonstrates improvements. CE refers to the transfer of strength as opposed to bilateral transfer which refers to the transfer of skills (Farthing, 2009). CE was first documented in the literature in healthy populations (Scripture EW, Smith TL, Brown EM, 1894) over 130 years ago. Despite the long history, research is scarce if this phenomenon occurs for individuals with MS. Although CE is not an established rehabilitation strategy (Russell et al., 2018), CE has the potential to reduce asymmetries following stroke, MS, or neuromuscular damage (Farthing and Zehr, 2014) and evidence of validity and efficacy of CE for rehabilitative purposes is necessary. This phenomenon would initiate a safer option to successfully "train" a weaker or uncoordinated limb and user engagement would still be feasible.

There are two possible theories behind CE. The first is that training of the limb causes a "spill-over" effect or spill-over of neural drive to the contralateral side; secondly, training one limb may result in neural adaptations that are accessible by the untrained limb (Carroll et al., 2006). It is speculated that neither of these theories is independent and a combination of the two may also occur during the phenomenon (Carroll et al., 2006). In an attempt to provide a deeper dive into the mechanistic components to CE, it is important to categorize into muscular and neural mechanisms.

Muscular Mechanisms

CE is often evidenced by increases in strength of the untrained limb. To investigate the potential muscular mechanisms behind CE, it is also important to understand the mechanisms behind the increase in strength. CE may involve muscular adaptations such as increased muscle via fiber activation and hypertrophy in the untrained limb. Intervention based studies investigating CE typically involve maximal resistance training from 12-18 sessions (Farthing et al., 2021). The physical training of the engaged muscles allows for adaptations in force-generating capacity such as: hypertrophy, change in muscle enzyme concentrations, and changes in contractile proteins (Carroll et al., 2006). Muscle hypertrophy is defined as the increase in size of individual muscle fibres. Muscle hypertrophy can occur through myofibrillar hypertrophy, which involves an increase in the size and number of contractile proteins within muscle fibers. It can also occur through sarcoplasmic hypertrophy, which involves an increase in the volume of non-contractile fluid and organelles within the muscle cell (Duchateau et al., 2021). Both types of hypertrophy contribute to increased muscle strength. Secondly, changes in muscle enzyme concentrations can directly affect muscular strength by modulating the rate of ATP production, energy metabolism, and muscle contractile function (Duchateau et al., 2021). There is evidence to suggest that low-load strength training elicit strength gains similar to heavy-load strength training (Burd et al., 2010; Schoenfeld et al., 2017). This is likely due to progressively recruiting motor units to compensate for fatigue towards the end of a given set (Duchateau et al., 2021). It can be speculated that these peripheral muscle adaptations contribute to the CE effect (Carroll et al., 2006). There are three levels to induce CE of the upper limb that involve input and output from the motor cortex and output from the peripheral muscles (Farthing, 2009). However, studies have reported increases in muscular strength in the untrained limb, without changes in muscle hypertrophy (Moritani & deVries, 1979) leading the mechanisms underlying CE relating to neural mechanisms.

Neural Mechanisms

The exact neural mechanisms behind CE remain elusive but there are three main pathways to consider: cortical pathways in the cerebral cortex, at a sub-cortical level (deep to the cerebral cortex) and spinal pathways. At the cortical level, the frontal lobe, involved in planning and execution of voluntary movements, at the sub-cortical level regions such as the basal ganglia are involved in motor control (Carroll et al., 2006). The basal ganglia, cerebellum and brain stem nuclei help regulate voluntary movements and movement control by modulating the activity of motor pathways in the cortex and brainstem. At the spinal pathway, interneurons that integrate sensory and motor signals and can modulate motor output. Training one limb may lead to changes in the excitability of spinal interneurons, which could facilitate motor learning and adaptations in the untrained limb (Carroll et al., 2006). Circuits in the spinal cord such as reflex action and motoneurons are also capable of influencing force-generating capacity via motor drive to muscles. To summarize, candidate mechanisms of CE include neural circuits that are involved in planning and execution (Figure 5) (Carroll et al., 2006). While the majority of pathways cross at the medulla, it is important to note that there are corticospinal fibers that project to motoneurons bilaterally and can contribute to the CE effect.

Many researchers have aimed to investigate these mechanisms with the use of electromyography (EMG), TMS and fMRI. A study by Farthing et al., 2007, aimed to investigate the neuro-physiological mechanisms. With one resistance training group of maximal isometric ulnar deviation four times per week for six weeks and one sham training group, imaging showed there was an enlarged region of activation in contralateral sensorimotor cortex and left temporal lobe during muscle contractions (as measured by fMRI). Results suggested that the CE was associated with adaptations within sensorimotor cortex. In addition to, Lee et al., 2009, investigated CE via TMS following four weeks of unilateral wrist extensor training. Results showed an 8% increase in strength in the untrained limb in addition to finding an increase in voluntary activation (measured as the difference in smaller superimposed twitch before and after training) of the untrained wrist extensors. Although no mechanistic conclusions were made, researchers reported that it is the motor cortical drive that contributed to the CE effect.

Most CE evidence for individuals with neurological conditions have been evaluated post-stroke and an important note from the current research is that none have reported any adverse effects (Russell et al., 2018). Some research with stroke survivors have reported greater strength gains in the untrained limb compared to healthy populations (Dragert & Zehr, 2013; Lim & Madhavan, 2023). After high-intensity maximal wrist extension strength training for 5 weeks of training, 3 days per week, Sun et al. (2018b) found 42 and 35% adaptions in strength in the trained and untrained limbs, whereas it has been reported that healthy individuals report an average of 17% of adaptation in the upper limb (Green & Gabriel, 2018). In a scoping review of the literature and CE in a stroke population, (Lim & Madhavan, 2023), all studies included consisted of strength training alone (either isometric, concentric/eccentric), with no motor learning component. Of the seven studies included in the scoping review, only three examined neural mechanisms. Urbin et al., 2015, investigated changes in MEPs from pre-to-post wrist extensor strength following 16 training sessions of sub-maximal resistance training. Although mechanisms were inconclusive, results reported no change in interhemispheric inhibition or corticospinal excitability. Similarly, (Salehi Dehno et al., 2021) investigated resting and active thresholds and MEP changes in the upper limb in stroke survivors following resistance training and reported no changes for outcomes of the trained muscle but interestingly reported a 9% decrease in resting motor threshold, 16% decrease in active motor threshold, and 42% increase in MEP amplitude of the untrained muscle.

In addition to examining the mechanism behind CE, research should examine the clinical significance of this phenomenon. Does training one limb contribute sufficient neural and muscular improvements in the opposite limb to a point that is functionally or clinically meaningful?

A Model of Cross-education of Strength in the Upper Limbs

LEVEL 1: Motor Planning (Input to M1)

BEFORE TRAINING **Dominant** and **Nondominant** limbs have access to the same information at this level -Task requirements (target muscles involved, postural requirements, body position) -Related motor programs, prior knowledge or general experience with strength movements if any -Familiarization trials (use feedback)	***AFTER DOMINANT TRAINING*** **Dominant Limb** -Task has been mastered, movement knowledge (memory) -Prior training experience with specific strength movement -Motor plan is optimized **Nondominant Limb** -Uses knowledge of task from dominant limb (memory) -Prior experience with strength movement (dominant limb) -Motor plan is optimized	***PROPOSED MECHANISM OF CROSS-EDUCATION*** -Plasticity in the cortical pathways involved in motor planning input to M1 (*e.g.*, visual cortex, parietal cortex, prefrontal cortex, premotor cortex, supplementary motor area and temporal lobe) ***OUTCOME MEASURES*** -Functional imaging of the whole brain during voluntary execution of the motor task before and after training -Examine cortical activation in both brain hemispheres

LEVEL 2: Motor Command (Output from M1)

BEFORE TRAINING **Dominant Limb** -*Maximal or near maximal* neural drive -Good coordination of agonist and antagonist, synergist and stabilizer muscles -Good postural control **Nondominant Limb** -*Submaximal* neural drive -Poor coordination of agonist and antagonist, and synergist and stabilizer muscles -Sub-optimal postural control	***AFTER DOMINANT TRAINING*** **Dominant Limb** -Enhanced neural processing in M1 and increased neural drive -*Optimal* coordination of agonist and antagonist, and synergist and stabilizer muscles, optimal postural control **Nondominant Limb** -Enhanced neural processing in M1 and increased neural drive -*Improved* coordination of agonist and antagonist, and synergist and stabilizer muscles, improved postural control	***PROPOSED MECHANISM OF CROSS-EDUCATION*** -Plasticity in M1 including increased activation and enhanced coordination of neural drive during voluntary execution of the strength task -Output of M1 during unilateral movement is increased due to reduced interhemispheric inhibition. ***OUTCOME MEASURES*** -Map area of M1 activation via functional imaging -TMS: interhemispheric inhibition, excitability of M1 -EMG and twitch interpolation to examine muscle activation -Before and after training for each limb

LEVEL 3: Peripheral Muscles

BEFORE TRAINING -**Dominant Limb** is similar or slightly larger in size than **Non-dominant Limb**	***AFTER DOMINANT TRAINING*** -Muscle hypertrophy has occurred in the **Dominant Limb** -The muscles of the **Nondominant Limb** are unaltered and smaller than the dominant limb.	***OUTCOME MEASURES*** -Muscle size should be measured in both limbs -Comparing muscle size of the limbs at baseline is important to understand the origin of strength asymmetry -Changes in muscle size of either limb impact strength

Output: Force or Strength

BEFORE TRAINING -Force produced by the **Dominant Limb** is closer to the max potential and likely exceeds the force produced by the **Non-dominant limb**	***AFTER DOMINANT TRAINING*** **Dominant Limb** -Strength has increased and is at *max* potential -Relative strength increase is smaller than the Nondominant limb due to a ceiling effect **Non-dominant Limb** -Strength has increased and is *near max* potential -No muscle hypertrophy, therefore neural adaptation contributes relatively more to strength increase	***OUTCOME MEASURES*** -The increase in strength of the untrained limb is the primary outcome measure that defines cross-education of strength -Relative and absolute changes in strength should be examined and the magnitude of change compared between limbs

Figure 5. A model of cross-education of the upper limb (retrieved from Farthing, 2009)

2.7.2 Cross-Education and MS

Impairments in MS differ from those following a stroke. Central impairments in MS are caused by a decreased neural drive to the muscle, resulting in failure defined by force capability and reduced muscle recruitment and neural transmission (Larson et al., 2013). Even though impairments are caused by the CNS, they often exhibit lateral imbalances. A study assessing the ambulation and gait of individuals with MS found statistically significant bilateral differences in leg strength and performance (Larson et al., 2013). These laterality differences are similar to stroke survivors and can lead researchers to believe that CE could also benefit PwMS. To date, there is little evidence of CE and MS rehabilitation, but the little research that does exist is promising. Manca et al., 2017, found that resistance training of the dorsiflexors for six weeks improved in the contralateral limb as effectively as direct training, with strength retained at the 12-week follow-up. If the limb is too compromised to undergo direct training, contralateral or indirect training may be a viable alternative. It was estimated that the neurophysiological adaptations of CE occurred between four and six weeks of training, whereas for the direct training group significant improvements were observed mid-way through the intervention at week three. This has also been documented for healthy individuals this has been noted around the three-week mark from the beginning of training (Enoka, 1997).

2.8 Summarized Research Gaps

MS remains an incurable disease and there remains a need for new, innovative rehabilitation techniques that are essential to improve the quality of life for those living with the disease. Robotics offer an individualized and adaptive approach to the rehabilitation process. Adaptive assistive technology has been well explored and a need for exploration of a resistive approach that encompasses the benefits of strength training and skill acquisition, capitalizing on the repetitive nature to induce neuroplastic changes should be considered. Lastly, given the bilateral asymmetries associated with symptoms of MS, and the limited existing literature, CE should be explored as a rehabilitative option whereby directly training a paretic or more symptomatic limb is not viable.

Chapter 3 – Wristful thinking: Exploiting the effects of robotic rehabilitation and cross-education for persons with multiple sclerosis

3.1 Purpose

The purpose of this dissertation was to examine the effects of an adaptive upper limb robotic training program on clinical and functional outcomes in both the trained and untrained limbs of PwMS. As a result, this work will provide further evidence for the use of adaptive upper limb robotics, will examine cross-education, and will explore how these combined, robotic, and cross-education approaches might influence clinical and functional outcomes in PwMS. A summary of the dissertation design is outlined in Figure 6.

3.2 Objectives

This project had five objectives, which were addressed by conducting a literature review, developing a robotic training intervention and conducting one longitudinal research design:

1) Conduct a comprehensive review of existing literature on robotic rehabilitation for multiple sclerosis (MS) and strength adaptations to critically analyze robot prescription, training frequency, and adaptable algorithms.
2) Develop an adaptive training program using a novel haptic robot as the primary treatment modality. The program was exercise based with an adaptive force individually tailored to each participant throughout the sessions to maximize progressive training overload principles.
3) Complete an eight-week training intervention for PwMS using the adaptive program developed in Objective 2, to investigate adaptations in strength, motor control and function of the upper limb with pre, post and follow-up assessments.

4) Evaluate any evidence of cross-education or adaptations of strength and motor control in the contralateral/untrained limb following the 8-week training intervention for PwMS.
5) Complete a four-week training intervention with similar goals as the primary eight-week intervention. This work will contribute to the evaluation of optimal robotic rehabilitation training time for PwMS.

3.3 Hypotheses

1. Adaptations in strength will occur in the trained and untrained limbs in the MS groups following an eight-week adaptive training program.
2. Increases in corticospinal excitability will occur following the training program as evidenced from TMS measures (MEP amplitude).
3. MS participants will improve in robotic based performance measures (tracking error, active ROM) and clinical evaluations (ABILHAND questionnaire) in the trained and untrained limb following the eight-week adaptive training program.
4. Participants will increase in strength and motor control in both limbs following four-weeks of robotic training and will report evidence of cross-education.
5. The control group will improve in strength and robotic measures and will serve as healthy baseline for new novel robotic assessments.

It should be emphasised that human data collection for this thesis included one eight-week pre/post study design and one four-week pre/post intervention. The development of the adaptive robotic training program is presented in Chapter 5. The data analysis and results of an eight-week intervention is presented across three manuscripts (Chapters 6-8), each with a particular focus. Chapters 9 evaluates the effectiveness of a second longitudinal study involving a four-week intervention.

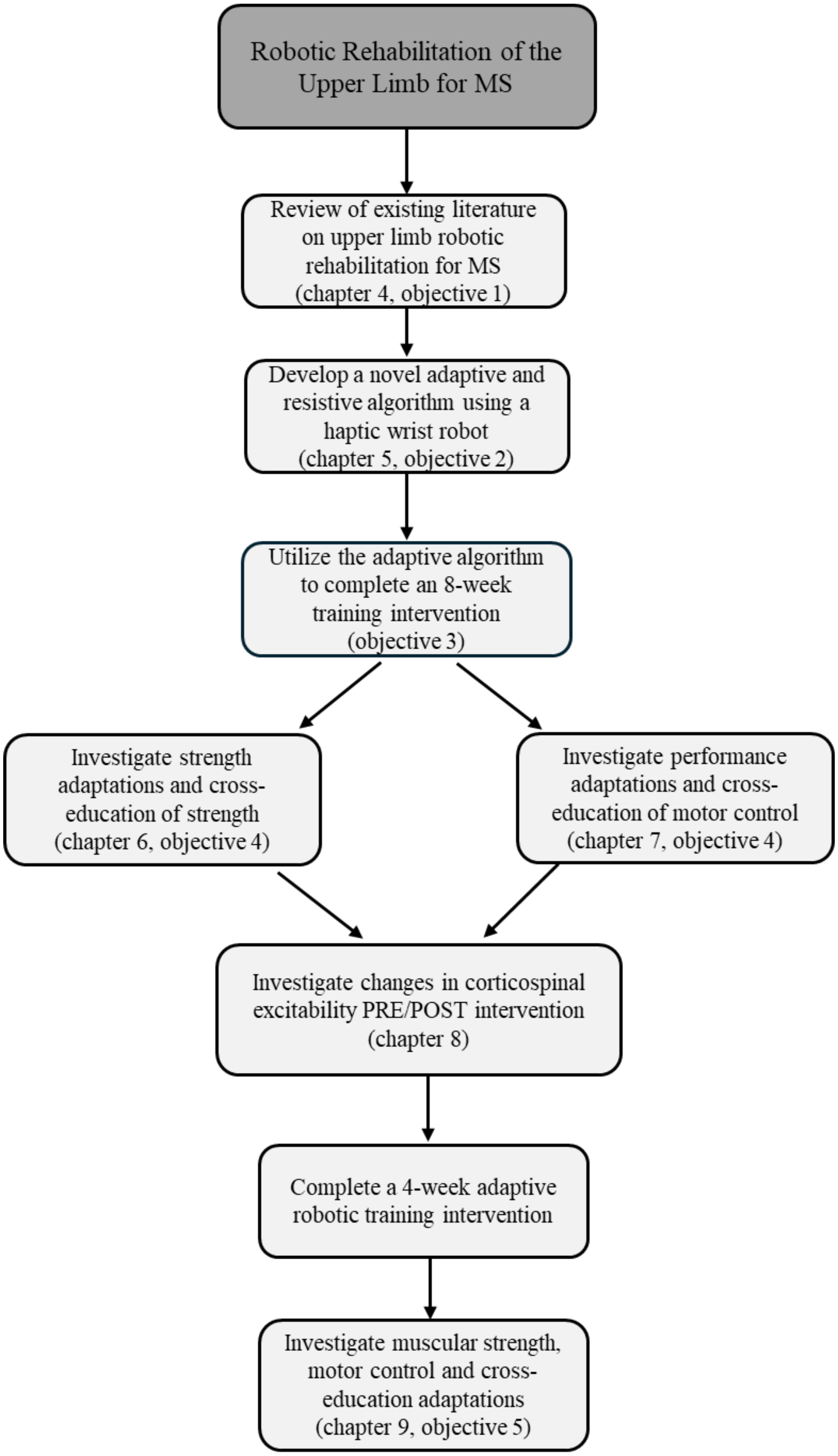

Figure 6. Summary of thesis design and development

Chapter 4 – Muscular Strength Adaptations Following a Robotic Training Program: A Scoping Review

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Abstract

Muscular weakness and loss of motor function are common symptoms of multiple sclerosis. Robotic rehabilitation can improve sensorimotor function and motor control in this population. However, many studies using robotics for rehabilitation have overlooked changes in muscular strength, despite research demonstrating its utility in combating functional impairments. The purpose of this scoping review was to critically examine changes in muscular strength following robotic rehabilitation interventions for individuals with multiple sclerosis. A literature search of five databases was conducted and search terms included a combination of three primary terms: robotic rehabilitation/training, muscular strength, and multiple sclerosis. Thirty-one articles were found, and following inclusion criteria, 5 remained for further investigation. Although muscular strength was not the primary targeted outcome of the training for any of the included articles, increases in muscular strength were present in most of the studies suggesting that robotic therapy with a resistive load can be an effective alternative to resistance training for increasing muscular strength. Outcome measures of isometric knee-extensor force (kg) (right: $p < 0.05$, left: $p < 0.05$), isometric knee flexion and extension torque (Nm) ($p < 0.05$), ankle dorsiflexion and plantarflexion torque (Nm) (all $p < 0.05$) and handgrip force (kg) ($p < 0.05$) all improved following a robotic training intervention. These adaptations occurred with sustained low resistive loads of hand grip or during gait training. This scoping review concludes that, despite a lack of studies focusing on strength, there is evidence robotics is a useful modality to improve muscular strength in

combination with motor control and neuromotor improvements. A call for more studies to document changes in strength during robotic rehabilitation protocols is warranted.

Keywords: multiple sclerosis, rehabilitation, robotics, neurorehabilitation, strength

Introduction

Multiple sclerosis (MS) is a demyelinating and neurodegenerative disease of the central nervous system. It is estimated that every 5 min someone is diagnosed with MS globally (1). Despite the unpredictable and varying symptoms of the disease, one of the most clinically relevant and common complaints in this population is muscular weakness and loss of motor function (2). In most cases, rudimentary tasks such as bathing and feeding become increasingly more difficult. Approximately 45% of individuals with MS report loss of motor function within the first month of diagnosis and 90% report motor disability within the first year (3). Muscular strength can be defined as the maximum voluntary force produced against an external resistance (4). Decreased motor function contributes to strength decrements in individuals with MS. In addition, those with MS often demonstrate muscle atrophy via denervation, leading to muscle morphological changes which can contribute to reduced muscular strength and overall functional impairments (5). Decreased force capability can lead to muscle weakness and affects motor or muscle performance (6). Robotic rehabilitation is a relatively novel rehabilitative tool for MS, but the literature demonstrates robotics can be effective for improving motor capabilities (7). Although there is a gap in the literature on the effects of strength training and functional outcomes, muscle weakness is a classic symptom of MS and there is evidence to suggest reductions in strength are associated with gait dysfunction, overall fatigue and increased disability (8). This knowledge leads to a hypothesis that reversing these effects with strength training may be important to improve gait and abilities of the upper limbs. Resistance training has been documented to improve overall muscular strength in MS by up to 11.6% following resistive exercise training 23 times per week for a range of 8-20 consecutive weeks (9). However, typical heavy load training or conventional resistance training may not be optimized or safely completed due to immobility and motor impairments of the disease.

Robotics can provide assist-as-needed algorithms, giving the user sufficient support to complete a task that may otherwise be unsuccessful. The high dose of repetitive movements applied with robotics show positive results for developing or restoring motor pathways, increasing muscular strength and improving function in MS (10). Neurologically, there are central motor impairments that contribute to muscle weakness (5) and repetitive, low resistance movements exploited with robotics, may contribute to neuromuscular adaptations and improvements in strength rather than increases in muscle size (hypertrophy) (11). In healthy populations, low resistance loads at a high dosage have been shown to elicit mean strength gains of 28% following resistance training programs, as compared to a 35.4% increase in mean strength following 1 repetition maximum training (12). These results support the indication that lighter loads can still elicit increases in muscular strength (12), which may be important for the MS population. Given the current literature, if increased muscular strength is the targeted outcome, low resistance loads with a high volume would be conducive to reduce the risk of injury and increase overall muscular strength. This is a novel topic that has yet to be exploited in rehabilitation interventions.

This research is important to the field because improvements in strength may provide the foundation for individuals to relearn functional tasks. The literature surrounding robotic rehabilitation for MS focuses primarily on motor control and performance measures, with improvements in muscular strength largely disregarded. Despite evidence that robotic devices are a beneficial and well-tolerated rehabilitative modality for inducing neuromuscular strength adaptations and that an increase in muscular performance can contribute to overall functional impairments (11), current systematic and scoping reviews have omitted to report on outcome measures surrounding grip force or muscular strength assessments (13, 14). Therefore, the purpose of this scoping review was to critically examine the literature to gain insight into adaptations in muscular strength following robotic rehabilitation interventions for individuals with MS. Interpretation of the findings will be critical within the broader context of MS because improved strength could mean delayed fatigue impairments, which could translate to task performance as well as optimal motor learning and rehabilitation.

Methodology

This study was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (15) and registered with PROSPERO, an international database of prospectively registered reviews (April 14, 2021; ID CRD42021246486).

Search strategy

Searches were conducted from six databases: MEDLINE, Ovid Healthstar, Cochrane Database of Systematic Reviews, Embase, Web of Science and CINAHL. The following search strings and keywords were used to carry out the search: multiple sclerosis OR (multiple sclerosis AND chronic progressive OR relapsing-remitting) AND robotic rehabilitation OR (robotics AND exercise therapy OR resistance training OR endurance training OR neurological rehabilitation) AND muscle strength OR (muscle contraction OR isometric contraction OR isotonic contraction). Search strategies were completed with the assistance of the institutional Librarian services and all database searches were completed on the same day (March 31, 2021).

Eligibility Criteria

Eligibility criteria included peer-reviewed journal publications or conference proceedings that have been published in the last 20 years. Randomized controlled trials, controlled studies, cohort studies, case control studies, pilot studies and case series/case reports were included in the search. Studies were considered if they included participants with MS (any level/progression of disease) and used robotic rehabilitation (upper or lower extremity) for a minimum of 3 training sessions/days. Articles were excluded that did not directly measure muscular strength. For the purpose of this search, muscular strength was defined as a measurement of maximal voluntary isometric contraction (MVC) and the maximum force produced against an external resistance (4). Exclusion criteria comprised of books, editorials, dissertations, or if the article was not published in English. Studies were further excluded if the following were not included: outcomes (strength measures), intervention (robotic training), or based on study design (minimum of 3 training days).

Methodological Approach

All database searches were completed by a single researcher, followed by a double-blinded screening from two researchers. Articles that met the search terms within each database were extracted and collated into Covidence (Veritas Health Innovation, Melbourne, Australia). After removing duplicates, title/abstract screening was completed using the inclusion/exclusion criteria independently by two researchers. Following this initial screen, all qualifying articles underwent full-text screening using the same inclusion/exclusion criteria by the same researchers as the primary screening. Conflicts regarding inclusion/exclusion were resolved by a meeting between these two researchers until all disagreements were settled. A PRISMA flow diagram outlines the search strategy in Figure 1.

Assessment of Methodological Quality and Risk of Bias

Methodological quality of the included studies was assessed with the Downs and Black Quality Checklist (16) and risk of bias assessment using Cochrane Handbook for Systematic Reviews of Interventions (17). The modifications to the original Downs and Black Quality Checklist included 16 items from the checklist that were relevant to this specific review (Table 1). Risk of bias assessment was based on bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result (Table 2).

Results

Search

The literature search resulted in a total of 31 articles: 6 (MEDLINE), 6 (Ovid Healthstar), 2 (Cochrane Database of Systematic Reviews), 17 (Embase). After duplications were removed and articles were screened for inclusion criteria, 5 articles were included for extraction and included pilot studies (n = 2), randomized controlled trials (n = 2) and controlled trials (n = 1). Data extraction included study subject size, duration of interventions, outcome measures of strength during baseline, post intervention and follow-up. Robotic training targeted the upper limb/reaching tasks (n = 2) and lower body/gait training (n = 3); upper limb focused training was unilateral training whereas the lower limb studies were primarily gait training interventions with bilateral exercises. Of the studies included, 3 reported MS phenotype which included participants with relapsing-remitting, primary progressive and secondary progressive MS, the remaining 2 studies did not report disease phenotype. Sample sizes ranged from 6 to 20 participants with a mean sample size of 12.7 ± 5.2. Expanded Disability Status Scale (EDSS) scores ranged from 6.0 to 8.0 and a disease duration ranging from 15 to 25 years. Number of training sessions ranged from 5 to 24 total active sessions with an average duration of 38.3 ± 11.0 minutes per session. Table 3 provides an overview of each study included in this review and Table 4 represents an article summary from the data extraction.

Unilateral Upper Limb Robotic Training

The Haptic Master was used for robot-mediated upper limb rehabilitation training. In combination with I-TRAVL it allows for reaching tasks within a 3-dimensional workspace. Gravity compensation at the hand and elbow are individualized and allow for stabilized endpositions to aid the participant to a successful completion of the task. In both studies using the Haptic Master, participants underwent 30-minutes of task-oriented nd dynamic movement training (10, 11). Specific outcomes and interventions of each study are reported in the article summary (Table 4). Handgrip force (kg) significantly increased in one of the two upper limb studies ($p < 0.05$), following a robotic training intervention between baseline and post training, and perceived strength (visual analog scale—$p < 0.05$) also significantly increased (22).

Bilateral Lower Limb/Gait Robotic Training

The Lokomat system was used for the objective of robotic gait training. The Lokomat system was used as body weight supported orthosis and required extension and flexion of muscles of the hip and knee joints. This robotic rehabilitation also includes an interactive component inducing feedback-controlled training. In both studies using the Lokomat, leg movements were assisted by the robotic device with a preprogrammed physiological gait pattern. Body-weight support assistance was reduced as a progression throughout the training. Mean knee- extensor force increased by 3.5 and 3.3kg for right and left side, respectively (right: $p < 0.05$ left: $p < 0.05$)

(18); knee and hip flexion and extension torque increased by 7.1 and 3.7Nm, respectively ($p < 0.05$) (21). The IntelliStretch was implemented to investigate ankle sensorimotor function in individuals with MS. The IntelliStretch is an ankle rehabilitative robot with controlled passive stretching and active movement. This robotic device also incorporates a computer game interface for feedback-control and participant engagement. The training program consisted of concentric and eccentric contraction of the dorsi and plantar flexors with a combination of passive and active stretching. Ankle dorsiflexion and plantarflexion torque increased by 11.4 and 10.7 Nm (all $p = 0.028$) (20).

Discussion

The primary objective of this scoping literature review was to explore muscular strength adaptations following a robotic training program for a MS population, a novel topic in robotic rehabilitation research. The current literature appears to focus on the efficacy of robotics as a rehabilitation modality in respect to motor training and proprioception rather than strength outcomes, despite existing knowledge that muscular strength can be beneficial to one's quality of life (23). The overall purpose of improving strength is often to improve function, but adequate strength is fundamental for task success. Results of this review suggest that robotic rehabilitation can lead to strength adaptions following a robotic training program in both the upper and lower limbs. Regardless of the low resistance and a variety of dosage protocols in these studies, strength increases were still observed in this population. Despite a lack of studies focusing on strength included in this review, there is evidence robotics is a useful modality to improve muscular strength in combination with motor control and neuromotor improvements. A call for more studies to document changes in strength during robotic rehabilitation protocols and more care for effects on MS phenotype is warranted.

TABLE 1 | Article quality assessment using Downs and Black checklist.

Included Article	1	2	3	4	6	7	9	10	11	12	17	18	20	21	23	26	Total
Beer et al. (18)	1	1	1	1	1	1	1	1	U	1	1	1	1	0	1	1	16
Feys et al. (19)	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	U	13
Lee et al. (20)	1	1	1	1	1	1	1	1	U	U	0	1	1	U	0	1	11
Lyp et al. (21)	1	1	1	1	1	1	1	1	U	U	1	1	1	U	U	1	12
Maris et al. (22)	1	1	1	1	1	1	0	1	U	0	1	1	1	U	0	1	11

1, "yes"; 0, "no"; U, "unable to determine".

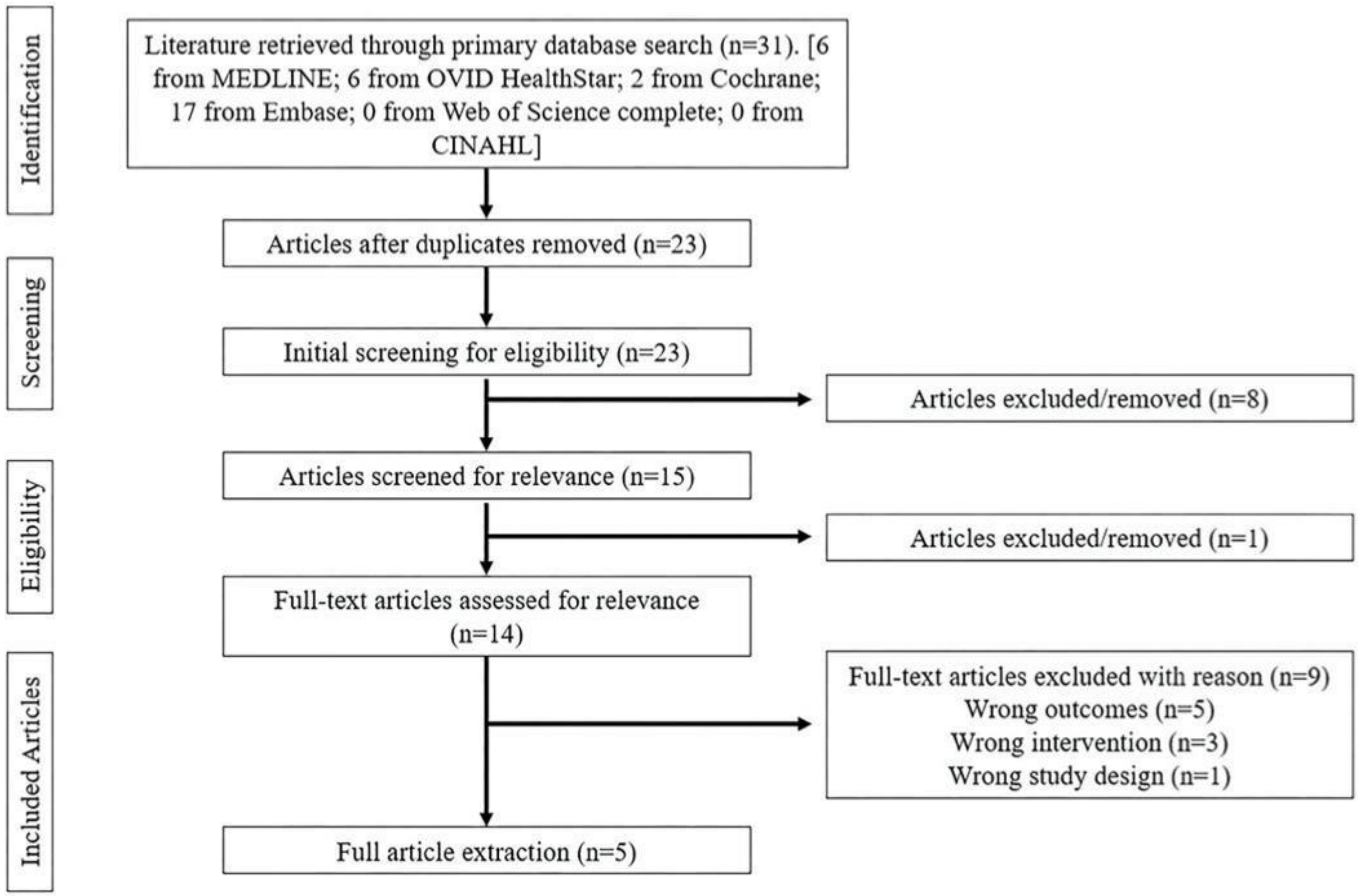

FIGURE 1 | PRISMA flow-chart of literature search strategy and results.

TABLE 2 | Risk of bias assessment using Cochrane Handbook for Systematic Reviews of Interventions.

Included Article	Bias Domain 1	2	3	4	5	Overall
Beer et al. (18)	L	L	L	L	L	L
Feys et al. (19)	L	L	L	L	L	L
Lee et al. (20)	L	L	L	L	L	L
Lyp et al. (21)	L	L	L	S	L	S
Maris et al. (22)	L	L	L	L	L	L

L, "low risk"; H, "high risk"; S, "some concerns".

Bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, (5) bias in selection of the reported result.

TABLE 3 | Summary of extracted articles included in this re.

Study	Aim of Study		*n*	EDSS	Disease duration (years)	Type of MS (RR/SP/PP)
Beer et al. (18)	To evaluate feasibility and perform an explanatory analysis of the efficacy of robotic gait training in MS patients with severe walking disabilities.	Exp Con	14 15	6.0-7.5	15 ± 8	RR: 2 SP: 8 PP: 9
Lyp et al. (21)	To examine the effect of a robot-assisted body weight supported treadmill training on the walking ability of MS patients with impaired gait.	Exp Con	20 0	NR	NR	RR: 7 SP: 0 PP: 13
Lee et al. (20)	To perform and evaluate the efficacy of a 6-week robot-assisted training program for the treatment of ankle sensorimotor function in MS patients with lower limb impairments.	Exp Con	6 0	5.2 ± 2.5	16.0 ± 6.5	NR
Feys et al. (19)	To investigate the effects of additional robot-supported upper limb training in persons with MS compared to conventional treatment only.	Exp Con	17 0	8.0	25	NR
Maris et al. (22)	To investigate proof-of-concept efficacy of an individualized, robot-mediated training regime for people with MS and stroke patients.	Exp Con	13 0	6.5	17	RR: 5 SP: 6 PP: 2

TABLE 4 | Detailed data extraction from included articles.

Study	Robotic device	Days/ week	Session (n)	Session duration (min)	Strength measure	Baseline results (mean ± SD)	Post-intervention Results	Effect size (Cohen's D)	Follow-up results
Beer et al. (18)	Lokomat	5	15	60	Knee-extensor strength—right/left (kg)	Right: 15.9 ± 7.5 Left: 13.6 ± 6.3	Right: 19.4 ± 7.5 Left: 16.9 ± 6.4	0.47 0.52	6-month: Results returned to baseline
Lyp et al. (21)	Lokomat	2	12	35	Flexion/extension muscles of the hip and knee joints (torque, Nm)	NR	Δ Torque 3.68±1.64 – 7.06 ± 1.95	NR	No follow-up
Lee et al. (20)	Intellistretch	3	18	45	Dorsiflexion and plantarflexion MVC (Nm)	Dorsiflexion: 0.73 ± 12.72 Plantarflexion: 24.27 ± 9.89	Dorsiflexion: 12.08 ± 11.67 Plantarflexion: 34.97 ± 8.01	0.93 1.26	6-week: Dorsiflexion: 9.36 ± 11.69 Plantarflexion: 32.82 ± 0.49
Feys et al. (19)	Haptic Master	3	24	30	Handgrip strength (kg)	21.3±12.0	21.0±10.7	0.02	No follow-up
Maris et al. (22)	Haptic Master with I-TRAVLE	5	10	30	Handgrip strength (kg) Perceived strength (VAS)	Handgrip: 13.2 ± 9.1 VAS: 3.9 ± 3.0	Handgrip: 14.8 ± 1 VAS: 7.4 ± 5.1	0.15	3-month: Improved from baseline (p's = <0.05)

Intervention volume, pre- post-intervention strength measurement results and effect size are reported. VAS; visual analog scale, NR; not reported.

Muscular Strength Adaptations

Although muscular strength was not the targeted outcome of the training in the included studies, increases in maximal contractions were present in most of the studies and illuminate the benefits of using robotics as a rehabilitation modality. Included studies with a focus on the upper limb showed increases in handgrip force through sustained end-effector manipulation. These muscular strength adaptations were supplementary to the goal of the intervention and occurred as a result of the training. Regardless of the mechanism behind the improvements in grip force, handgrip strength can be an important predictor and component of basic activities of daily living (22). For training interventions focused on the lower limb, voluntary eccentric muscle contraction of the quadriceps, and increased knee joint moment was required that, in turn, improved neuromuscular control and gait patterns, resulting in increased muscular strength compared to conventional gait support training (18, 21). None of the selected studies reported on training volume (i.e., number of repetitions, sets or training load) and only reported on the duration and frequency of the training sessions (Table 4). There is basis for improvement for future studies to report such information as training volume is critical when participating in conventional resistance training and is suggested to be of importance for rehabilitation as well (12). Due to low load requirements for MS, increased volume is necessary to increase strength. As such, the premise behind robotic therapy is to use a high volume of repetitions with minimal resistance added to the robotic device or acting against the participant's voluntary movements. It is plausible that the low loads exerted during gripping of the device or the eccentric movement of the quadriceps at a high dosage elicited adaptations in muscular strength in the studies included in this review. This theoretical speculation is based on evidence in healthy populations, proving that resistance training at low loads and a high dosage can still provoke strength gains (16). The work investigated here did not report changes in muscle size (hypertrophy), so it can only be speculated that the mechanisms of strength changes are from neural adaptations. This could be a deconditioning effect; all studies included were acute resistance trained (<12 weeks in duration) and likely, participants were not highly resistance trained prior to the intervention. With acute resistance training, there is often little to no change in muscle mass but still a greater max torque is produced (21). This is caused by neural adaptations as opposed to chronic resistance training whereby there is a larger increase in muscle mass and a smaller change in neural adaptations over time (24).

Frequency of Interventions

In general, a consensus on proper therapy dosage and a link between total therapy time and strength outcomes is lacking in the MS literature. The studies included had therapy session frequencies ranging from 2 to 5 days, with total sessions completed ranging from 3 to 24 and duration times of 30– 60min. Typically, 8-week studies are chosen and are based on previous literature of non-robotic exercise focused studies (exercise/resistance training) (20, 23) and previous robotic literature (24, 25). However, only one study included in this review utilized an 8-week duration (19). All studies included in this review had time-dependent sessions as compared to repetition-dependent and omitted any resistance progressions throughout the therapy protocol despite knowledge that progression guidelines exist in the literature for resistance and cardiovascular exercise (6). Future work is necessary to develop guidelines for robotic therapy that are based on individual characteristics such as severity of disease, age, joint angle range of motion and progressions that clinicians can refer to like the physical activity guidelines that exist (26). If these general fitness principles are incorporated, the changes noted in strength following robotic rehabilitation may be even more apparent.

MS Phenotype

There is clinical importance in individualizing rehabilitative treatment according to MS phenotype as symptoms, impairments and rehabilitative responses may differ between relapsing remittent, primary progressive and secondary progressive MS. Three of the five included studies (18, 21, 22) reported MS phenotype of their participants however, all neglected to categorize the results according to disease impairment. For example, it is unknown based on these findings if individuals with differing phenotypes or EDSS scores benefit from this rehabilitative modality.

Beer et al. (18) included participants with severe walking impairments only (EDSS 6.0- 7.5) and report improvements in knee-extensor strength post- intervention (Table 4). It is suggested that future studies consider MS phenotype as response to treatment can be affected by disease progression. It is important to note that no studies reported adverse effects to the training protocols. Thus, this therapy modality is well tolerated by individuals with MS.

Upper Limb vs. Lower Limb

Robotics used in the included studies have examined clinical uses for both upper and lower limb rehabilitation. Lower limb robotic devices focused primarily on improving gait and mobility, and upper extremity robotics focused on tasks that require reaching and grasping, both are common movements affected by symptoms of MS and critical in everyday lives. In this review, three studies examined robotics for the lower limb and two studies examined robotics for the upper limb. One out of the two studies focusing on the upper limb did not show significant improvements in muscular strength and because of the lack of focus on handgrip force during the training, perceived fatigue and the inability to complete the task overpowered any potential improvements in strength outcomes (19, 22). Conversely, all studies of the lower limb reported improvements in muscular force and torque production following the intervention/training program. All studies with an upper or lower limb focus are limited by lack of progression overload and protocol individualization. Though, all studies showed significant improvements in most of their primary measures aside from muscular strength, including motor performance and accuracy.

Limitations

There are a few limitations to this review that should be considered. Firstly, only five studies met the criteria for full- text analysis. Therefore, results are limited, and further work is necessary in this field. However, given the documented important link between muscle strength and daily function, this should highlight a call for more work in the area. Secondly, the included studies failed to report any rationale for the prescribed intervention including therapy dosage, frequency or load. This is a gap in robotic rehabilitative literature whereby intervention guidelines should be developed so clinicians know how long and how often they should prescribe robotic therapy to their clients. Lastly, none of the included studies considered MS phenotype or how response to treatment differs depending on level of disability or disease progression. There is not enough research in this field to yet identify this. For future work, this is necessary to investigate given that MS has a wide range of debilitating symptoms according to level of disability.

Conclusion

The purpose of this scoping review was to critically examine changes in muscular strength following robotic rehabilitation interventions for individuals with MS. The current literature appears to have a focus on the effectiveness of robotic training comparative to conventional therapy, with strength outcomes acting as a secondary analysis. Targeted outcomes of the training were focused on motor performance but increases in muscular strength were present in 3 of the 5 studies and identifies robotics as a beneficial therapy tool for this population for a variety of outcomes. Included studies with a focus on the upper limb showed increases in handgrip force through sustained end- effector manipulation, while robotic interventions for the lower limb forced eccentric movement of the quadriceps, improving neuromuscular control and gait patterns. The premise behind robotic therapy is to utilize a high frequency dosage and this review indicates plausibility that the high repetitions with minimum resistance can stimulate improvements of handgrip force or torque of the quadriceps. Future work is vital to investigate progressions and individualization during a robotic rehabilitation training program to enhance the overall treatment. The low number of included studies in this review highlights the need for more studies to document changes in strength during robotic rehabilitation protocols.

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Chapter 5 – Adaptive algorithm and intervention development

5.1 Introduction

Multiple Sclerosis (MS) is a debilitating disease of the central nervous system that impairs strength and motor function. Despite knowledge that MS causes demyelinating nerve fibres causing disrupted communication between the brain and muscle (Weiner & Stankiewicz, 2012), there is no cure and few non-pharmacologic therapeutic approaches. Most studies to investigate non-pharmacological approaches (such as strength training) have focused on the lower extremity, mobility, and balance (Lee et al., 2017a; Manca et al., 2017). It is astounding that research on the upper extremity is rudimentary, considering upper limb disability is observed in 75% of PwMS (Johansson et al., 2007). As inflammation accumulates in the brain and spinal cord, neurodegeneration and demyelination of pathways affect motor capabilities of the upper limb (Lamers & Feys, 2014). A lack of hand function, dexterity and declining grip strength hinders an individual's ability to perform activities of daily living such as bathing, dressing, and feeding. Upper limb impairments can translate to loss of self-worth, inability to work or play and a dependence on caregivers (Lamers et al., 2015).

In addition to pharmacologic approaches, rehabilitation is critical to maximize and prolong function in PwMS. Numerous studies have demonstrated that resistance training exercise in PwMS can positively influence functional capacity (Lamers & Feys, 2014; Lamers et al., 2016). Evidence suggests that repetitive movement therapy is effective at increasing motor control and muscular strength of the upper limb, stimulating improvements in quality of life and limiting disease burden (Lee et al., 2017a; Manca et al., 2017; Johansson et al., 2007). Recently, robotic devices overall have gained popularity for upper limb rehabilitation as a complement to traditional therapy. Robotics can be advantageous for clinicians, as they provide real-time information during task performance. Robotic training can exploit low resistive loads at high repetitions, a modality known to stimulate neuroplasticity (Gandolfi M. et al., 2018). In addition, robots are a safer modality for severely weakened limbs whereby conventional resistance training may not be optimal (Manca et al., 2017). Assist-as-needed control paradigms have been the most used strategies in robotic rehabilitation as this algorithm can estimate the user's intent and can modify the robot applied forces to enhance active participation in the rehabilitation process (Krebs et al., 2007). In the same fashion, a combination of assistance and resistance have been proven effective for improving performance metrics of the upper limb for MS (Mannella et al., 2021). Less is known surrounding resistive only algorithms although resistive robotics can incorporate the advantageous aspects of resistance training along with motor learning/motor control.

To date, there are few studies focused on the upper extremity and robotics are not exploited to their full potential due to poor implementation of therapeutic progression based on user output. Existing literature has reported increases in strength following robotic rehabilitation despite strength not being the objective or main outcome of the study (Mannella et al., 2022). Additionally, many robotic interventions do not report intensity (number of repetitions or sets) and lack rationale for duration and frequency of the training (Mannella et al., 2022; Lamers et al., 2014). Therefore, the purpose of this work was to address objective 2, to develop a novel, adaptive force training paradigm with a haptic wrist robotic device that follows optimal training principles for PwMS.

5.2 Methods

To assess objective 2 of this dissertation, of exploiting the device for individualized training that improves clinical and functional outcomes, an adaptive algorithm needed to be programmed. The goal was to develop an adaptive algorithm that updated the force/resistance in real-time to allow for individual progressions of force based on performance. For the robotic training sessions, a haptic wrist robot known as the Wristbot was used (ReWing, Genova, Italy) (Iandolo et al., 2019). 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 (<.0001 degrees) 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. Pronation/supination has one motor of 70W, a maximum continuous torque of 2.87Nm and torque constant of 1.09 Nm/A. Abduction/adduction has two motors of 50W, a continuous torque of 3.81Nm and torque constant of 1.53 Nm/A and flexion/extension has one motor of 30W, continuous torque of 1.56Nm and torque constant of 1.44 Nm/A. This allows for visual, auditory and haptic 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.

The training protocol consisted of an eccentric contraction-based exercise to promote increases in strength (Schoenfeld et al., 2021). The eccentric contraction was also chosen to promote cross-education of strength as according to literature reviews by (Manca et al., 2020; Voskuil et al., 2022), studies that performed an eccentric contraction showed increased levels of CE of strength compared to concentric and isometric training protocols. Frequency is described as the number of training days per week. It is recommended that increasing the frequency can increase the rate of CE (Voskuil et al., 2022). Therefore, this work included three training days per week. Eight total weeks of training is proposed based off previous upper limb robotic rehabilitation literature demonstrating that between six-eight weeks of training resulted in the greatest improvements in motor control, performance, or strength (Lamers et al., 2016).

Mean velocity of the target icon, completion time and number or repetitions/sets was standardized across all participants, but the force adaptation as a percentage of the user's maximum voluntary contraction (MVC) was individualized (Table 3). To develop initial force requirements, participants completed one isometric MVCs for each wrist direction of motion (flexion, extension, radial deviation, ulnar deviation) against a force transducer and 40 % of the lowest force value (MVC) in each respective direction was then calculated as Newton-Meters (Nm) using the MVC and participant's hand length (meters) and inputted into the robot algorithm as the starting resistive torque. The program was developed based on a low-intensity, high repetition basis that is typically used in robotic rehabilitation work (Iandolo et al., 2019). Intensity of training is described as the performed level of effort. To promote CE, it is recommended that "high intensities" be performed (Voskuil et al., 2022). For typical resistance training for PwMS, 60-80 % 1RM is recommended for 15 repetitions (Halabchi et al., 2017b). However, it is also suggested that to elicit the CE effect, it is necessary to perform numerous repetitions under tension or force (Farthing & Zehr, 2014). As a compromise between intensity and repetition, and to avoid fatigue, the intensity was set to 40 % MVC, with the opportunity to adapt to 45 % MVC or decrease to a minimum of 38.5 % MVC within the first 3 repetitions if the tracking component of the training was not performed well. Due to the nature of the performed task, it was important that the participant be close to the target (i.e., resist the force to elicit an eccentric contraction) and therefore tracking error was deemed the optimal performance evaluator and determined the force increase or decrease throughout the intervention.

Once the parameters of the protocol were developed, the training had participants track a moving dot visually located on a monitor in front of them as it moved along four directions: flexion (F), extension (E), radial deviation (RD) and ulnar deviation (UD) (Force Training (youtube.com)). Participants accomplished this by moving the end effector handle of the robotic device, which displayed the participant's dot (Figure 7). The robotic resistance for the task was acting against the line of action of the muscle causing an eccentric contraction by means of a virtual spring. The spring had the greatest resistance (our input of individualized 40% MVC) at the initial action of the movement as the task was eccentric, thus, as the spring lengthened the force linearly decreased reaching 0% at the end-point. The stiffness of the spring (F=kx) whereby k of the spring was modulated, and x remained constant therefore, the change in F was proportional to the change of k (dampening was minimum with respect to kx). The participant then concentrically contracted against no resistance and a second repetition was conducted. Participants were instructed to resist the force in a slow and controlled motion as the muscle lengthened towards the target position. This velocity was controlled by tracking the target on the computer screen. There were no forces acting upon the end-effector in the opposing/concentric contraction.

Table 3. Robotic parameters

Duration (min)	25 minutes
Number of sets	5-7
Number of repetitions	16 (per set)
Velocity (°/s)	15 °/s
MVC flexion (Nm)	Reassessed each week
MVC extension (Nm)	Reassessed each week
MVC radial deviation (Nm)	Reassessed each week
MVC ulnar deviation (Nm)	Reassessed each week
Starting resistance	40 % MVC
ROM (% full ROM)	80 % of individual ROM

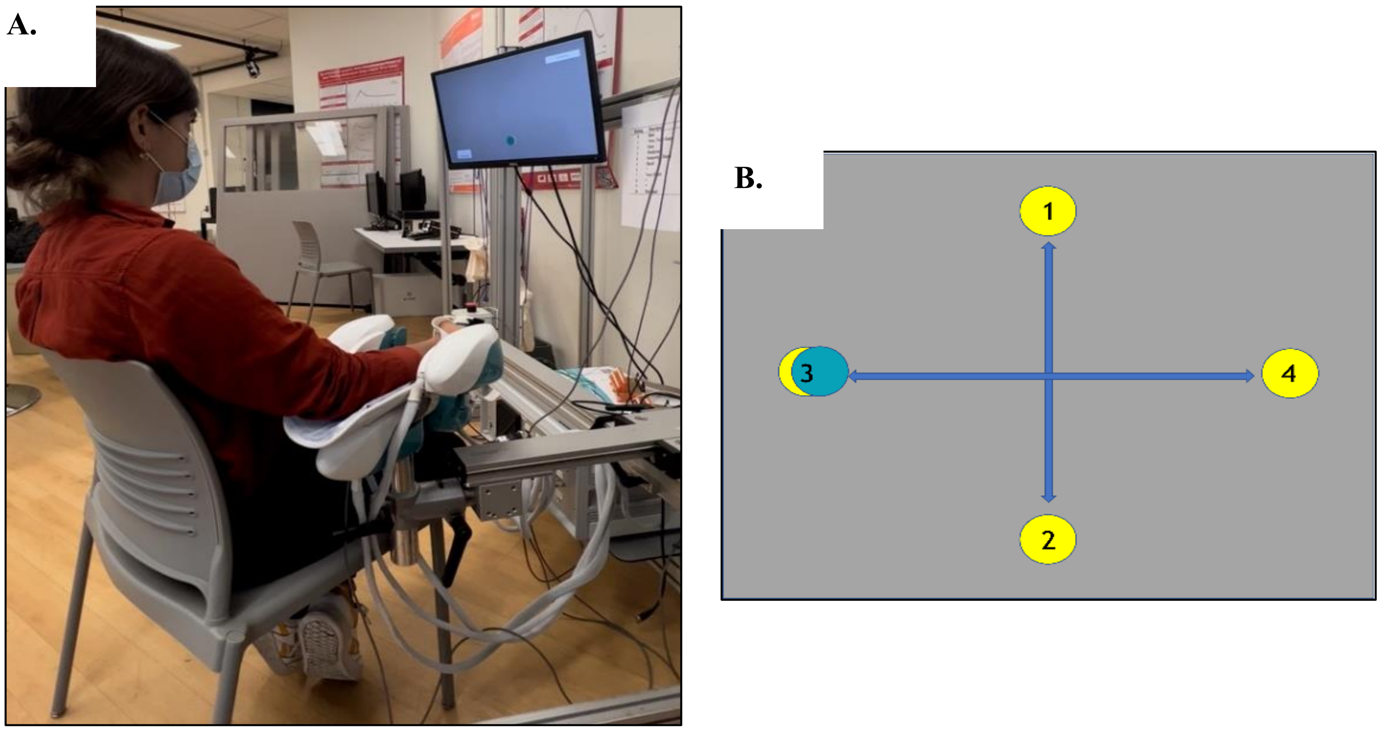


Figure 7. Training session protocol. A) Participant positioned in the robotic device prepared for training. B) The four targets/trajectory of the tracking (flexion/extension, radial/ulnar deviation)

The following addresses details of the adaptive intervention:

- Repetitions – There were four target directions with four repetitions completed per direction, in a randomized order, for a total of 16 repetitions per set. There were five sets in one training session, totaling 80 repetitions in a complete training session. The direction of the targets (F/E/RD/UD) was chosen as they are the main four directions that a human wrist moves in activities of daily living. Pronation and supination motors were locked in a neutral position to isolate F/E/RD/UD.
- Progression of workload – Participants performed five sets in weeks one through four, totalling 80 repetitions in a session. The volume increased to seven sets in weeks five through eight, totalling 112 repetitions per session (Table 4). This progression was done to increase the difficulty of the task as the participant progressed throughout the training.

Table 4. Repetition/sets throughout the intervention

	Repetitions	Sets	Reps per Session	Reps per Week	Total Reps
Weeks 1-4	16	5	80	240	4608
Weeks 5-8	16	7	112	336	

- Total working time –To ensure each participant received the same time under tension, the mean velocity of the target and end-effector remained constant across all participants (15 °/s). Participants had a standardized one-minute of rest between sets. Totalling approximately 25 minutes per training session.
- Mean velocity – The mean velocity began at 15 °/s and remained constant through each training day across the eight weeks. This was chosen based on our previous work whereby the target moved at 20 °/s (Mannella et al., 2021). Here, the task consists of eccentric contractions, so our pilot testing determined that the velocity needed to be slower and

controlled under tension thus, we determined the mean velocity should be 15 °/s. This velocity allows the user to follow the typical tempo of eccentric contractions in traditional resistance training of a three second lengthening phase, two second pause and a one second concentric phase.

5.2.1 Adaptive Force

The force was implemented as a virtual spring pulling the end-effector towards the final point of the trajectory. Based on how well the user was able to track the target object during the single axis motion (calculated as the mean instantaneous distance of the tracking error), the force increased to challenge the participant or decreased to aid the user along the task. Each week the MVCs were reassessed, and the force was adjusted to 40 % of their maximum effort with respective to the four directions (relative to each participant). CSEP guidelines for PwMS indicate that an individual should be resistance training at 10-15 repetitions in a set with a load that one can barely, but safely finish the set (Canadian Society of Exercise Physiology, n.d.). Due to the high volume of repetitions implemented in our training design, a lower force at a low to moderate intensity (40 % of maximum) was chosen.

The force adapted every three targets according to the user's performance (tracking error – Section 5.2.2). Briefly, we assessed how closely the user could track the robot presented dot on the computer screen. If the task was performed with a smaller tracking error than in the previous 3 targets/repetitions, the force increased by 5 %. If tracking error increased in the previous three targets, the force decreased by 2.5 %, which would contribute to making the task easier to execute. It is important to note that the forces were purely resistive forces, there were no assistive forces acting upon the end-effector to help guide the participant. The force was implemented as a virtual spring $(modulation * k * \Delta\theta)$. The end-effector was pushed away from the moving target (causing an eccentric contraction when resisted) according to instantaneous distance $(\Delta\theta)$ and the selected spring stiffness (40 %MVC). For the adaptable force, $modulation$ was adjusted for the previous three repetitions as a computation of tracking error and the force or resistive levels of the previous repetitions and was computed with the following equation:

$$modulation_{new} = modulation_{old} + a * (TE_{last3} - TE_{old}) + b$$

Where TE_{last3} refers to the previous 3 repetitions and TE_{old3} is the error from the previous three repetitions, proceeding the repetitions performed with $modulation_{old}$. a and b are experimental parameters ($a = 5rad^{-1}$ and $b = -0.1$) that managed the changes of $modulation$ in its range variability. Since $modulation$ changes linearly with the changes in tracking error, a and b represented the slope and the intercept of the line, respectively.

The adaptive force equation is as follows:

$$\begin{cases} Force_{j+1} = Force_j + 0.05Force_0 & TE_j < TE_{j-1} \\ Force_{j+1} = Force_j - 0.025Force_0 & TE_j < TE_{j-1} \end{cases}$$

Where $Force_1$ = previous applied force and $Force_0$ = initial force (40 %MVC). j represents each time there is a change of force (e.g., j=1 refers to the 1st time the adaptation algorithm changed in force.

It was expected that performance and therefore applied force would increase throughout the intervention. $Force_0$ was constant throughout the week. $Force_1$ was used as the last force applied from the day before then at the beginning of the following week, MVCs were reassessed, and the $Force_0$ was adjusted accordingly. Mean velocity was set to 15 °/s and remained constant to ensure that time under tension was absolute for each participant.

5.2.2 Tracking Error

Tracking error was used as a measure of performance to determine the adaptive force. Tracking error was defined as the mean angular distance in degrees between end-effector and target position at each time point, represented as the point at the center of the sphere that is visually presented during the training (Albanese et al., 2022) (Figure 8). The instantaneous distance between target and end-effector was summed over the total tracking trial and divided by the total number of samples. Tracking error was computed starting from the data recorded by the encoders along flexion/extension (x[deg]) and radial/ulnar deviation (y[deg]). The measure was given by the following equation:

$$Tracking\ Error = \frac{\sum_{i=1}^{N} \sqrt{\left(x_{T,i} - x_{H,i}\right)^2 + \left(y_{T,i} - y_{H,i}\right)^2}}{N}$$

Where, T,i = is the target at each time sample and H,i = is the end-effector position at each time sample.

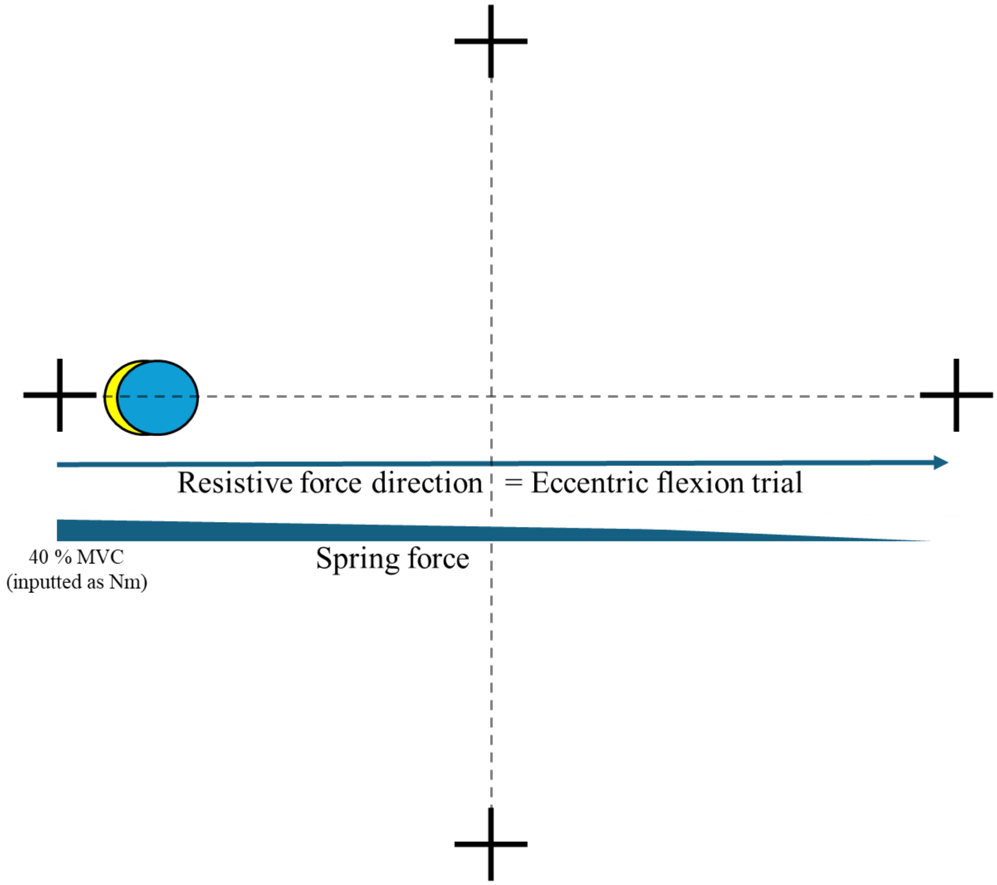


Figure 8. Tracking task example for a right-hand user

*Figural error represents how accurate the user can follow along the (hypothetical) dotted line. Tracking error represents how closely the user (blue dot) can track the target (yellow dot) while resisting the given forces along each direction. The blue bar represents the force of the virtual spring – at 40% MVC at the initial and linearly decreasing towards the end-point of the trajectory.

5.2.3 Training Intervention

A total of 14 individuals with MS and 8 non-MS controls participated in the eight-week training intervention. Detailed group demographics and intervention methods are further outlined in Chapter 6 – section 6.2.1. Strength was assessed on the first training session of each week to determine the initial force (40 %MVC) of the training. Results of strength adaptations across the 8-week robotic training intervention are presented below.

5.3 Results

All 14 participants with MS and the 8 non-MS controls completed the training intervention in its entirety, with no drop-outs or reported adverse affects. These results confirm overall safety of the protocol whereas the reference 40 %MVC and adaptability was well tolerated and executed during the intervention. General trends show a linear increase in strength across the eight-weeks for the MS group (Figure 9) and control group (CON) (Figure 10). Figures 9 and 10 show the group average absolute wrist MVC force (N) across weeks. MVCs were assessed at the first session of each week and results suggest that participants improved in strength across the weeks. Initial force began at 40 %MVC and was calculated as a final torque, indicating that each week, the participant's began at a force (Nm) greater than the previous week. The MS group showed an average percent change in strength per week of 6.59% flexion, 8.5% extension, 8.26% radial and 11.61% ulnar deviation. The CON group showed an average percent change in strength per week of 2.89% flexion, 8.39% extension, 15.96% radial and 6.91% ulnar deviation.

5.3.1 Maximum voluntary contractions across 8-weeks

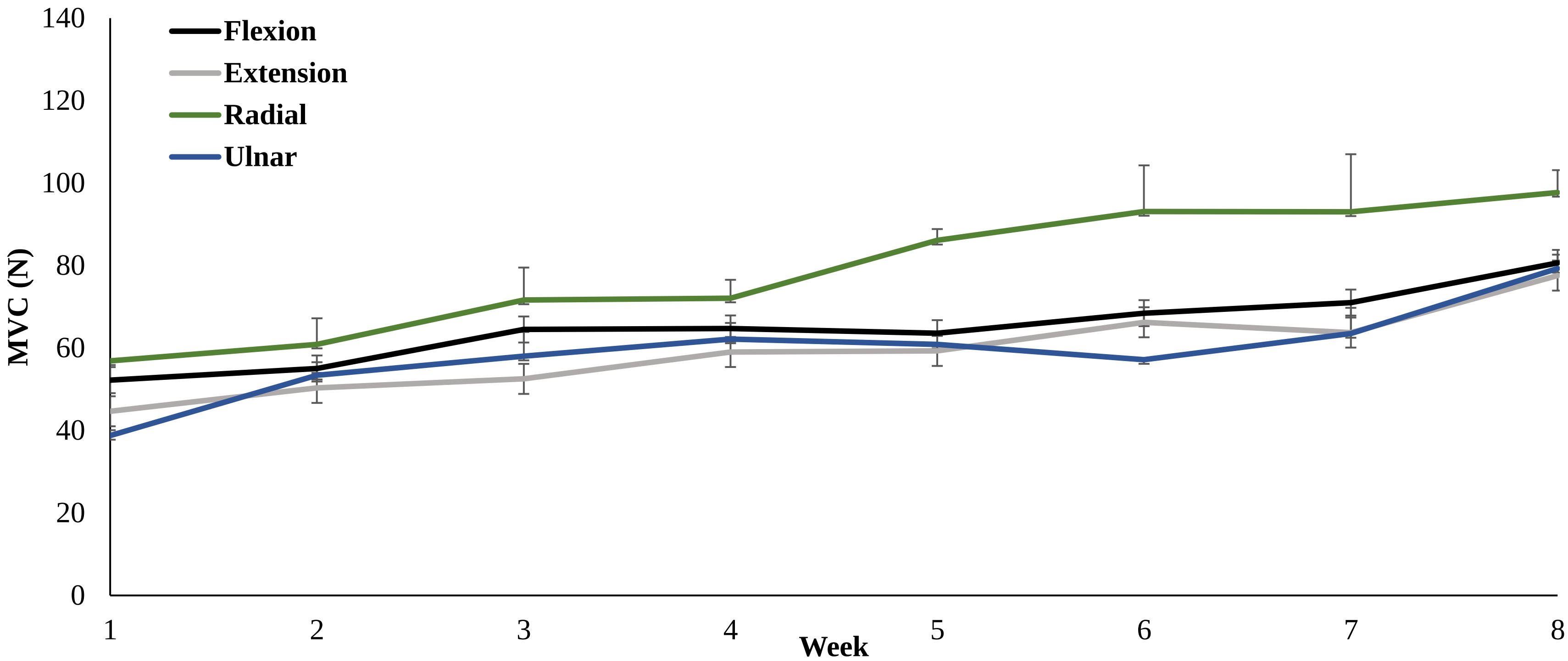


Figure 9. Maximum Voluntary Contraction force of the trained limb averaged across the MS Group - reassessed throughout the 8-weeks. Data are presented as group means and standard error

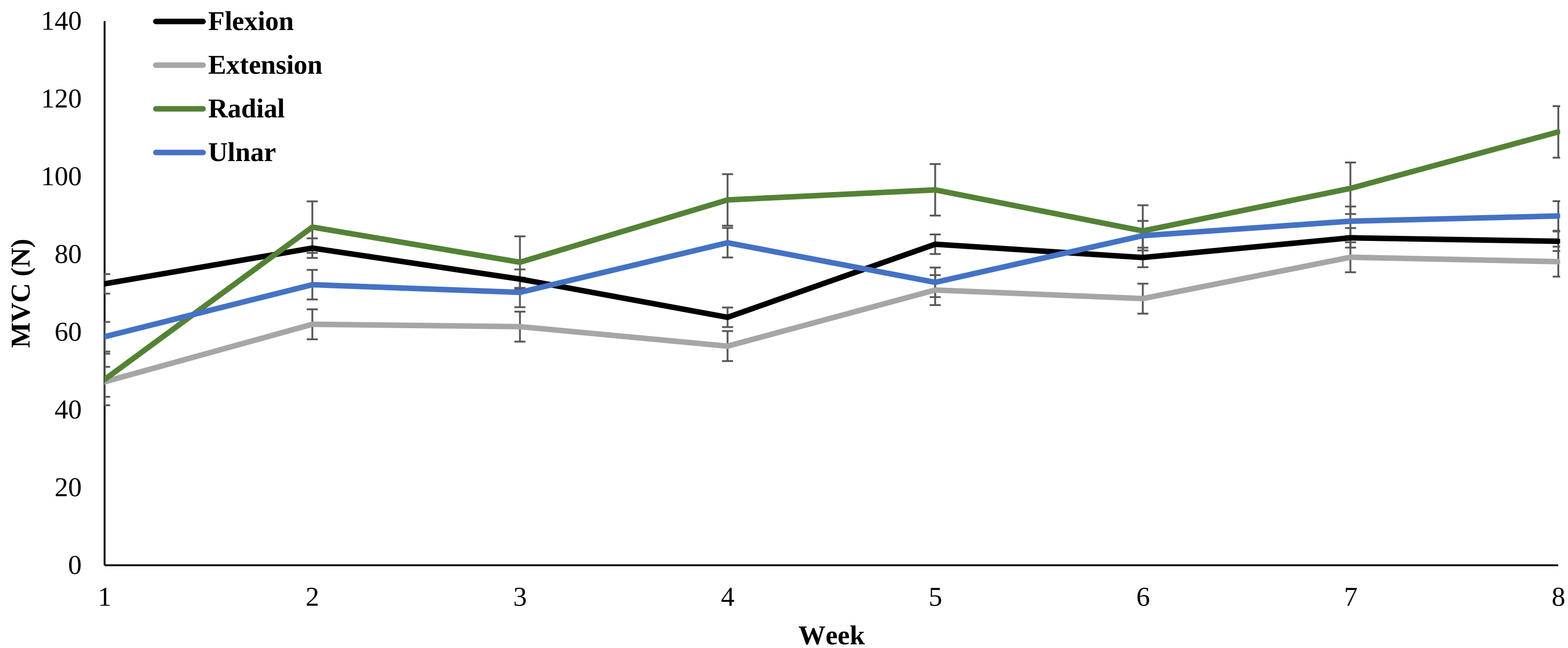


Figure 10. Maximum Voluntary Contraction force of the trained limb averaged across Control Group - reassessed throughout the eight-week. Data are represented as group means and standard error

5.4 Discussion

Within the robotic rehabilitation literature, a call for adaptive algorithms to allow for individual progressions of force based on performance for PwMS in the upper limb was required. As such, the purpose of this work was to utilize a robotic device as a rehabilitation modality for individualized training in a MS population. Results provided proof-of-concept that robotics are an effective tool, when individualized, and can be a useful, integrated modality to a rehabilitation program.

The application of the force adaptation paradigm based on user output/performance allows for personalization as critical for both user safety and enhancing rehabilitative benefits. MS is a complicated disease, whereby one therapeutic approach for all is not optimal. Robotic literature over the past decade have demonstrated various effective ways to implement adaptive algorithms to assist-as-needed, add resistance or assist-only paradigms with differing performance evaluations to adapt these forces. Performance evaluators are defined as the output in performance of the user of the task that allows the device to adapt or alter the assistance or resistance accordingly. Previously, a minimum jerk ratio was implemented as an adjust assist as needed paradigm and this has been proven successful (Xydas & Louca, 2012). Tracking error of angular position has also been used as a performance evaluator (Masia et al., 2009; Vergaro et al., 2010) and figural error has been proven effective in previous work (Mannella et al., 2021). In this work, due to the nature of the performed task, it was important that the subject be close to the target (i.e., resist the force to elicit an eccentric contraction) and therefore tracking error was deemed the optimal performance evaluator and determined the force increase or decrease throughout the intervention. The resistive paradigm in this work was aimed to deliver a low-intensity but high-repetition workload. For typical resistance training for PwMS, 10-15 repetitions for 3 sets per exercise and ranging from 4-10 exercises per day is recommended (Halabchi et al., 2017b). Based on this, the recommended repetitions range from as few as 40 and at most 150 repetitions in total. Therefore, for this work, 16 repetitions per set at a low-intensity (40 %MVC) was chosen to avoid overall central fatigue. With the adaptive component, our approach allowed for the opportunity to increase resistance by 5 % MVC every 3 repetitions. As a result, participants could have reached a working load of up to 65 %MVC. Contrary, if the task was not well tracked, the robot could decrease 2.5 %MVC every 3 repetitions, which could have decreased to a workload as low as 27.5 %MVC in a single set whilst still performing the same total number of repetitions in a total training period (80 repetitions between weeks 1-4 and 112 repetitions between weeks 5-8).

Throughout the eight weeks of training, the MS group improved isometric wrist strength each week (as evaluated at the start of each week to determine individualized 40% values) with no user-reported adverse effects. MS presents with varying symptoms, often bilaterally and can vary from person-to-person but also change daily. The unpredictability of these symptoms has been a documented weakness of robotic devices for rehabilitation with PwMS as recently reported in a SWOT analysis (Albanese et al., 2024). More specifically, spasticity has been reported to pose as a threat or risk to the therapy whilst strapped into, holding on or engaging with an operating robotic device (Albanese et al., 2024). Participants included in this work presented a range of MS phenotypes, severity of disease and years since diagnosis. It is noteworthy that none of the included participants reported any negative interactions with the device, nor did their spasticity or MS related symptoms inhibit or terminate the training. This provides further emphasis that robotic rehabilitation can be beneficial even with a variety of symptoms.

In general, robotic rehabilitation literature lacks guidelines or therapy recommendations for robotic rehab for PwMS of both upper and lower limbs (Chapter 4). Following a systematic review by Lamers et al., 2016, showed that training duration, frequency of training and intensity of training were rarely reported in upper limb rehabilitation studies for MS, and any studies that did report these details lacked any supporting evidence or background reasoning for these choices.

The goal of this work was to transparently deliver a robotic therapy intervention to induce performance and strength gains whilst providing an in-depth rationale for the development of the algorithm and study design. Results provide evidence that three training sessions per week for eight consecutive weeks at the given repetition-to-set ratio was appropriate to achieve changes in wrist strength pre- to post-training. Further adaptations (clinical, motor control and proprioceptive) are reported in Chapter 7, that highlight the benefits of an adaptive force training paradigm of the upper limb and its relation to activities of daily living for PwMS.

5.5 Limitations

This study is not without limitations. The maximum achievable resistance per session was 65% MVC based on the adaptive process. This was due to a few factors, including limitations of the robot motor capacity and consideration for tolerable resistance for participants given the large number of repetitions. Future work should include a higher resistance should the participant well tolerate the exercise. The given frequency, load and duration of training cannot be confirmed as optimal and was developed in reference to previous literature. More research is needed to determine the optimal prescription and rehabilitation guidelines. In addition, this exercise design did not include pronation and supination. As many activities of daily living require the use of pronation and supination, movement along this axis should be considered for future work.

5.6 Conclusion

This work contributes to the limited existing literature investigating robotic rehabilitation modalities for the upper limb in MS. This work provides evidence that a high frequency, repetition, and moderate load is safe for a variety of symptoms of MS, MS phenotype and is effective at eliciting muscular strength gains. Future work should seek the lowest effective frequency of therapy to elicit performance and/or strength changes in this population.

Chapter 6 – An adaptive 8-week robotic training program for multiple sclerosis and the cross-education of muscular strength

6.1 Introduction

Multiple sclerosis (MS) can affect anywhere in the CNS and with progression tends to affect people bilaterally but there is often a more affected limb which creates functional asymmetries that can lead to disuse of the more affected limb (Larson et al., 2013). Manual therapy and exercise for the limb that is more spastic, weak, and paretic can be challenging to rehabilitate (Vergaro et al., 2010). To combat this, some have applied novel unilateral training approaches (Manca et al., 2017). Unilateral training (of the less affected limb) can affect neural pathways (Krebs et al., 2007) and is known as cross-education (CE). CE is a neurophysiological phenomenon whereby one limb undergoes a training protocol, and the contralateral (untrained) limb exhibits muscular strength and skill improvements (Carroll et al., 2006). CE has been highly researched in healthy adults (Scripture EW, Smith TL, Brown EM, 1984) and stroke survivors (Sun et al., 2018) and effects are amplified in clinical populations with a 29% increase in strength compared to a 15% increase in healthy participants (Green & Gabriel, 2018). In clinical settings involving persons with MS (PwMS), the effects of CE have led to improvements in ankle strength and mobility in the untrained limb (Manca et al., 2017) following isometric strength training as measured by peak moment (Nm) and maximal work (J) ($p<0.03$). However, less is known about CE in the upper limbs. It is hypothesized that neurological changes in the upper limbs are different than in the lower limbs due to a more direct monosynaptic connection within the corticospinal pathway to the upper limb (Carroll et al., 2006). Literature suggests that high intensity training (capable with robotics) can induce the neurophysiological changes of CE (Carroll et al., 2006). While the exact mechanisms of CE remain elusive, a recent consensus statement suggests that CE is likely mediated by changes in primary motor cortex (Manca et al., 2020). However, very little research has focused on CE in

PwMS and thus the site of neural adaptation in neurologically impaired groups is unknown despite many activities of daily living require coordination of both limbs to complete tasks.

Integrating robotics into the rehabilitation process can be a beneficial adjunct strategy to unilateral treatment in neurological conditions whereby the affected limb is untrainable or becomes fatigued. A benefit to robotic systems are the ability to adapt in real-time according to performance (Iandolo et al., 2019). It has been suggested that adaptive assistance or resistance during anaerobic training is best when it is tailored to the motor skills of the user, therefore offering a personalized approach (Albanese et al., 2024). There have been numerous robotic rehabilitation strategies ranging from assist-as-needed paradigms, to purely resistive that have demonstrated an increase in muscular strength performance post-intervention in handgrip strength, flexion/extension of the hip and knee and ankle dorsiflexors (Mannella et al., 2022). Similarly, results of previous work found that low resistance and high repetition upper limb robotic training was beneficial for PwMS as 4-weeks of robotics training significantly increased muscular strength and endurance in the untrained limb (Mannella et al., 2021). This initial finding will serve as leverage for this proposed work and a building block for a new approach to the adaptive protocol.

Despite robotics for rehabilitation being well studied for various conditions and diseases, there is a gap in the literature surrounding therapy dosage, frequency, and load recommendations for robotic rehabilitation for MS. Following a systematic review of the literature, intensity was hardly reported and background or rationale for the therapy dosage given was severely lacking (Lamers et al., 2016). The Canadian Society of Exercise Physiology created resistance training guidelines in 2020 for PwMS however, these guidelines do not have a direct relation to robotic rehabilitation leaving the optimal prescription up for debate. Therefore, to address objectives 3 and 4, the purpose of this robotic rehabilitation intervention was to intentionally implement an adaptive algorithm (Chapter 5) that clearly reports duration, frequency, and load to encourage increase in strength, and induce the effects of CE in the upper limb for individuals with MS.

6.2 Methods

6.2.1 Participants

Participants were sought from the local community and rehabilitation centers via recruitment posters. A total of 14 individuals with MS participated in the 8-week training intervention, 8-non-MS controls participated in the 8-week training intervention and 6 individuals with MS underwent no training intervention but participated in two assessment sessions separated by 4-weeks (Table 5). The purpose of this non-training group was to establish that any training effects that did occur were a result of the intervention and not due to varying symptoms of MS. Participants with MS were required to have a medical diagnosis of MS and were required to have functional use of at least one upper limb as the robotic protocol did not offer assistance. Participants were excluded if they were currently undergoing a relapse or suffered from any trauma to the upper limb other than impairments due to MS related symptoms (i.e., broken bones). Inclusion criteria of the non-MS group consisted of being free from neurological impairments and participants were excluded if they had any broken bones, sprains, or injury to the upper limbs. Participants were asked to complete 3 training sessions per week for 25-minutes for the entirety of the 8-weeks and were excluded if missed more than two sessions throughout the intervention. No participants were excluded for attendance. Participant adherence is also reported in Table 5. A one-way ANOVA was conducted to report statistical significance between groups for mean EDSS, years since diagnosis and years of age. For mean EDSS, indirect and double baseline groups significantly differed from one another (direct/indirect – p=.528, direct/double baseline – p=.309, indirect/double baseline – p=.034). Mean years since diagnosis did not differ between groups (direct/indirect – p=.222, direct/double baseline – p=.606, indirect/double baseline – p=.214). Mean years of age did not differ between groups (direct/indirect – p=.15, direct/double baseline – p=.145, indirect/double baseline – p=.028, control/direct – p=.199, control/indirect – p=.103, control/double baseline – p=.39).

Table 5. Participant demographics

Group	Weeks Trained	Group Size	Limb Trained		EDSS	MS Phenotype	Years Since Diagnosis	Years of Age	Handedness (Dominant)	Total Attended Training Sessions
Indirect Training	8	N=7	Less affected	3– Left 4– Right	5.28±1.22	3-RRMS 3-SPMS 1-PPMS	24.33 ± 14.57	61.71± 6.34	1– Left 6– Right	23.43 ±0.49
Direct Training	8	N=7	More affected	3– Left 4– Right	4.5±2.6	2-RRMS 4-PPMS 1-SPMS	16.14 ± 10.48	56.29 ±7.31	2– Left 5– Right	22.83 ±0.89
Non-MS Control	8	N=8	Dominant	1– Left 7– Right	0	--	--	45.63±17.7	1– Left 7– Right	23.75 ±0.43
Double Baseline	0	N=6	--	--	2.43±1.02	6-RRMS	10 ± 6.78	41.67±6.55	5– Right	0

Values are represented as group means ± standard deviation. Double dash lines (--) depicts that no participant was relevant for that specific column. Abbreviations: RRMS – relapsing remittent MS, PPMS – primary progressive MS, SPMS – secondary progressive MS, DB – double baseline

To promote inclusivity, individuals of various MS phenotypes, severity of disease based on the EDSS (Kurtzke, 1983), and years since diagnosis were included. Participants were excluded if they were undergoing other types of therapy for the upper limb and participants were asked to keep daily activities consistent. This work strived for a representative sample considering prevalence of MS across sex. Participant reported pharmaceuticals were recorded and categorized based on inhibitory, excitatory, disease modifying or recreational drugs and are reported in Table 6. Inhibitory Drugs were considered beta-adrenergic blockers, anticholinergics, dopamine receptor antagonists, anticonvulsants, GABA-ergic medications (Chaves, Snow, et al., 2021). Excitatory Drugs were considered dopamine agonists, serotonin receptor agonists, noradrenergic receptor agonists. Disease modifying drugs (DMDs) included immunosuppressants, immunomodulators (i.e., Ocrevus, Tecfidera, Copaxone) and recreational Drugs included marijuana for medicinal purposes.

Table 6. Participant medication usage

Group	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5	Participant 6	Participant 7	Participant 8
Indirect Training	Inhibitory Inhibitory Inhibitory Excitatory	Inhibitory Excitatory	DMD	N/A	DMD	Recreation	DMD	--
Direct Training	Inhibitory Inhibitory	N/A	DMD Inhibitory	DMD	N/A	N/A	N/A	--
Control Group	N/A	N/A	Excitatory	N/A	N/A	N/A	Inhibitory	Excitatory
Double Baseline	DMD	DMD	DMD	N/A	N/A	--	--	--

Medication usage is presented per participant. Double dash lines (--) depicts that no participant was relevant for that specific column
Abbreviations: N/A – not applicable (no pharmaceuticals were taken), DMD – disease modifying drug

6.2.2 Intervention and Experimental Protocol

This study was designed as a pre-post training program (Figure 11). Strength and clinical outcome measures were evaluated at baseline (PRE), post-intervention (POST) and a sub-group performed a 14–16-week post intervention follow-up (FU) assessment (MS group N=3, Control N=3).

Participants were placed into four groups by the researchers based on participant demographics:

1) **Indirect training group (IT):** Participants with MS (N=7) visited the lab 3 times a week for approximately a 25-minute training session using their <u>self-reported less affected limb</u> regardless of hand-dominance although it was recorded for reference.

2) **Direct training group (DT):** Participants with MS (N=7) visited the lab 3 times a week for 8-consectuive weeks for approximately a 25-minute training session using their <u>self-reported more affected limb</u>, regardless of hand dominance. It is important to allow for a self-reported most-affected limb because that is the limb that is most impaired during basic function and activities of daily living which are important to one's quality of life.

3) **Control group (CON):** Participants with no neurological disorders (N=8) visited the lab 3 times a week for approximately a 25-minute training session using their dominant limb (assessed using the Edinburgh Handedness Questionnaire – Appendix E).

4) **Double Baseline (DB):** Participants with MS (N=6) did not participate in training sessions but underwent pre and post assessments separated by 4-weeks. The double baseline group was essential to use as a comparative group to explain that any changes which may occur during the training was due to the intervention and not due to the varying symptoms of MS.

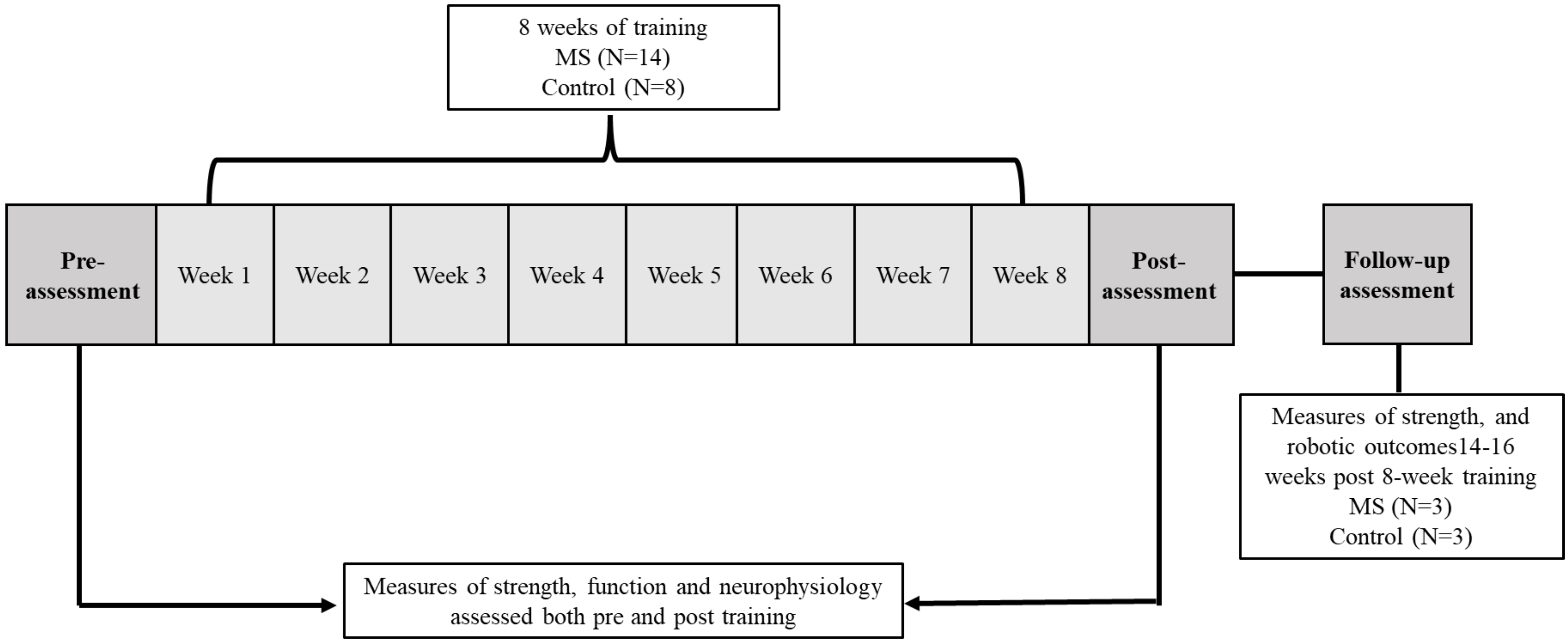


Figure 11. Timeline of intervention

6.2.3 Training Sessions

Training sessions consisted of having the participants track a moving dot visually located on a monitor in front of them as it moved along four directions: flexion (F), extension (E), radial deviation (RD) and ulnar deviation (UD) (Force Training (youtube.com)). Participants accomplished this by moving the end effector handle of the robotic device, which displayed the participant's dot (Figure 12). The forces throughout the task were acting against the line of action of the muscle causing an eccentric contraction. Participants were instructed to resist the force in a slow and controlled motion as the muscle lengthened towards the target position. There were no forces acting upon the end-effector in the opposing/concentric contraction. Parameters are further described in Table 7, however a more detailed explanation and rationale for the training are documented in Chapter 5.

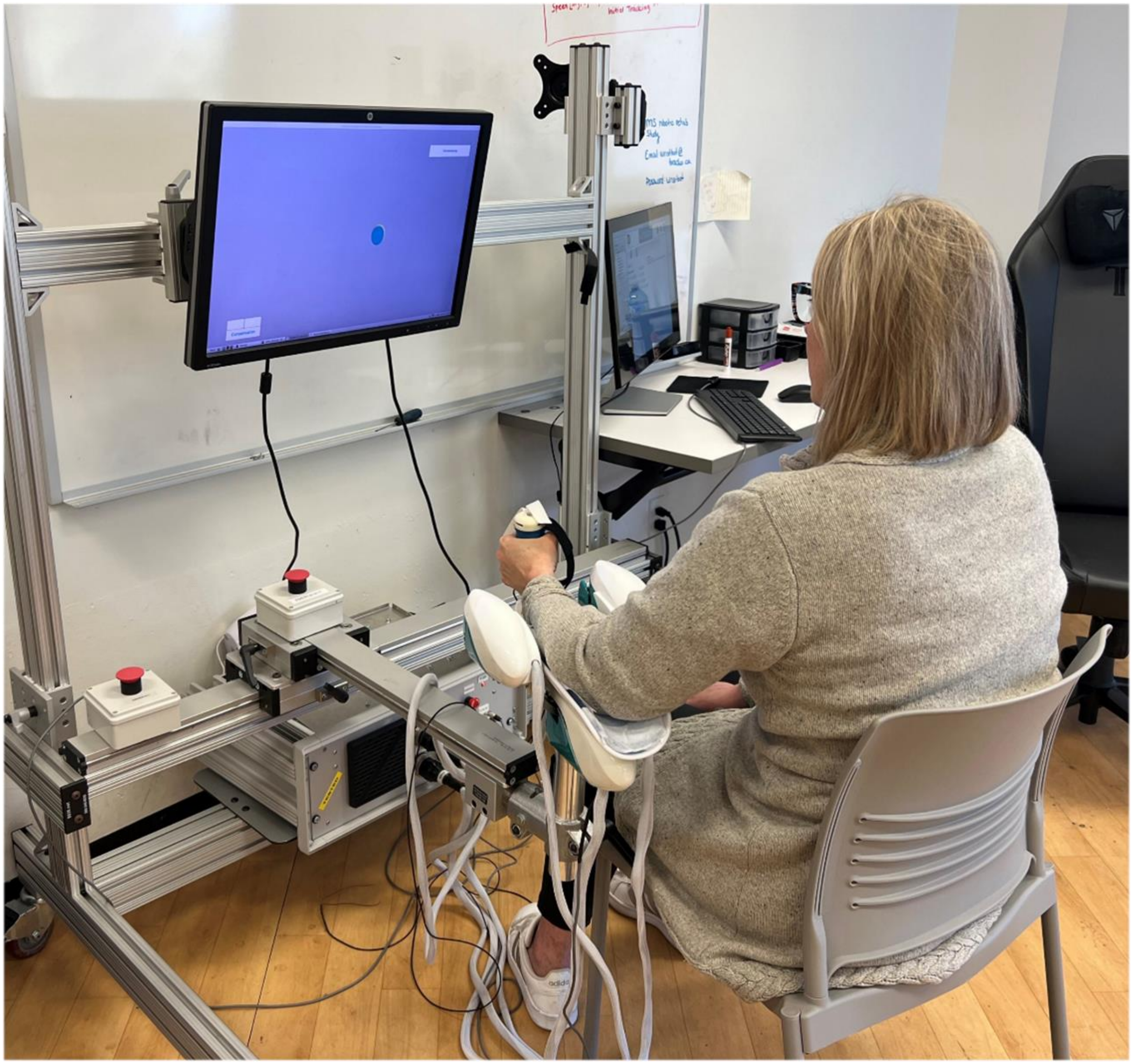


Figure 12. Training session protocol. Participant is positioned in the robotic device prepared for a training session

Table 7. Robotic parameters

Duration (min)	25 minutes
Number of sets	5-7
Number of repetitions	16 (per set)
Velocity (°/s)	15 °/s
MVC flexion (Nm)	Reassessed each week
MVC extension (Nm)	Reassessed each week
MVC radial deviation (Nm)	Reassessed each week
MVC ulnar deviation (Nm)	Reassessed each week
Starting force	40 %MVC
ROM (% full ROM)	80 % of individual ROM Reassessed each training session

6.2.4 Assessment Sessions

To minimize the risk of peripheral and central fatigue, assessment sessions were conducted on separate days from training days. The assessment sessions included musculoskeletal strength and clinical measures to classify level of disability (Table 8). The PRE assessment was conducted following initial screening and familiarization to provide baseline results. The POST assessment days were conducted within 7 days of the last training session to ensure accurate representation of changes in strength. Lastly, to investigate whether the adaptations were from transient learning or long-term learning (Kantak & Winstein, 2012), or if strength was retained, a follow-up session (FU) of strength was taken 14–16-weeks post intervention to investigate the long-term neuroplastic and CE adaptations. Each of the assessments were conducted bilaterally.

Table 8. Outcome measures assessed pre, post and follow-up intervention

Clinical Assessments	Neuromuscular Assessments
EDSS	Maximum grip force
--	Maximum isometric wrist strength (flexion, extension, radial, ulnar)

Muscular Strength Assessments

Maximum Grip Strength: Maximum grip strength is a quantitative measure of muscular strength (Musalek & Kirchengast, 2017). Participants were asked to complete one trial of a maximum grip test using a Smedley Digital Hand Dynamometer (Baseline Evaluation Instruments – Figure 13). Held with a straight arm, 45° abduction by the side and hand/wrist neutral (Figure 14), participants were asked to squeeze the handle as hard as possible for 3 seconds and grip force (Newton) was recorded.

Figure 13. Smedley Digital Hand Dynamometer used to record maximum grip strength

Figure 14. Participant performing maximum grip strength assessment

Isometric Wrist Strength: Isometric wrist force or maximum voluntary contraction (MVC) was assessed using a table mounted force transducer (Model: BG 500, Mark-10 Corporation, New York, USA – Figure 15) and was used as a quantitative measure of muscular strength. The force transducer has a measurement range from 0 to 10000 N with a resolution of 0.0001 N and an accuracy of 0.1 % of full scale. To isolate the wrist joint to the best of our abilities, the participant's arm was fully extended and rested on the table, and participants were instructed to exert force at the wrist joint (in flexion/extension, radial/ulnar deviation) as hard as they could against the stationary load cell that rested on the metacarpophalangeal joints (Figure 16). If a participant was unable to fully extend their arm due to impaired shoulder range of motion, participants were instructed to focus on wrist movement only and manual palpitation was used to ensure biceps and triceps were not fully engaged. Participants wrists were positioned in supination for maximal wrist flexion, pronated for maximal wrist extension and maintained a neural wrist position for radial and ulnar deviation.

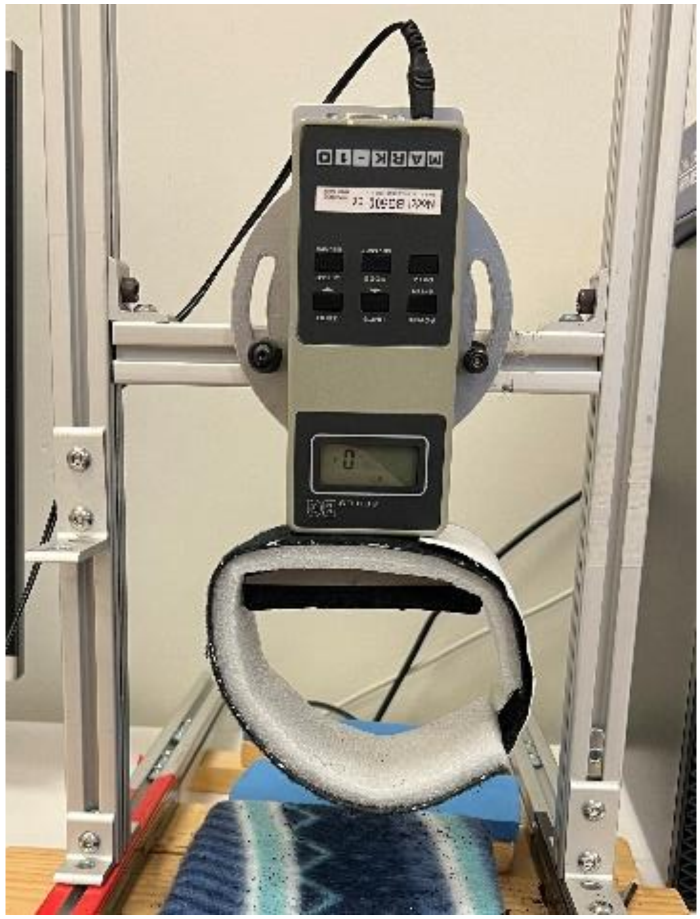


Figure 15. Force transducer used to record maximal isometric wrist strength (Mark-10 Corporation, New York, USA)

Figure 16. Participant performing the maximum isolated wrist strength assessment. A. flexion, B. extension, C. radial deviation, D. ulnar deviation

6.3 Data Analysis

6.3.1 Statistical Analysis

A two-way, arm (2 – trained and untrained) x time (2 – pre and post) repeated measures ANOVA was used to compare outcome measures (grip and 4 wrist strength directions) at each time point (SPSS Statistics for Windows, Version 26.0. IBM Corp.: Armonk, NY, USA). Significance was set to $p < .05$. A post-hoc Bonferroni was used to assess interaction effects. Percent change scores were also conducted to calculate strength changes (N) PRE/POST training and to evaluate clinically meaningful adaptations (Lang et al., 2008). As per Lang et al., 2008, a minimum of a 16-30% change score would be needed to be considered clinically meaningful for the strength measures. Percent change scores were calculated using the equation:

$$\frac{(V_2 - V_1)}{|V_1|} \times 100\%$$

Whereas v_1 depicts muscular strength (N) at PRE and v_2 depicts muscular strength (N) at POST.

Follow-up: Due to the small sample size (MS: N=3; CON: N=3), statistical analysis was not completed, and mean values and overall trends are reported and presented. Data are presented as percent change scores from POST/FU as calculated with the same equation noted above.

6.4 Results

6.4.1 Strength Results

It is important to note that there were no adverse effects from the intervention reported and the training sessions were well tolerated by the participants.

For grip, there were no main effects of limb ($F_{(1,22)}$=.420, p=.524), time ($F_{(1,22)}$=2.839, p=.106) or between group effects ($F_{(3,22)}$=.300, p=.825). For flexion, there was no main effect of limb ($F_{(1, 22)}$=4.561), or between groups ($F_{(3,22)}$=.363, p=.780), but there was a main effect of time ($F_{(1,22)}$= 9.525, p=.005). For extension, there were no main effects of limb ($F_{(2, 22)}$=2.193, p=.153), or between groups ($F_{(3,22)}$=.794, p=.510), but there was a main effect of time ($F_{(2, 22)}$=9.745, p=.005). For radial, there were no main effects of limb ($F_{(1,22)}$=1.446, p=.242) or between groups ($F_{(3,21)}$=.967, p=.121) but there was a main effect of time ($F_{(1,22)}$=36.583, p=.000). For ulnar deviation, there were no main effects of limb ($F_{(2,21)}$=.238, p=.631), or between groups ($F_{(3,21)}$=.535, p=.664) but there was a main effect of time ($F_{(1,21)}$=14.114, p=.001). Limb (trained/untrained) by time (PRE/POST) results are presented below in respect to training groups.

Indirect Training Group

There were no significant changes in grip in the trained limb (PRE: 297.56±148.58; POST: 311.71±114.02; p=.273; η^2=.054) and untrained limb (PRE: 242.14±142.78; POST: 269.79±107.63; p=.237; η^2=.063). There was a significant increase in flexion of the trained (PRE: 63.43±35.32, POST: 92.01±45.57; p=.001; η^2=.428) and untrained limb (PRE: 59.57±40.97; POST: 92.29±50.65; p=.003; η^2=.331). There was a significant increase in extension of the trained (PRE: 57.28±24.48; POST: 87.43±35.99; p=.010; η^2=.268) but not in the untrained limb (PRE: 63.14±36.11; POST: 63.14±36.11; POST: 80.57±43.17; p=.102; η^2=.117). There was a significant in radial deviation of the trained (PRE: 78.43±70.65; POST: 103.71±53.48; p=.006; η^2=.296) and untrained (PRE: 75.57±57.62; POST: 100.71±52.97; p=.013; η^2=.248) and in ulnar deviation of the trained (PRE: 59.29±35.96; POST: 86±45.56; p=.015; η^2 =.251) but not in the untrained limb (PRE: 57.14±39.61; POST: 70.57±33.03; p=1.00; η^2=.124).

Percent change scores were used to calculate the clinically significant difference between strength PRE/POST intervention (Table 9 and Figures 17-18).

Table 9. Indirect Training Group: Strength results for the trained and untrained limb represented by group means and percent change scores (PRE/POST) reported in newtons ± standard deviation

	Grip	p-value	Flexion	p-value	Extension	p-value	Radial	p-value	Ulnar	p-value
Pre trained	297.5± 148.58	.273	63.43± 35.32	.001*	57.28± 24.48	.010*	78.43± 70.65	.039*	59.29± 35.96	.015*
Post trained	311.7± 114.02		92.01± 45.57		87.43± 35.99		103.71± 53.48		86± 45.56	
Percent Change		4.75 ±7.29%		45.06 ±25.77%		52.64 ±16.58%		32.23 ±46.29%		45.05 ±24.31%
Pre untrained	242.1± 142.78	.421	59.57± 40.97	.003*	63.14± 36.11	.102	75.57± 57.62	.001*	57.14± 39.61	.100
Post untrained	269.7± 107.63		92.29± 50.65		80.57± 43.17		100.71± 52.97		70.57± 33.03	
Percent Change		11.42 ±14.75%		54.92 ±45.43%		27.61 ±27.81%		33.27 ±48.08%		23.51 ±48.83%

*denotes statistical significance, values in red denotes a clinically significant percent change score

Direct Training Group

There were no significant changes in grip in the trained limb (PRE: 229.49±147.39; POST: 217.31±102.66; p=.479; η^2=.023) and untrained limb (PRE: 274.69±137.61; POST: 314.33±106.91; p=.114; η^2=.246). There was no change in flexion of the trained (PRE: 64.33±40.53; POST: 62.33±36.97p=.473; η^2=.024) and untrained limb (PRE: 83.2±57.47; POST: 84.4±33.99; p=.236; η^2=.063). There was a significant increase in extension of the trained (PRE: 47±12.59; POST: 69.33±48.26; p=.022; η^2=.215) and untrained limb (PRE: 64.57±34.79; POST: 87.6±50.65; p=.010; η^2=.268), radial deviation of the trained (PRE: 72.5±45.03; POST: 87.5±41.03; p=.039; η^2=.180) and untrained (PRE: 95.4±49.77; POST: 129.6±54.00; p=.001; η^2=.434) and in ulnar deviation of the trained (PRE: 43.33±19.43; POST: 77.5±33.19; p=.005; η^2=.320) and untrained limbs (PRE: 54.6±34.7; POST: 78.8±23.73, p=.009; η^2=.282).

Percent change scores were used to calculate the clinically significant difference between strength PRE/POST intervention (Table 10 and Figures 17-18)

Table 10. Direct Training Group: Strength results for the trained and untrained limb represented by group means and percent change scores (PRE/POST) reported in Newton ± standard deviation

	Grip	p-value	Flexion	p-value	Extension	p-value	Radial	p-value	Ulnar	p-value
Pre trained	229.49± 147.39	.479	64.33± 40.53	.473	47 ± 12.59	.022*	72.5± 45.03	.039*	43.33± 19.43	.005*
Post trained	217.31± 102.66		62.33± 36.97		69.33± 48.26		87.5 ±41.03		77.5± 33.19	
Percent Change		-5.31 ±15.87%		-3.12 ±40.52%		47.52 ±72.75%		20.69 ±29.51%		78.86 ±67.7%
Pre untrained	274.69± 137.61	.114	83.2± 57.47	.236	64.57± 34.79	.010*	95.4± 49.77	.001*	54.6± 34.7	.009*
Post untrained	314.33± 106.91		84.4± 33.99		87.6± 50.65		129.6± 54.99		78.8± 23.73	
Percent Change		14.43 ±78.12%		1.44 ±78.15%		35.67 ±44.84%		35.67 ±14.32%		44.32 ±112.09%

*denotes statistical significance, values in red denotes a clinically significant percent change score

Control Group

There were no significant changes in grip in the trained limb (PRE: 308.09±62.74; POST: 293.69±75.66; $p=.234$; $\eta^2=.064$) and untrained limb (PRE: 254.84±67.74; POST: 272.27±66.77; $p=.421$; $\eta^2=.030$) and no changes in flexion of the trained (PRE: 78.25±22.19; POST: 85.13±31.60; $p=.308$; $\eta^2=.047$) and untrained limb (PRE: 83.25±22.83; POST: 90.88±32.74; $p=.436$; $\eta^2=.028$). There was a non-significant increase in extension of the trained (PRE: 59.38±20.90; POST: 77.63±28.10; $p=.082$; $\eta^2=.131$) but not in the untrained limb (PRE: 63.75±23.82; POST: 71.5±29.34; $p=.449$; $\eta^2=.026$). There was a significant increase in radial deviation of the trained (PRE: 70±32.92; POST: 107±45.79; $p=.001$; $\eta^2=.508$) and untrained (PRE: 77.25±39.69; POST: 104.38±44.50; $p=.005$; $\eta^2=.304$). There was a significant increase in ulnar deviation of the trained (PRE: 70.38±24.65; POST: 93.5±29.52; $p=.023$; $\eta^2=.223$) but not in the untrained limb (PRE: 75.25±24.52; POST: 86.13±24.86; $p=.151$; $\eta^2=.096$).

Percent change scores were used to calculate the clinically significant difference between strength PRE/POST intervention (Table 11 and Figures 17-18).

Table 11. Control Group: Muscular strength results for the trained and untrained limb represented by group means and percent change scores (PRE/POST) reported in Newton ± standard deviation

	Grip	p-value	Flexion	p-value	Extension	p-value	Radial	p-value	Ulnar	p-value
Pre trained	308.09± 62.74	.273	78.25± 22.19	.308	59.38± 20.90	.082	70± 32.92	.001*	70.38± 24.65	.023*
Post trained	293.69± 75.66		85.13± 31.60		77.63± 28.10		107± 45.79		93.5± 29.52	
Percent Change		-4.67 ±8.934%		8.79 ±23.79%		30.73 ±56.03%		52.85 ±59.34%		32.85 ±53.36%
Pre untrained	254.84± 67.74	.237	83.25± 22.83	.436	63.75± 23.82	.449	77.25± 39.69	.005*	75.25± 24.52	.151
Post untrained	272.27± 66.77		90.88± 32.74		71.5± 29.34		104.38± 44.50		86.13± 24.86	
Percent Change		6.84 ±8.64%		8.84 ±31.15%		12.16 ±63.23%		35.12 ±74.50%		14.46 ±41.42%

*denotes statistical significance, values in red denotes a clinically significant percent change score

Double Baseline

There were no significant changes in grip in the trained limb (PRE: 247.26±100.43; POST: 249.36±110.79; $p=.901$; $\eta^2=.001$) and untrained limb (PRE: 243.64±67; POST: 255.31±84.92; $p=.702$; $\eta^2=.007$), in flexion of the trained (PRE: 59±23.25; POST: 65±27.84; $p=.526$; $\eta^2=.018$) and untrained limb (PRE: 68±35.28; POST: 75±35.52; $p=.599$; $\eta^2=.013$), in extension of the trained (PRE: 51.02±24.4; POST: 57.25±24.40; $p=.663$; $\eta^2=.009$) and untrained limb (PRE: 60.75±22.4; POST: 55.75±19.86; $p=.715$; $\eta^2=.006$), in radial deviation of the trained (PRE: 69.25±22.53, POST: 77.25±22.29; $p=.474$; $\eta^2=.024$) and untrained (PRE: 66.5±26.12; POST: 67.75±32.75; $p=.920$; $\eta^2=.000$) and in ulnar deviation of the trained (PRE: 75.25±35.11; POST: 68±42.59; $p=.582$; $\eta^2=.014$) and untrained limb (PRE: 68.25±21.14; POST: 71±39.43; $p=.792$; $\eta^2=.003$).

Percent change scores were used to calculate the clinically significant difference between strength PRE/POST intervention (Table 12 and Figures 17-18).

Table 12. Double Baseline: Strength results for the trained and untrained limb represented by group means and percent change scores (PRE/POST)

	Grip	p-value	Flexion	p-value	Extension	p-value	Radial	p-value	Ulnar	p-value
Pre trained	247.26± 100.43	.901	59± 23.25	.526	51.02± 24.4	.663	69.25± 22.53	.474	75.25± 35.11	.582
Post trained	249.36± 110.79		65± 27.84		57.25± 24.40		77.25± 22.29		68± 42.59	
Percent Change		4.78 ±8.19%		10.29 ±13.49%		-8.23 ±23.49%		1.88 ±21.84%		11.35 ±28.31%
Pre untrained	243.64± 67	.702	68± 35.28	.599	60.75± 22.4	.715	66.5± 26.12	.920	68.25± 21.14	.792
Post untrained	255.31± 84.92		75± 35.52		55.75± 19.86		67.75± 32.75		71± 39.43	
Percent Change		4.79 ±15.47%		10.29 ±43.27%		-8.23 ±5.09%		1.88 ±22.32%		11.36 ±16.16%

*denotes statistical significance, values in red denotes a clinically significant percent change

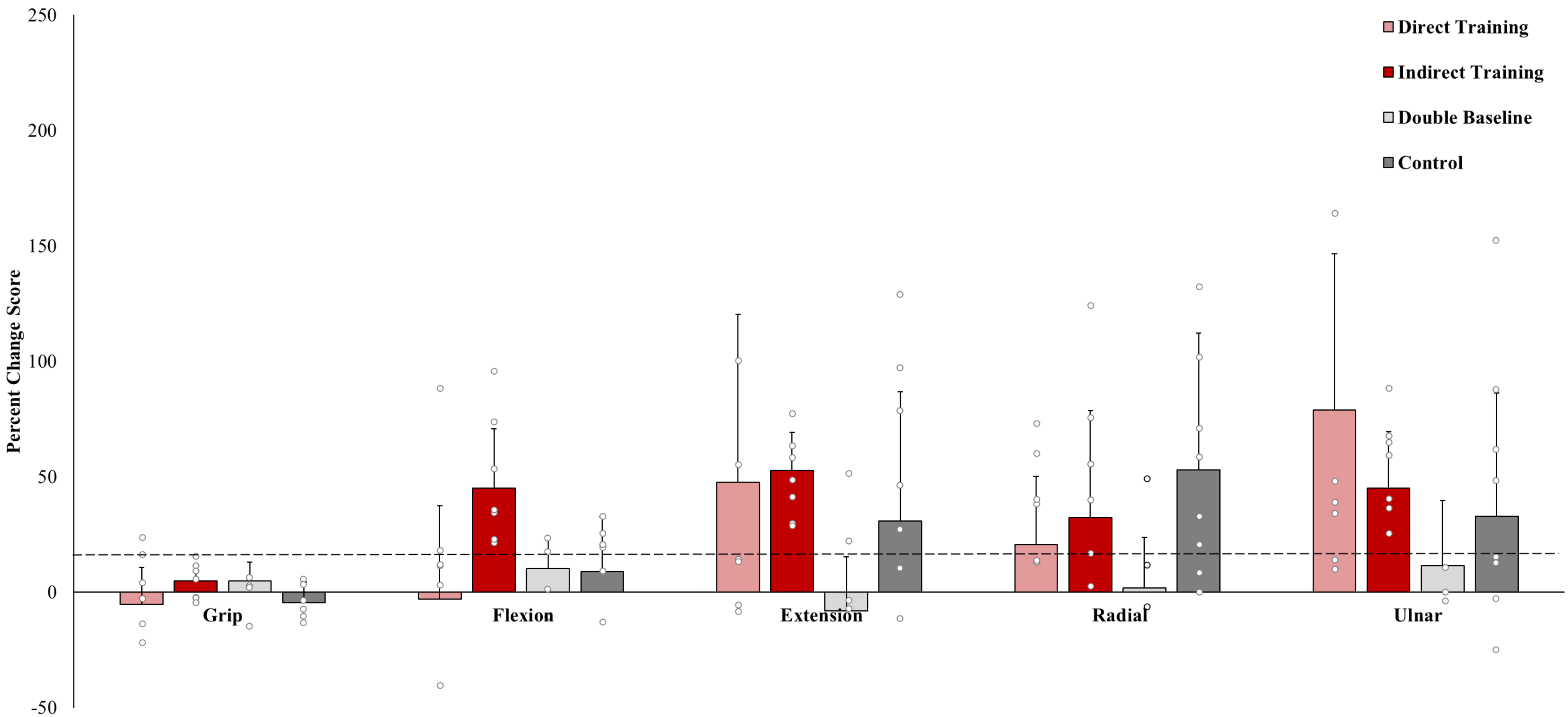


Figure 17. Percent change scores of strength of the trained limb across groups. Data are presented as mean percent change scores (bars), individual data points (circles) and standard error. Dashed black line represents the minimal threshold for clinical significance.

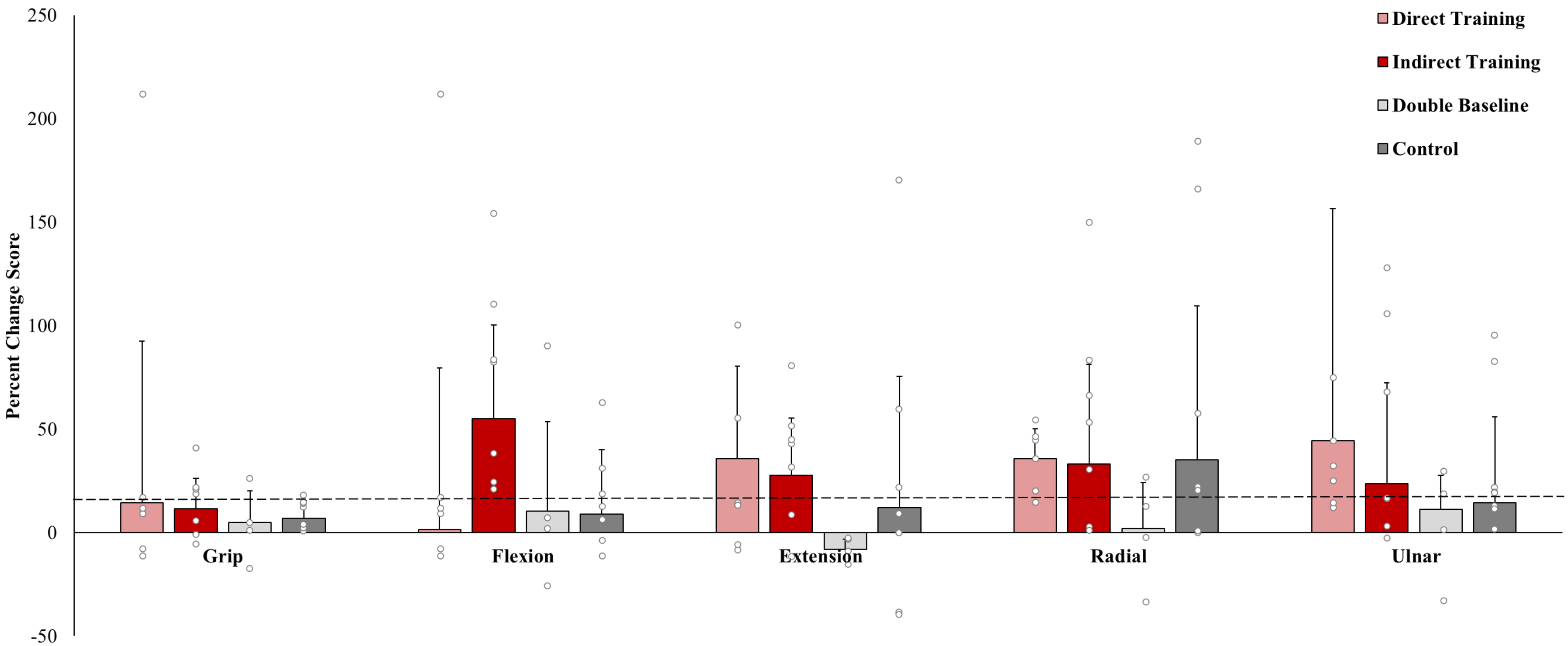


Figure 18. Percent change score graph of the untrained limb. Data are presented as mean percent change scores (bars), individual data points (circles) and standard error. Dashed black line represents the minimal threshold for clinical significance.

6.4.2 Follow-up Results

Assessments of strength were conducted 14-16-weeks post-intervention for a sub-group of MS (N=3) and the Control group (N=3). Follow-up assessments (FU) were conducted to determine the lasting effects of the intervention.

<u>Strength – MS Group</u>

Strength reported as force (N) did not differ from POST to the FU assessment for any of the outcomes for the MS group (Table 13). Group averages for the trained limb show an average decrease across all directions of 11.67%, 14-16 weeks FU. Group averages for the untrained limb showed a 10.25% decrease in strength 14-16 weeks POST intervention (Figure 19).

Table 13. MS Group average strength reported in Newton ± standard deviation (N=3) from PRE/POST/FU for the trained and untrained limbs

Trained	Grip (N)	Flexion (N)	Extension (N)	Radial (N)	Ulnar (N)
PRE	331.27±73.01	80±40.89	69.67±17.75	143±40.01	91.33±14.88
POST	357.64±91.38	117.67±60.58	106.33±42.32	152.67±43.25	125.33±35.87
FU	371.28±77.44	102.33±36.46	97±34.42	129.67±40.75	103.33±17.55
Untrained					
PRE	351.71±68.54	86.67±40.53	83±35.69	126±37.49	93±14.31
POST	357.94±71.42	121.33±61.08	107.67±46.43	148.33±34.27	100±21.74
FU	322.35±84.33	98.67±28.77	101.33±25.22	136.33±29.22	91.33±9.74

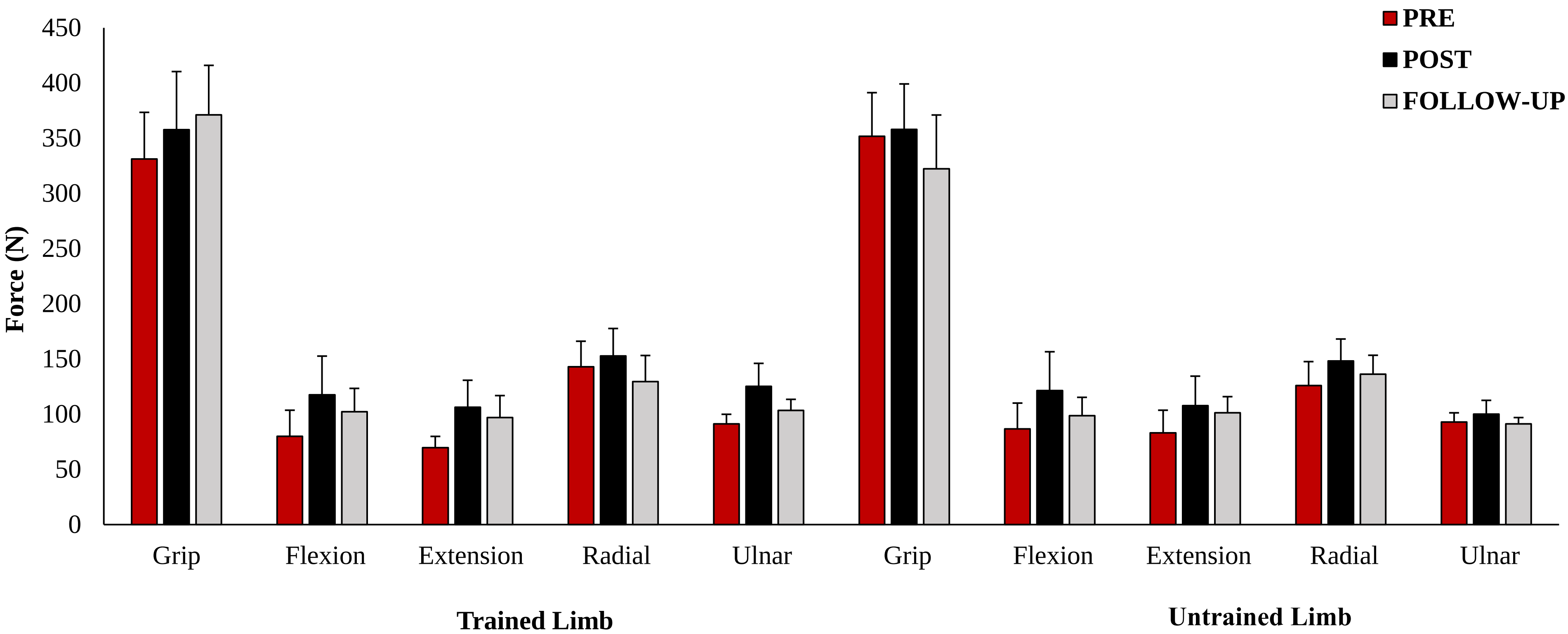


Figure 19. Strength PRE/POST/FU intervention for the MS Group. Represented as group means and standard errors

Strength – Control Group

For the CON group, group average results for the trained limb showed a 7.44% decrease in strength from POST/FU (Table 14). For the untrained limb, group averages showed a 12.51% decrease in strength from POST/FU (Figure 20).

Table 14. Control Group average strength reported in Newton ± standard deviation (N=3) from PRE/POST/FU for the trained and untrained limbs

Trained	Grip (N)	Flexion (N)	Extension (N)	Radial (N)	Ulnar (N)
PRE	282.56±33.39	59.57±11.89	51.67±19.07	67±25.81	87±15.51
POST	263.94±63.03	60.67±24.85	63.67±31.46	81.33±34.87	84±23.42
FU	273.12±58.95	65.33±12.55	66±20.83	77.33±30.45	69.33±29.01
Untrained					
PRE	245.61±21.78	71.33±17.91	57.33±29.33	72±34.09	81.67±20.17
POST	253.25±35.53	74.67±36.53	69.33±31.54	78.67±34.37	73.67±15.06
FU	236.35±46.96	79±28.33	52.33±22.65	75.33±22.84	57.67±15.69

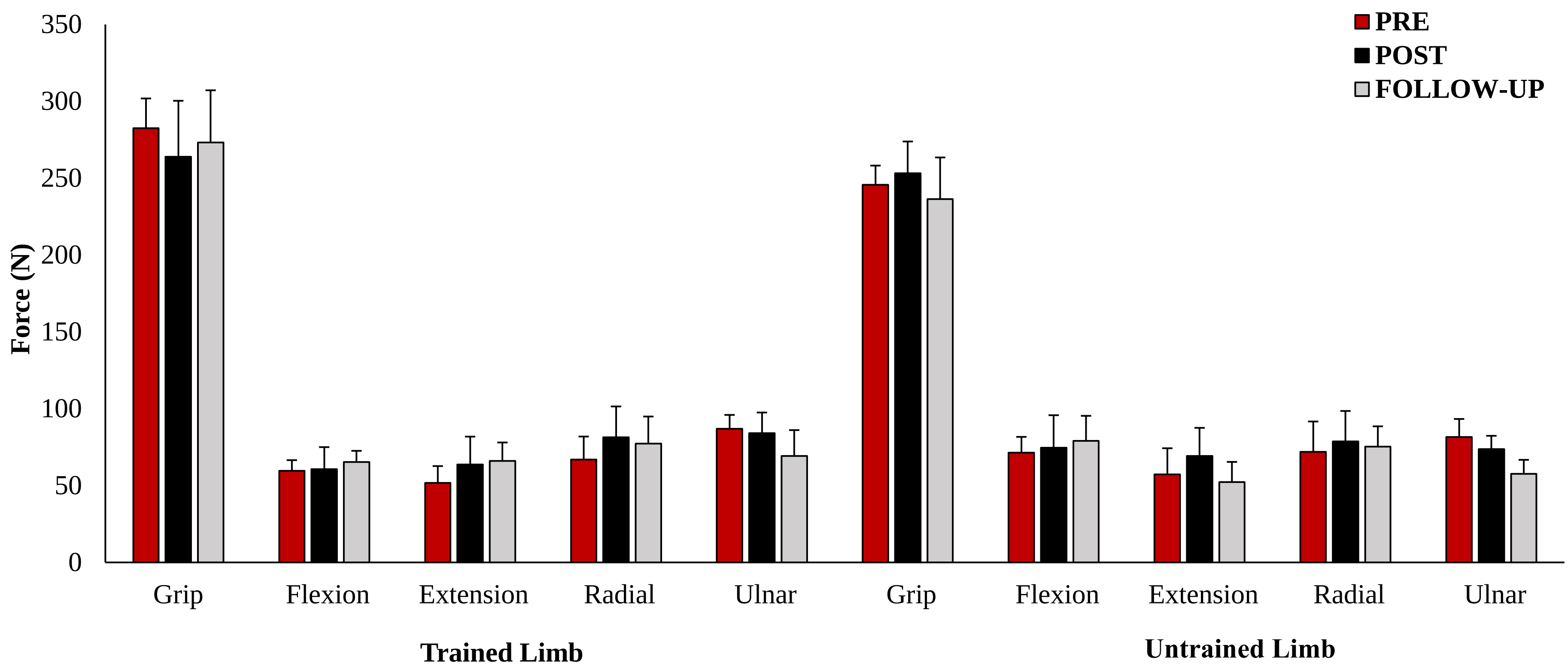


Figure 20. Strength PRE/POST/FU intervention for the CON group. Represented as group means and standard errors

6.5 Discussion

Following eight-weeks of an adaptive robotic training intervention for the upper limb, this work evaluated changes in grip and wrist strength for both the trained and untrained limbs. The primary objective was to evaluate changes in strength. Secondary objectives were to evaluate cross-education adaptations from pre- post robotic training by investigating the strength changes in both the trained and contralateral/untrained limb. In this work, seven PwMS were placed in the direct training group, where they trained the self reported more affected limb. Seven PwMS were placed in the indirect training group, were they trained they self reported less affected limb. Six PwMS participated in a double baseline to help strengthen claims about the intervention. Finally, eight non-MS controls completed the same training program using their dominant limb and provided normative healthy baseline values. In support of hypothesis 1, strength increased in both the trained and untrained limb for DT and IT MS. Strength of the CON improved in the trained limb but did not show significant changes in the untrained limb and DB values did not change from week one to four. The IT group trained limb reported an overall average strength increase (across grip, flexion/extension, radial/ulnar) between 14.67-70.53%, 13.79-90.32% for the DT group and 8.79-52.85% for the CON group. The IT group untrained limb reported an overall average strength increase between 20.37-59.51%, 16.74-45.87% for the DT group and 8.41-51.42% for the CON group. Results provide evidence that the robotic training intervention, working at 40% MVC and with 4,608 repetitions was sufficient for inducing strength adaptations in the MS group

Strength

Strength is an important factor in performing activities of daily living and thus, maintaining independence for someone living with MS (Carlos et al., 2014). It has been proven that robotic rehabilitation for PwMS results in an increase in muscular strength (Chapter 4). Results of this work have also demonstrated an increase in strength as represented as an increase in isometric force at the wrist. Results were presented as a percent change score from PRE/POST training and supported by clinical significance. When assessing health-related outcomes in MS such as strength, it is important to also evaluate the minimal clinically important difference (MCID). The MCID helps in deciding if a treatment effect is large enough to be considered beneficial in a clinical setting Used to assess the practical, real-world impact of a treatment. The MCID of grip strength and upper limb isometric force has been suggested in stroke and can be used as a reference for MS work and have been established as a minimum of a 16-30% change score would be needed to be considered clinically meaningful for the strength measures (Lang et al., 2008). While not statistically significant, the IT group reached the MCID in all strength outcomes and 7/7 and 5/7 participants demonstrated a meaningful increase in flexion and extension, respectively. DT met the MCID in strength in the extension, radial and ulnar deviation directions for the trained limb from pre- to post-intervention and a total of 5/7 participants of this sub-group reached MCID in at least 2 outcomes (grip, flexion, extension, radial, ulnar). The CON Group reported a MCID in extension, radial and ulnar deviation in the trained limb and only increased in radial and ulnar deviation in the untrained limb from pre- to -post-intervention.

The robotic training intervention had participants working at 40% of their maximum strength with the opportunity to increase by 5% MVC every 3 repetitions for a maximum workload of 65 %MVC in a single set. These resistive forces were potentially not intense enough to elicit significant strength adaptations in a non-MS control sample. Furthermore, the American College of Sports Medicine suggests that when healthy adults focus on strength, they should train at a load of 60-70 % max for novice or intermediate and 80-100 % max for advanced experienced trainers (ACSM, 2019), further emphasizing that the load prescribed in this work was a low intensity for healthy strength training. Additionally, the CON group could have been constrained by a ceiling effect, whereby significant increases in strength were not achievable (Lim & Madhavan, 2023). However, as both MS groups demonstrated increases in strength post-intervention, it can be concluded that resistive forces from the robotic motors of 40% MVC was an appropriate load for the MS group to induce strength adaptations while also preserving safety and without the presence of adverse effects. Our reported difference in strength as a percent change from PRE to POST intervention are in line with stroke literature, as a review by Lim & Madhavan, 2023, reported that the non-paretic or trained limb improved within a range of 19-53% following resistance training interventions. PwMS have reported a worse musculoskeletal strength and endurance when compared to normative non-MS individuals (W Motl, 2013). This deconditioning effect is caused by a vicious cycle whereby the severity of disease impacts one's capabilities to perform activity or resistance train and this directly results in further deconditioning (W Motl, 2013). Additionally, it has been proposed that PwMS require greater central motor drive to achieve a maximal exertion compared to heathy adults (Ng et al., 1997) and that central motor drive had a strong correlation to disease severity. This could explain the baseline differences and greater improvements in maximum strength of the IT and DT groups compared to the CON group.

Lastly, during the training protocol, participants were asked to grasp the handle but were not required at any point to squeeze or conduct a change in grip force against the handle. Thus, the intervention focused on wrist adaptations and strengthening the muscles that control wrist/hand movements. There are many other muscles involved in gripping, including intrinsic finger flexors that contribute to overall grip force. Task specificity could explain why grip force did not increase post-training and that the slight decreases in grip may be day-to-day variability in grip strength. The DB group showed no changes in strength from week 1 to week 4 with no training aside from an 18% change in wrist extension of the dominant limb. These findings demonstrate a low variability between strength impairment of MS across 4-weeks and can help confirm that the strength adaptations that occurred across the other groups were a result of the training intervention.

Follow-up Measures

A subgroup of MS (combination of IT and DT) and CON participants completed strength assessments 14-16-weeks following their last training session to evaluate strength retention. The MS group strength values decreased from POST assessment but did not return to baseline (PRE), demonstrating some maintenance of strength. Radial deviation of the trained limb, as well as grip and ulnar deviation of the untrained limb were the only measures that returned to baseline (PRE). The CON subgroup showed a similar pattern, with strength measures decreasing from POST assessment but still reporting greater maximum strength than PRE. Grip strength of the trained and untrained limbs, extension for untrained and ulnar deviation of both the trained and untrained limbs were the only values that returned to baseline (PRE). These results match the results of previous literature by Carlos et al., 2014, whereby MS participants performed concentric/eccentric seated knee-extensor exercise 2 times per week for 12 week, working progressively from 35% to 70% of maximum. Maximum isometric voluntary contractions returned to baseline 12-weeks post-training, but muscle power effects were maintained or still greater than baseline, 12 weeks post-training. It has been hypothesized that resistance training for individuals with MS allows for neural plasticity and increases maximal neural drive as measured from surface electromyographic recording from vastus lateralis, rectus femoris and semitendinosus during maximal isometric knee extension and knee flexion from pre-to-post training (Dalgas et al., 2013). There is evidence that these effects from the lower limb resistance training intervention persisted after 12 weeks, suggesting that the neural drive can be preserved in MS). Additional evidence of the persistent neural drive is demonstrated by Mason et al., 2012, whereby following 8-weeks of full-body vibration, MS participants improved in gait performance and results were maintained 2-weeks post-training. These results may also be evidence of maintained neural drive post-training in MS. Considering maximum strength from our work was generally reported greater than baseline, supports this evidence that the preservation of neural drive may partially explain the results. It is also important to address the decrease of strength 14-16 weeks post-training. This can likely be explained by detraining effects as participants did not report to have continued to exercise or train with use of robotics following the intervention. It has been known for healthy participants that detraining can effect previously sedentary individuals more than chronic trained or athletes (Andersen et al., 2005). Most participants in this work were previously sedentary, and to our knowledge did not continue to strength train, use robotics, or participate in any rehabilitation within the 14-16 weeks post-training. The decrease in maximal strength could partially be explained by this behaviour. Similarly, the CON group demonstrated a slight return to baseline strength and were also mainly novice or sedentary adults. These results suggest that the phenomenon of "use it or lose it" may hold true for maximal strength in PwMS.

Cross-Education

CE was evaluated by training one limb while having the contralateral limb remain rested on the participant's lap. The purpose was to evaluate any cross-over effects to the untrained limb. CE is important for MS, as MS is a bilateral disease but there is often a more/less affected limb (Larson et al., 2013). This objective was important because it is valuable to examine if it is feasible to train the opposing limb in a case where the more-affected limb is unable to be directly trained. Following this eight-week robotic training intervention, although there were no significant group differences, there were some general trends that should be addressed. IT appeared to have demonstrated a greater percent change of strength from pre-post training when compared to the DT group. This overall trend suggests greater effects of CE – representative of larger strength adaptations (and percent change scores) in the untrained limb when compared to the DT group. The IT group reported an average (of all directions: flexion, extension, radial, ulnar) percent change score of 62.59% in the trained limb and 53.26% in the untrained limb whereas the DT group reported an average percent change score of 47.47% in the trained limb and a 35.29% in the untrained limb. Similar results were presented in the literature whereby unilateral resistance training of the dorsiflexors demonstrated a greater increase in strength in the less-affected limb for MS participants. Results showed a greater cross-over effect to the more affect lower limb versus directly training the more-affected limb (Manca et al., 2017a; Manca et al., 2016). Similarly, in stroke research, strength has been reported to increase in the untrained limb by upwards of 93% (Lim & Madhavan, 2023) and in some cases, improve more than the trained limb.

These results are interesting, especially from a clinician's point of view. If the participant is unable to directly train their affected limb, there appears to be success in focusing on the less affected limb to gain improvements. Perhaps the focus should be placed on training both limbs to maximize the therapy process and not just focus on the impaired or more symptomatic limb. There was less evidence of CE in the CON group as the average percent increase in strength (flexion, extension, radial, ulnar) was 31.31% in the trained limb and 24.26% in the untrained limb. These average percent change scores for the untrained limb are greater than a meta-analysis by (Carroll et al., 2006) that concluded an average change score of 52% in the trained limb and 7.6% in the untrained limb following resistive exercise ranging from 12-14 weeks in duration and an intensity of 55-100% of maximal contraction. Therefore, the CON group in our work demonstrated an above average increase in strength in the contralateral limb. It has been known that within-subject studies have their limitations as simply baseline testing the untrained limb can be enough to elicit an increase in strength (Carroll et al., 2006), and could explain the greater increase with the CON group. Although this is the first study to examine the cross-over effects in the upper limb for MS and therefore there is limited evidence on average increases in strength to form any firm conclusions. However, it is known that the use of robotics can eliminate the "slacking effect" whereby the user loses motivation or no-longer engages in the activity (Albanese et al., 2024). Perhaps with the use of robotics and their engagement and consistency, the robot holds the user accountable to given repetitions and sets and actively engages the user – producing larger strength gains than previous traditional resistance training literature.

6.6 Limitations

Participants included in this training intervention had a vast array of symptoms, classified severity of disease and years since diagnosis. Although the therapy was beneficial for improving group mean strength, it can only be hypothesized that participants that experienced greater upper limb disability improved to the same extent as participants with a lesser upper limb impairment. Future studies should include equal participant groups categorized by upper limb impairment to address this concern and investigate the benefits of robotic therapy along different stages of disease. Additionally, this work was limited by a small sample sizes amongst groups. The double baseline group is beneficial for monitoring variability of outcomes. Future studies should attempt a larger double baseline cohort to confirm changes in disease across the entire eight weeks. Lastly, the protocol parameters and rehabilitation prescription were based on existing literature, but it cannot be concluded whether the frequency, load and duration of training is optimal.

6.7 Conclusion

This study proved that an eight-week robotic training program of the upper limb is safe and effective for PwMS. Clinically relevant increases in strength measures for the MS groups conclude that with robotic rehabilitation and working at 40% MVC with high-repetitions was sufficient for inducing strength adaptations in the MS group, however this load does not appear sufficient for a non-MS control group. It can be suspected that CE did occur in both MS groups as both increased strength in the trained and untrained limbs. Our findings suggest that it may be more efficient to train the indirect limb as IT showed trends of greater changes in strength in the untrained limbs. Although, it should be noted that strength gains decreased following a 14–16-week post-training evaluation, however, did not necessarily return to baseline (PRE). Our work clearly demonstrated evidence of CE, regardless of the direct or indirect training group and this was strongest in wrist strength measures (rather than grip).

To our knowledge, this is the first study to investigate upper limb cross-education in MS. This work contributes to the field of CE in a MS population and contributes to existing literature in robotic rehabilitation that can be used to drive correct dosage, load, and frequency to induce strength changes.

Chapter 7 – The effects of an 8-week robotic training program of the upper limb on cross-education of motor control

7.1 Introduction

Cross-education (CE) or the cross-transfer effect have been well documented for over a hundred years (Scripture EW, Smith TL, Brown EM, 1894) and have been deeply studied since (Carroll et al., 2006). Most evidence of cross-education are reported as changes in muscular strength (Ehrensberger et al., 2016) in the untrained limb despite some evidence that motor control or task performance is also transferable (Barss et al., 2016). Motor control is defined as “the CNS’ ability to produce purposeful, coordinated movements in its interaction with the rest of the body and the environment” (Latash et al., 2010). Individuals with MS can experience both motor control and cognitive impairments and it is assumed that this results in deficits in the ability to acquire new motor skills (Tablerion et al., 2020). As outlined by Winstein et al., 2014, capacity, motivation and skill are required to successfully complete activities of daily living with the impaired limb. Therefore, the CE effect of motor control and performance are just as important as strength and deserves further exploration, specifically, for individuals with neurological conditions whereby one limb is often impaired. CE in stroke survivors has been investigated for rehabilitation purposes, with meaningful benefits (Munn et al., 2004). Studies have also suggested that benefits are greater when compared to healthy participants (Carroll et al., 2006). As such, CE is known to be paradoxical to the current rehabilitation (i.e., not focusing on the impaired limb) but has still been well received from clinicians for a promising future (Russell et al., 2018). Although this research exists for stroke populations, there remains little evidence of the effects of CE in multiple sclerosis (MS) and the benefits to rehabilitation despite individuals of MS benefiting from neuroplastic changes, motor learning of activities of daily living and overall rehabilitation. The question remains whether the motor control effects of CE in MS are a beneficial component to add to the rehabilitation paradigm.

Robotics have been well documented as a rehabilitative modality to improve muscular strength and motor control in MS participants (Lamers et al., 2014). Comparative to traditional resistance training, robotic devices have the potential to target strength and motor learning simultaneously in a single training session. In previous work, our team demonstrated that a four-week robotic training paradigm incorporating assistive and resistive forces was able to increase strength while improving overall performance in hand tracking error, thus suggestive of motor learning (Mannella et al., 2021). These results were similar to existing literature, using a reach-and-grasp task whereby stroke survivors were able to re-create a figure with decreased degree of error post- training (Vergaro, Casadio, et al., 2010). Interestingly, studies that primarily focused on the motor control aspect also reported an increase in strength despite strength not being the secondary or overlooked objective (Mannella et al., 2022). Further emphasizing that robotic tasks, regardless of the primary objective, can train both strength and control over a training intervention.

The relationship between muscular strength and performance in activities of daily living are currently under debate. Some studies have argued that planned and structured exercise is the single most effective non-pharmacological intervention for managing symptoms of MS, whereas some have argued against this statement because of a lack of research (Motl & Sandroff, 2015). Following a review of 54 papers, (Motl & Sandroff, 2015) found inconclusive evidence regarding the link between exercise and overall quality of life. Regardless, it is important to consider that increasing strength could result in improved quality of life, and it is important that the skills used in therapy transfer to functionality. Robotic rehabilitation is a modality that in adjunct to exercise can increase muscular strength (Mannella et al., 2022).

Clinical evaluations used to determine severity of disease for MS are often clinician-based assessments and there is a lack of functional assessments aimed towards the upper limb. There is a need to develop quantitative and novel assessments to determine severity of disease, functionality and further, predict disease progression. A lack of sensitive quantitative tools can impact the effectiveness and clinicians' decision for therapeutic approach (Scott & Dukelow, 2011). Robotic devices are a quantitative tool that have been used as a functional assessment of the upper limb and cognition for individuals with MS (Simmatis et al., 2020).

The purpose of this Chapter was to investigate objectives 3 and 4 of this dissertation, to evaluate adaptations of motor control and performance following 8-weeks of robotic training of the upper limb for PwMS and to examine any cross-over effects of performance to the contralateral/untrained limb.

7.2 Methods

7.2.1 Participants

A total of 14 individuals with MS and 8-non-MS controls participated in this study. The MS group was further broken down based on limb trained in the intervention. Six participants completed a double baseline, with no training intervention. Detailed group demographics and intervention methods are further outlined in Chapter 6. Participants with MS were required to have a medical diagnosis of MS and were required to have functional use of at least one upper limb as the robotic protocol was did not offer assistance. Participants were excluded if they were currently undergoing a relapse or suffered from any trauma to the upper limb other than impairments due to MS related symptoms (i.e., broken bones). Inclusion criteria of the non-MS group consisted of being free from neurological impairments and participants were excluded if they had any broken bones, sprains, or injury to the upper limbs

Participants were placed into four groups by the researchers based on participant demographics:

1) **Indirect training group (IT):** Participants with MS (N=7) visited the lab 3 times a week for approximately a 25-minute training session using their <u>self-reported less affected limb</u> regardless of hand-dominance although it was recorded for reference.

2) **Direct training group (DT):** Participants with MS (N=7) visited the lab 3 times a week for 8-consectuive weeks for approximately a 25-minute training session using their self-reported more affected limb, regardless of hand dominance. It is important to allow for a self-reported most-affected limb because that is the limb that is most impaired during basic function and activities of daily living which are important to one's quality of life.

3) **Control group (CON):** Participants with no neurological disorders (N=8) visited the lab 3 times a week for approximately a 25-minute training session using their dominant limb (assessed using the Edinburgh Handedness Questionnaire – Appendix E).

4) **Double Baseline (DB):** Participants with MS (N=6) did not participate in training sessions but underwent pre and post assessments separated by 4-weeks. The double baseline group was essential to use as a comparative group to explain that any changes which may occur during the training was due to the intervention and not due to the varying symptoms of MS.

This study was designed as a longitudinal training program (Chapter 5 – Figure 11). As part of the test battery, robotic sensorimotor and clinical outcome measures of performance were evaluated before (PRE) and after (POST) intervention to assess motor control adaptations in the trained limbs and untrained limbs. A sub-group of MS participants (N=3) and Control participants (N=3) completed a 14–16-week assessment of all outcome measures to assess retention of motor control and task transfer in the trained and untrained limbs.

7.2.2 Clinical Assessments

Typical clinical assessments of severity of disease were conducted pre- and post intervention to identify change of severity of disease post training and to compare to novel robotic assessments.

Clinical assessments included:

1. Expanded Disability Status Scale (EDSS)

   The EDSS is a universally used scoring system amongst clinicians to classify level of disease (Appendix D). The scale ranges from 0 to 10, increasing by 0.5 units. A higher level indicates a higher level of disability. Level 0 is classified as asymptomatic, whereas level 10 is classified as death by MS. It is based on measure of impairment in eight functional systems: pyramidal, cerebellar, brainstem, sensory, bowel/bladder function, visual function, cerebral functions and other. Levels 5 to 9.5 are quantified by impairment to gait and one's reliance on walking aids. The validity and reliability of the EDSS has been well tested. A systematic review by Meyer-Moock et al., 2014, confirmed that the literature has certified good validity of the assessment. Validity has been proven to have with strong correlations to functional clinical scales in diagnosing severity of disease such as the Functional Independence Measure (Brosseau & Wolfson, 1994). However, the EDSS has been proven to have a low inter and intra-rater reliability (Noseworthy et al., 1990; Meyer-Moock et al., 2014). Measures such as training users, and having the same investigator complete all assessments are methods to help strengthen the reliability of the scale.

2. ABILHAND Questionnaire

   The ABILHAND was included to further assess the level of disability in one's everyday life (Appendix F). The questionnaire consists of 23 questions if the participant is: 0 = not at all able to complete the activity without an assistive device, 1 = only partially or with great difficulty, or 2 = fully and easily able to complete a daily activity. The scores are then weighted and totalled. The scoring system is a linear unit that indicates the probability of success of an activity. A higher logit or percent of the range of measurement implies a higher probability of success. A total percentage score of 0 indicates minimum ability and a total score of 100 indicated maximum ability. The test-retest reliability of this assessment has been investigated by Ekstrand et al., 2014, from stroke survivors and has confirm high intraclass correlation coefficients. As well as a study with 300 MS participants confirmed that the assessment is robust, with high reliability as measured by the Person Separation Index, and is a beneficial way to measure upper limb function (Barrett et al., 2013).

7.2.3 Robotic Sensorimotor Assessments

Robotic sensorimotor assessments were completed pre- and post intervention. All robotic assessments were conducted on both trained and untrained limbs. The post assessment days (POST) were conducted within 7 days of the last training session to ensure accurate measure of changes of motor learning and that the changes in robotic and clinical measures are due to adaptations in motor learning and not due to acute learning. The tasks performed in both assessment sessions were different than that performed during the training sessions and using novel tasks as an assessment allows for investigation into transfer learning (Kantak & Winstein, 2012). Transfer learning is important for one's quality of life as it is important that the strength or performance increases can be transferred into activities of daily living. Lastly, to investigate whether the adaptations are from transient learning or long-term learning (Kantak & Winstein, 2012) a follow-up session (FU) of robotic sensorimotor assessments were taken 14–16-weeks post intervention to investigate the long-term neuroplastic and CE adaptations. Participants were positioned in the same position as the training (Figure 6) to complete the following assessments:

Hand Tracking Task

Participants were positioned in the same position as the training (Chapter 5), seated in an upright position and their arm rested in the Wristbot, with a neutral pronation/supination posture, gripping the handle. By moving the end-effector with their wrist, participants tracked a moving icon around a Lissajous-curve (Figure 21). Participants were instructed to follow the icon as closely as possible. The target icon moved at a velocity of 20 °/s and 5 total laps were completed. The Lissajous curve enabled the wrist to move in combination of flexion, extension, radial and ulnar deviation with no movement in pronation/supination. The robot provided no assistance or resistance during the tracking task. Tracking and figural error were calculated as measures of performance.

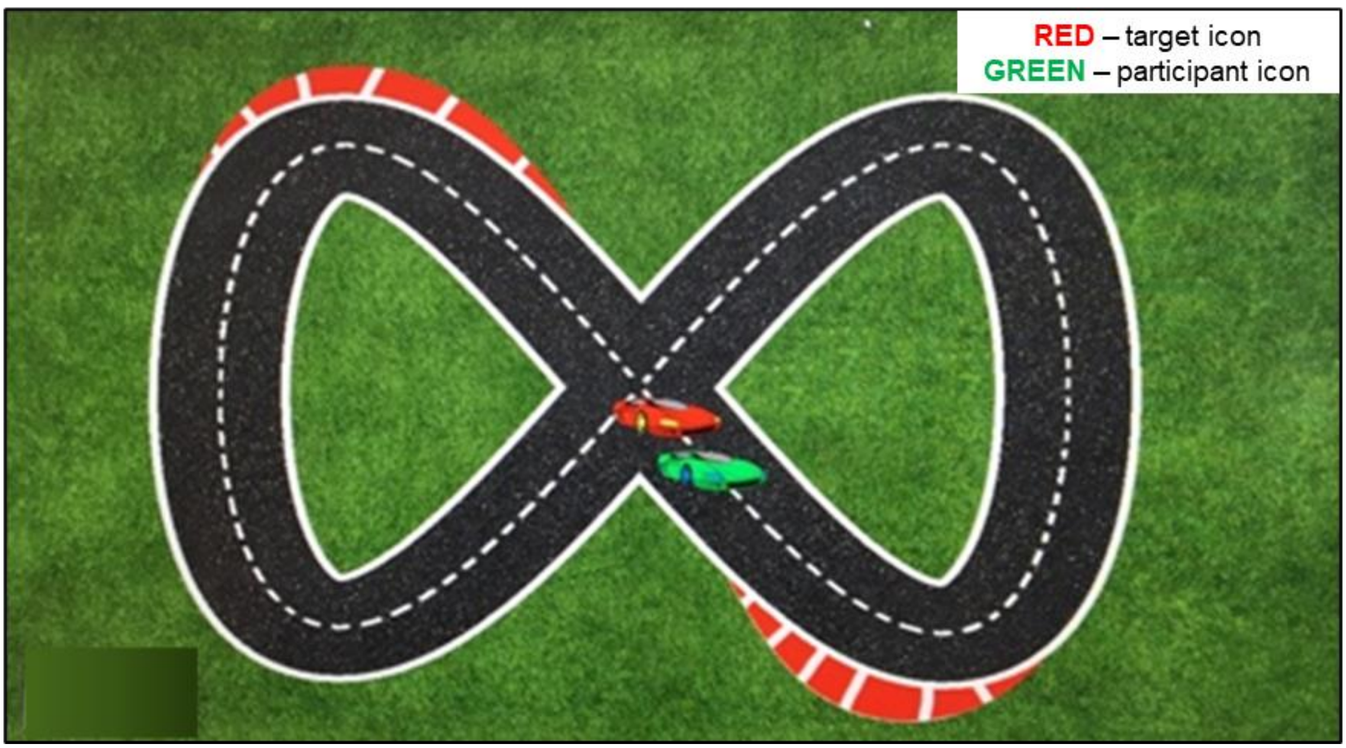


Figure 21. Lissajous-curve performed during the tracking assessment

Range of Motion

Seated in an upright position with the participant's hand grasping the end-effector, participants were asked to perform an active range of motion task (Figure 22). Target icons appeared on the monitor in front of them, participants were then asked to match the icon to the best of their abilities. When the user was at their maximal end-point range, the data was stored and recorded by the robotic device. This assessment consisted of two repetitions in flexion, extension, radial and ulnar deviation.

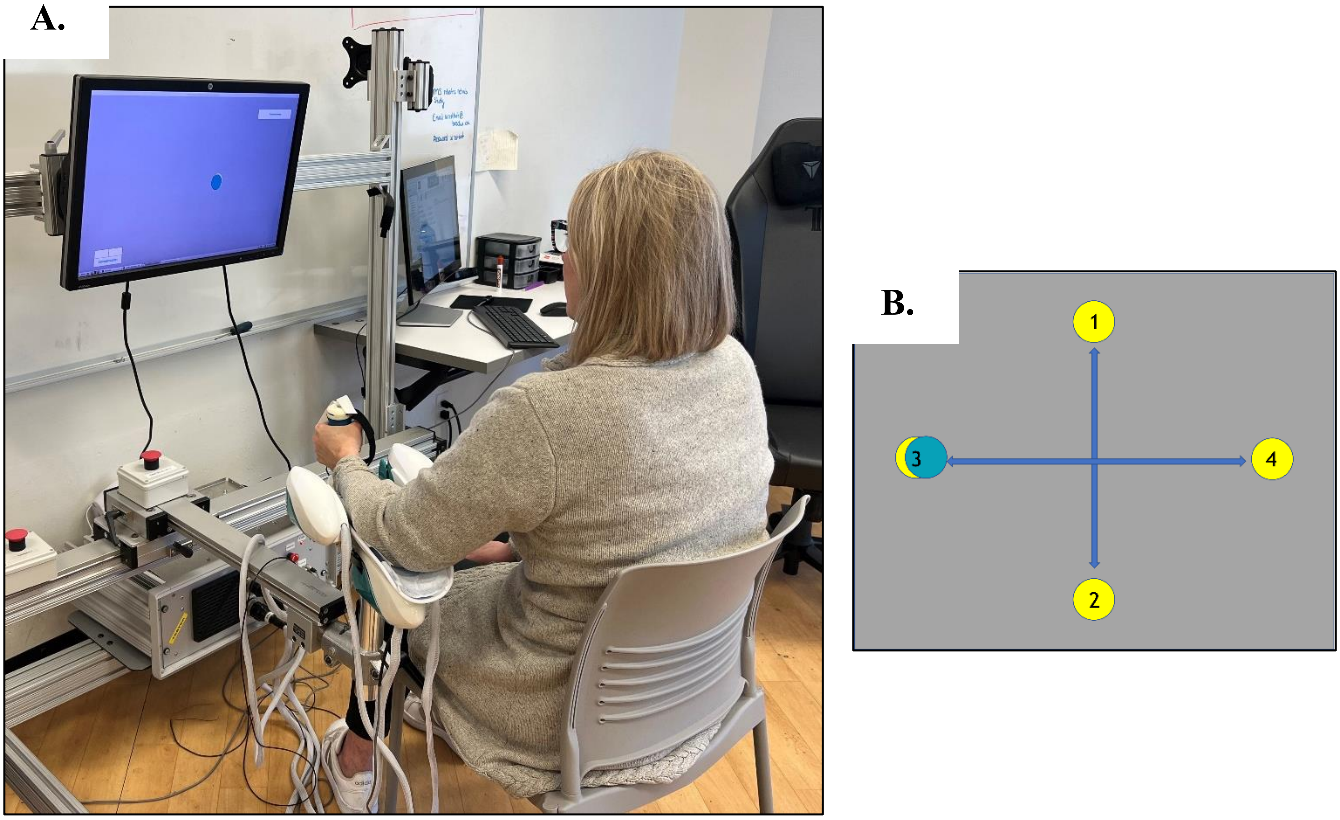


Figure 22. A) Participant performing active range of motion assessment, B) Directions (flexion, extension, radial and ulnar deviation) of the active range of motion targets

Proprioception

Proprioception was assessed using a joint position matching task. Participants were seated with their hand grasping the handle with their eyes closed (no vision of the monitor). The robot then moved the end-effector and therefore the participant's wrist to a randomized angle in flexion/extension. After a brief hold, the robot passively returned the participant to neutral, and an auditory signal indicated that the participant actively re-created the same joint angle or position (Figure 23). Matching error and error bias were calculated as measures of performance.

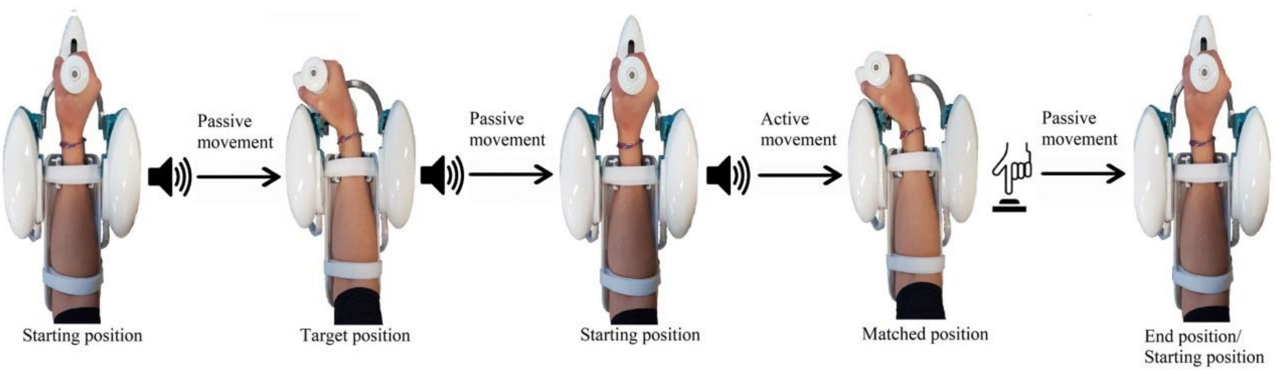


Figure 23. Proprioception assessment. Photo retrieved from (Albanese et al., 2021)

7.3 Data Analysis

Tracking and Figural Error

Tracking error was used as a measure of performance to determine the adaptive force, as previously described in Chapter 5 - section 5.2.2. Tracking error was defined as the mean angular distance in degrees between end-effector and target position at each time point, represented as the point at the center of the sphere that is visually presented during the training (Albanese et al., 2022). The instantaneous distance between target and end-effector was summed over the total tracking trial and divided by the total number of samples. Tracking error was computed starting from the data recorded by the encoders along flexion/extension (x[deg]) and radial/ulnar deviation (y[deg]). The measure was given by the following equation:

$$Tracking\ Error = \frac{\sum_{i=1}^{N} \sqrt{\left(x_{T,i} - x_{H,i}\right)^2 + \left(y_{T,i} - y_{H,i}\right)^2}}{N}$$

Where, T,i = is the target at each time sample and H,i = is the end-effector position at each time sample.

Figural error measured the differences between the participant’s trajectory and the template trajectory (degrees) regardless of the participant's speed and tracking error. The measure is given by the following equation:

$$
\begin{cases}
dist_{AB}(i) = \min\limits_{j} \left\| A_i - B_j \right\| & i = 1,2,..n \\
dist_{BA}(j) = \min\limits_{i} \left\| A_i - B_j \right\| & j = 1,2,..m \\
FE = \frac{\sum_{i=1}^{n} dist_{AB}(i) + \sum_{j=1}^{m} dist_{BA}(j)}{n+m}
\end{cases}
$$

Where A and n are the time series and total samples of the target trajectory. B and m represent the time series total samples of the end-effector trajectory (Conditt et al., 1997).

Active ROM

Active ROM was defined as the maximum distance in degrees a participant could actively reach along each direction (flexion/extension, radial/ulnar deviation). Participants were asked to move the end-effector to a target icon, moving their wrist as close to end range as possible. Once full ROM was achieved, the robot stored and recorded the values. From active ROM exercises the corresponding active excursion for each joint angle was derived and stored by the robot (degrees).

Proprioception (Joint Position Matching)

Participants were instructed to hold the end-effector with eyes closed. The robot moved the end-effector to a random angle along flexion/extension axis within a range from neutral, mid-range and end-point and then returned the participant's wrist to neutral. After an auditory cue, the participant recreated the angle to the best of their abilities. There were 6 trials in total, three in each direction. Changes in joint position matching (JPM) post training provides insight towards improved proprioception. From the JPM exercise, overall performance, actual (active) and desired (passive) positions were compared. The same angles and protocol were performed for PRE and POST assessment.

Matching error (ME) and error bias (EB) were assessed following the guidelines of (Marini et al., 2016). Matching error (ME) was used to quantify the overall accuracy of all trials (N=6) and is computed by the absolute mean distance in joint angle between the proprioceptive target and the subject's matched point:

$$ME = \frac{\sum_{i=1N} |\theta_i - \theta_T|}{N}$$

Where, θ_i = final angle of the wrist, θ_T is the target angle and N = number of trials (N=6).

Error bias (EB) was used to measure the average directional distance and deviation of error from the target angle. N=12, 6 targets in flexion, and 6 targets in extension. Undershooting the target is represented with a negative EB and overshooting is represented with a positive EB:

$$EB = \frac{\sum_{i=1:N} (\theta_i - \theta_T)}{N}$$

Where, θ_i = final angle of the wrist, θ_T is the target angle and N = number of trials (N=6).

7.3.1 Statistical Analysis

A 2 (limb: trained/untrained) x 2 (time: pre/post) repeated measures ANOVA with between group effects (IT, DT, CON, DB) was conducted to compare all outcome measures (tracking/figural error, ROM, JPM) (SPSS Statistics for Windows, Version 26.0. IBM Corp.: Armonk, NY, USA). A Bonferroni post-hoc was conducted to assess interactions. Significance was set to $p < .05$.

A one-way ANOVA with between group effects was conducted to compare mean group scores (IT, DT, CON, DB) of the ABILHAND and EDSS PRE/POST intervention (SPSS Statistics for Windows, Version 26.0. IBM Corp.: Armonk, NY, USA). Bonferroni pot-hoc was used to assess interactions. Significance was set to $p < .05$.

Follow-up: Due to the small sample size (MS: N=3; CON: N=3), statistical analysis was not completed. Mean and overall trends are reported and presented (group mean ± standard deviation).

7.4 Results

7.4.1 Clinical Assessment Results

According to the ABILHAND group mean scores, there was no change pre- and post intervention for IT, DT, CON or DB ($p>.05$) (Table 15). There was a between group effect ($F_{(3,23)}=4.71$, $p=.010$, $\eta^2=.381$). Post-hoc analysis revealed ABILHAND for DT was significantly different that CON at PRE ($p=.015$) and POST ($p=.05$), IT was significantly different than CON at PRE ($p=.038$) and POST ($p=.038$). IT and DT were not different from one another ($p=1.00$), IT did not differ from DB ($p=1.00$) and DT did not differ from DB (1.00).

Table 15. Group means of ABILHAND scores (± standard deviation)

Group	Participant Measure (group mean PRE)	Participant Measure (group mean POST)
Indirect Training	70 ± 7.09%	70 ± 7.09%
Direct Training	65.94 ± 6.19%	65.94 ± 6.19%
Control	100%	100%
Double Baseline	88 ± 10.98%	88 ± 10.98%

According to the EDSS group mean scores, there was no change pre- and post intervention for IT, DT, CON or DB ($p>.05$) (Table 16). There was a between group effect ($F_{(3,23)}=15.21$, $p<.001$, $\eta^2=.665$). Post-hoc analysis revealed DT was significantly different that CON at PRE ($p=<.001$) and POST ($p<.001$), IT was significantly different than CON at PRE ($p<.001$) and POST ($p<.001$). IT and DT were not different from one another ($p=1.00$), IT did not differ from DB ($p=.027$) and DT did not differ from DB ($p=.166$).

Table 16. Group means of EDSS (± standard deviation)

Group	EDSS PRE	EDSS POST
Indirect Training	5.28 ± 1.22	5.28 ± 1.22
Direct Training	4.5 ± 2.6	4.5 ± 2.6
Control	0	0
Double Baseline	2.43 ± 1.02	2.43 ± 1.02

7.4.2 Robotic Sensorimotor Results

Tracking Error

A 2 (trained/untrained x 2 (PRE/POST) x 4 (IT, DT, CON, DB) repeated measures ANOVA was conducted to assess changes in figural error PRE and POST across all participant groups. Analysis reported no main effects of limb ($F_{(1,18)}$=1.986, p=.176; η^2=.099). There were main effects of time ($F_{(1,18)}$=4.253; p=.05; η^2=.191) (Figure 24).

A Bonferroni post-hoc analysis showed a decrease in tracking error PRE/POST of the trained (PRE: 3.92±2.8°; POST: 2.87±2.35°; p=.029; η^2=.118) and untrained limb (PRE: 5.04±2.75°; POST: 2.85±1.57°; p=.012; η^2=.135) for the IT group. There was a decrease in tracking error PRE/POST of the trained (PRE: 1.88±.54°; POST: 1.24±0.31°; p=.045; η^2=.377) and untrained (PRE: 1.83±0.24°; POST: 1.19±0.19°; p=.013; η^2=.972) limb for the DT group (Figure 24).

There were no changes in tracking error PRE/POST for the trained (PRE: 2.72±2.19°; POST: 1.69±1.35°; p=.25; η^2=.412) and untrained (PRE: 2.33±1.38°; POST: 1.65±0.79°; p=.241; η^2=.254) limbs for the CON group. Lastly, there were no significant changes PRE/POST for the dominant (PRE: 2.04±.72°; POST: 2.18±0.84°; p=.642; η^2=.052) and non-dominant (PRE: 3.68±1.62°; POST: 3.52±1.41°; p=.862; η^2=.123) limb for the DB group. No group effects were found ($F_{(3,18)}$=2.301; p=.112, η^2=.277) (Figure 24).

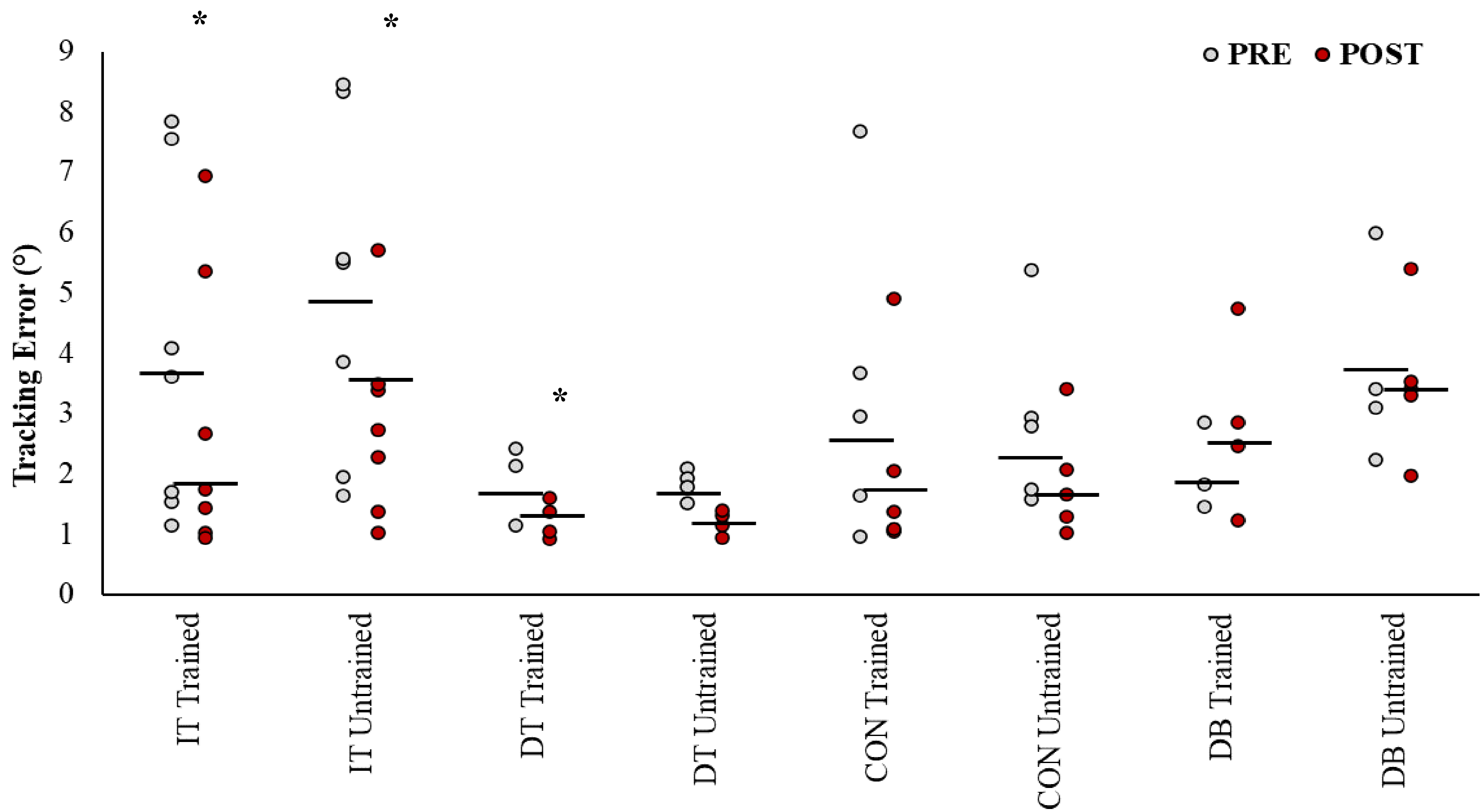


Figure 24. Tracking Error PRE/POST across all groups. Data is represented as mean and standard error of group values. Black line represents group means, grey dots represent individual data points at PRE and red dots represent individual data points at POST. Abbreviations: IT – indirect training, DT – direct training, CON – control, DB – double baseline. *denotes significance

Figural Error

A 2 (trained/untrained x 2 (PRE/POST) x 4 (IT, DT, CON, DB) repeated measures ANOVA was conducted to assess changes in figural error PRE and POST across all participant groups. Analysis reported no main effects of limb ($F_{(1,18)}$=3.209; p=.090; η^2=.151). There were main effects of time ($F_{(1.18)}$=18.063; p=.000; η^2=18.063).

A Bonferroni Post-hoc analysis reported a decrease in figural error PRE/POST of the trained (PRE: 1.19±.61°; POST: 0.75±0.23°; p=.038; η^2=.491) and untrained limb (PRE: 1.49±0.81°; POST: 1.02±0.53°; p=.028; η^2=.239) for the IT group. There was a decrease in figural error PRE/POST of the trained (PRE: 0.82±0.24°; POST: 0.54±0.13°; p=.032; η^2=.981) but not in the untrained (PRE: 0.76 ± 0.13°; POST: 0.58 ± 0.12°; p = .064; η^2=.991) limb for the DT group (Figures 25 & 26).

There were decreases in figural error PRE/POST for the trained (PRE: 0.73 ± 0.16°; POST: 0.56 ± 0.12°; p = .004; η^2=.390) and untrained (PRE: 0.75 ± 0.15°; POST: 0.78 ± 0.10°; p = .024; η^2=.111) limbs for the CON group (Figure 27 & 29). Lastly, there were no changes PRE/POST for the dominant (PRE: 0.74±0.16°; POST: 0.79±0.10°; p=.612; η^2=.058) and non-dominant (PRE: 0.96±0.25°; POST: 0.96±0.15°; p=.986; η^2=.050) limb for DB. Group effects show the IT group significantly different than the CON group ($F_{(1,18)}$=3.457; p=.038; η^2=.366) of the trained and untrained limbs ($F_{(1,18)}$=.259; p=.041; η^2=.006) (Figures 25 & 27).

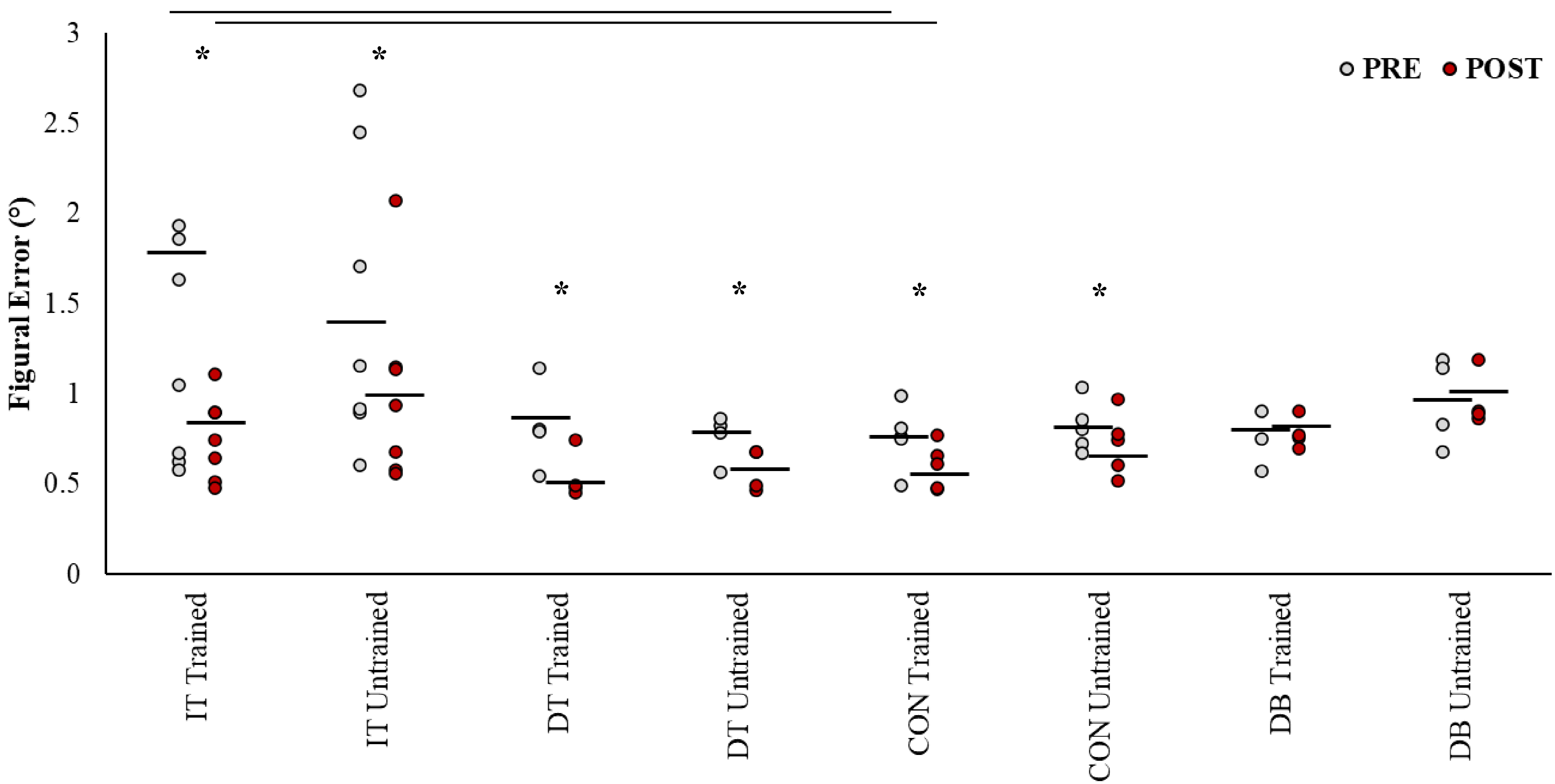


Figure 25. Figural Error PRE/POST for the across all groups. Data is represented as mean and standard error of group values. Black line represents group means, grey dots represent individual data points at PRE and red dots represent individual data points at POST. Abbreviations: IT – indirect training, DT – direct training, CON – control, DB – double baseline. *denotes pre/post significance, long horizontal lines denote significance between groups.

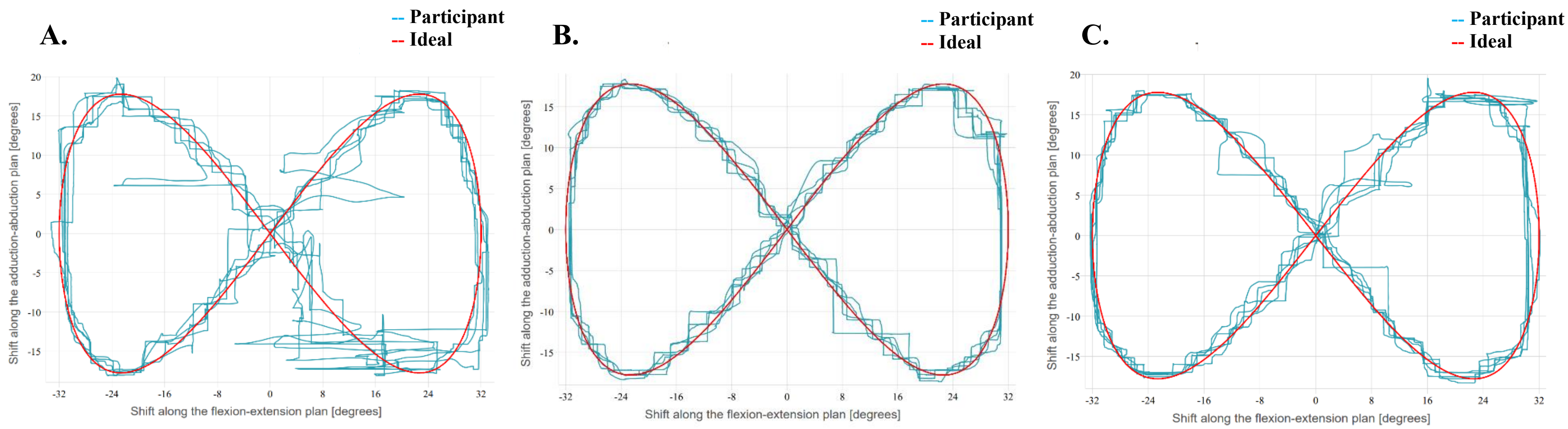


Figure 26. Raw tracking positional data represented from a participant (blue) in comparison to the target trace (red) for the MS Direct Training Group (representative of the right trained limb). A. PRE, B. POST, C. Follow-up

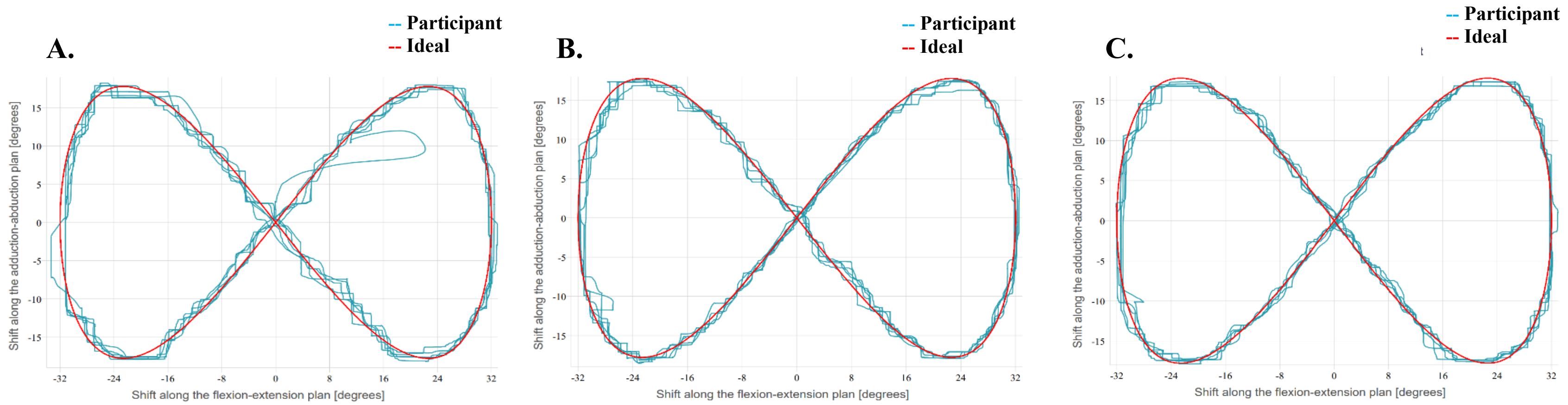


Figure 27. Raw positional data represented from a participant (blue) in comparison to the target (red) for the Control Group (representative of the right trained limb). A. PRE, B. POST, C. Follow-up

Active ROM

A 2 (trained/untrained x 2 (PRE/POST) x 4 (IT, DT, CON, DB) repeated measures ANOVA was conducted to assess changes in ROM (flexion, extension, radial deviation, ulnar deviation) PRE and POST across all participant groups (Figure 28).

Flexion

Analysis revealed no main effects of limb ($F_{(1,18)}$=4.547; p=.047; η^2=.202), time ($F_{(1,18)}$=1.617; p=.220; η^2=.082) or between groups ($F_{(3,18)}$=.130; p=.941; η^2=.021). Post-hoc analysis reported no significant changes PRE/POST in the trained and untrained limbs across all groups. No changes in IT ROM PRE/POST in the trained (PRE: 61.05±6.59; POST: 59.6±7.76; p=.784; η^2=.248) or untrained (PRE: 60.58±6.12; POST: 55.69±2.31; p=.093; η^2=.465). No changes in DT ROM PRE/POST in the trained (PRE: 63.99±3.53; POST: 58.25±8.68; p=.334; η^2=.068) or untrained (PRE: 63.04±7.23; POST: 55.72±8.28; p=.114; η^2=.333). No changes in CON in the trained (PRE: 60.1±3.83; POST: 60.77±4.93; p=.766; η^2=.055) or untrained (PRE: 58.72±5.49; POST: 60.6±5.99; p=.481; η^2=.105). No changes in DB ROM PRE/POST in the trained (PRE: 61.8±2.15; POST: 61.9±2.19; p=1.00, η^2=.050) or untrained (PRE: 56.35±6.17; POST: 57.7±4.52; p=.799; η^2=.064).

Extension

Analysis reported no main effects of limb ($F_{(1,18)}$=3.141; p=.093; η^2=.149), time ($F_{(1,18)}$=2.584; p=.125; η^2=.126) or between groups ($F_{(3,18)}$=.502; p=.686; η^2=.077). Post-hoc analysis reported no changes PRE/POST in the trained and untrained limbs across all groups. No changes in IT ROM PRE/POST in the trained (PRE: 54.57±9.44; POST: 50.97±11.26; p=.072; η^2=.051) or untrained (PRE: 53.83±10.12; POST: 54.61±11.54; p=.835; η^2=.061). No changes in DT ROM PRE/POST in the trained (PRE: 56.25±2.81; POST: 53.98±57.97; p=.564; η^2=.053) or untrained (PRE: 56.61±8.6; POST: 55.09±2.31; $p=.765$; $\eta^2=.229$). No changes in CON ROM PRE/POST in the trained (PRE: 59.09±3.42; POST: 51.65±7.79; $p=.224$, $\eta^2=.050$) or untrained (PRE: 58.93±7.95; POST: 53.86±5.54; $p=177$; $\eta^2=.136$). No changes in DB ROM PRE/POST in the trained (PRE: 55.33±7.61; POST: 55.14±8.19; $p=.796$, $\eta^2=.184$) or untrained (PRE: 60.96±5.32; POST: 59.59±6.63; $p=.831$; $\eta^2=.230$).

<u>Radial Deviation</u>

Analysis revealed no main effects of limb ($F_{(1,18)}=.141$; $p=.712$; $\eta^2=.008$), time ($F_{(1,18)}=2.471$; $p=.133$; $\eta^2=.121$) or between groups group ($F_{(3,18)}=.849$; $p=.485$; $\eta^2=.124$). Post-hoc analysis reported no changes PRE/POST in the trained and untrained limbs across all groups. No changes in IT ROM PRE/POST in the trained (PRE: 30.23±11.32; POST: 35.62±10.28; $p=.098$; $\eta^2.110$) or untrained (PRE: 28.86±12.87; POST: 37.59±7.19; $p=.339$; $\eta^2=.076$). No changes in DT ROM PRE/POST in the trained (PRE: 34.38±11.63; POST: 37.60±5.98; $p=.337$; $\eta^2.310$) or untrained (PRE: 35.23±11.48; POST: 36.92±5.73; $p=.599$; $\eta^2=.849$). No changes in CON ROM PRE/POST in the trained (PRE: 38.92±10.09; POST: 36.31±4.41; $p=.554$; $\eta^2=.129$) or untrained (PRE: 39.15±6.37; POST: 39.91±3.43; $p=.727$; $\eta^2=.061$). No changes in DB ROM PRE/POST in the trained (PRE: 37.89±11.34; POST: 40.27±8.92; $p=.158$; $\eta^2=.082$) or untrained (PRE: 38.96±3.49; POST: 38.25±4.34; $p=.822$; $\eta^2=.055$).

<u>Ulnar Deviation</u>

Analysis revealed main effects of limb ($F_{(1,18)}=.13.923$; $p=.002$; $\eta^2=.436$) and time ($F_{(1,18)}=17.175$; $p=.001$; $\eta^2=.488$). There were no between group effects ($F_{(3,18)}=.2.803$; $p=.069$; $\eta^2=.318$). Post-hoc analysis reported an increase in IT ROM PRE/POST in the trained limb (PRE: 31.24±3.08°; POST: 39.29±4.63°; $p=.021$; $\eta^2=.050$) and untrained limb (PRE: 28.26±4.39°; POST: 40.08±5.97°; $p=.001$; $\eta^2=.260$). There were no changes in ulnar deviation for DT PRE/POST in the trained (PRE: 37.65±3.73; POST: 37.83±4.38; $p=.927$; $\eta^2=.925$) and untrained (PRE: 26.78±4.49; POST: 31.93±5.28; $p=.148$; $\eta^2=.980$) limb. CON showed increases in ulnar deviation ROM PRE/POST for the trained limb (PRE: 33.87±4.88°; POST: 41.06±3.73°; $p=.019$; $\eta^2=.939$), but no changes in the untrained limb (PRE: 33.62±4.38°; POST: 37.44±5.25°; $p=.197$; $\eta^2=.283$). Lastly, DB showed no changes in ulnar deviation ROM PRE/POST in the dominant (PRE: 29.87±5.01; POST: 38.21±5.38; $p = .255$; $\eta^2=.077$) or untrained (PRE: 33.11±9.44; POST: 28.17±6.17; $p = .435$; $\eta^2.244$) limb.

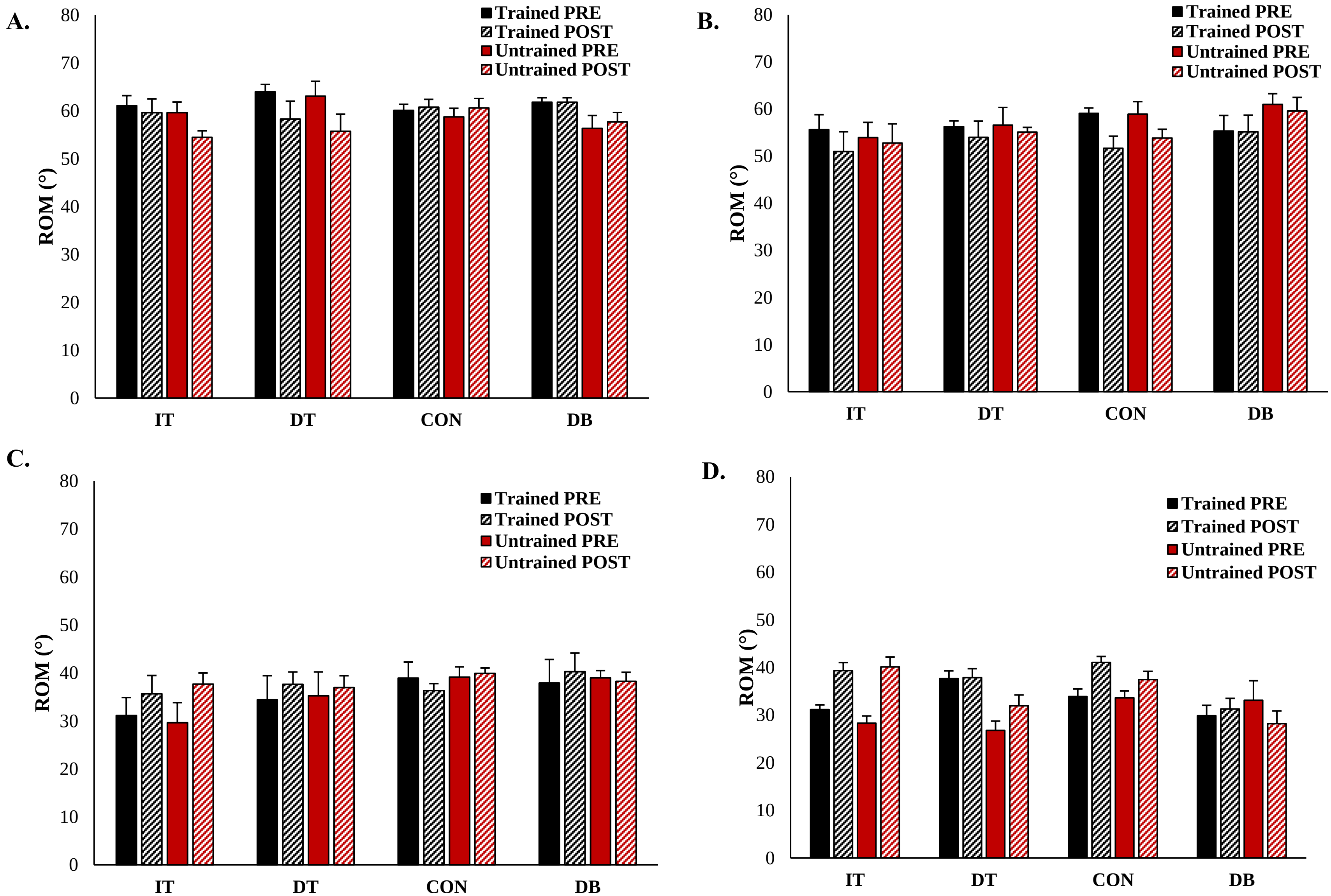


Figure 28. Active ROM (PRE/POST) across all groups. A. flexion, B. extension, C. radial, D. ulnar. Data represents mean and standard error of group values. Abbreviations: IT – indirect training, DT – direct training, CON – control, DB – double baseline

Proprioception

Matching Error – Flexion

A 2 (trained/untrained x 2 (PRE/POST) x 4 (IT, DT, CON, DB) repeated measures ANOVA was conducted to assess changes in Matching Error (flexion) PRE and POST across all participant groups. Analysis revealed no main effect of limb ($F_{(1,16)}$=2.546; p=.130; η^2=.137) or between groups ($F_{(1,16)}$=.310; p=.818; η^2=.055). There was a main effect of time ($F_{(1,16)}$=5.070; p=.040; η^2=.397) (Figure 29).

A Bonferroni post-hoc analysis reported no significant changes in ME in the trained (PRE: 10.57±7.77; POST: 10.10±7.89; p = .395; η^2=.979) or untrained (PRE: 6.4±3.78; POST: 8.66±6.86; p = .118; η^2=.055) for IT. There was significant decrease in ME in the trained (PRE: 13.45±7.67; POST: 3.25±1.7; p =.003; η^2=.057) or untrained (PRE: 4.49±1.92; POST: 4.94±2.36; p=.322; η^2.281) for DT.

There were no significant changes in ME in the trained (PRE: 8.26±3.08; POST: 8.53±3.89; p=.054; η^2=.262), untrained (PRE: 10.66±7.04; POST: 9.09±8.2; p=.214; η^2=.228) for CON. Lastly, there were no significant changes in ME in the trained (PRE: 4.27±2.52; POST: 8.53±3.89; p=.725; η^2=.059) or untrained (PRE: 4.27±2.52; POST: 5.18±2.53; p=.658; η^2=.079) for DB.

Matching Error – Extension

A 2 (trained/untrained x 2 (PRE/POST) x 4 (DT, IT, CON, DB) repeated measures ANOVA was conducted to assess changes in Matching Error (extension) PRE and POST across all participant groups. Analysis revealed no main effect of limb ($F_{(1,16)}$=2.353; p=.145; η^2=.128), time ($F_{(1,16)}$=.014; p=.906; η^2=.001) or between groups ($F_{(3,16)}$=2.096; p=.141; η^2=.282) (Figure 30).

A Bonferroni post-hoc analysis reported no significant changes in ME PRE/POST in extension across all groups. IT presented no significant changes in ME in the trained (PRE: 6.35±3.19; POST: 9.94±11.14; p=.157; η^2=.162) or untrained (PRE: 9.99±6.94; POST:

16.35±14.75; $p=.205$; $\eta^2=.050$). DT presented no significant changes in ME in the trained (PRE: 7.7±3.51; POST: 4.2±1.6; $p=.345$; $\eta^2=.248$) or untrained (PRE: 5.13±.53; POST: 4.9±4.9; $p=.711$; $\eta^2=.343$).

For the control groups, CON presented no significant changes in ME in the trained (PRE: 5.56±4.76; POST: 6.69±4.13; $p=.562$; $\eta^2=.080$), untrained (PRE: 8.8±4.89; POST: 5.16±4.38; $p=.172$; $\eta^2=.148$). Lastly, there were no significant changes in ME in the trained (PRE: 3.03±1.3; POST: 4.3±1.82; $p=.264$; $\eta^2=.069$) or untrained (PRE: 12.57±7.68; POST: 7.71±5.48; $p=.170$; $\eta^2.186$) for DB.

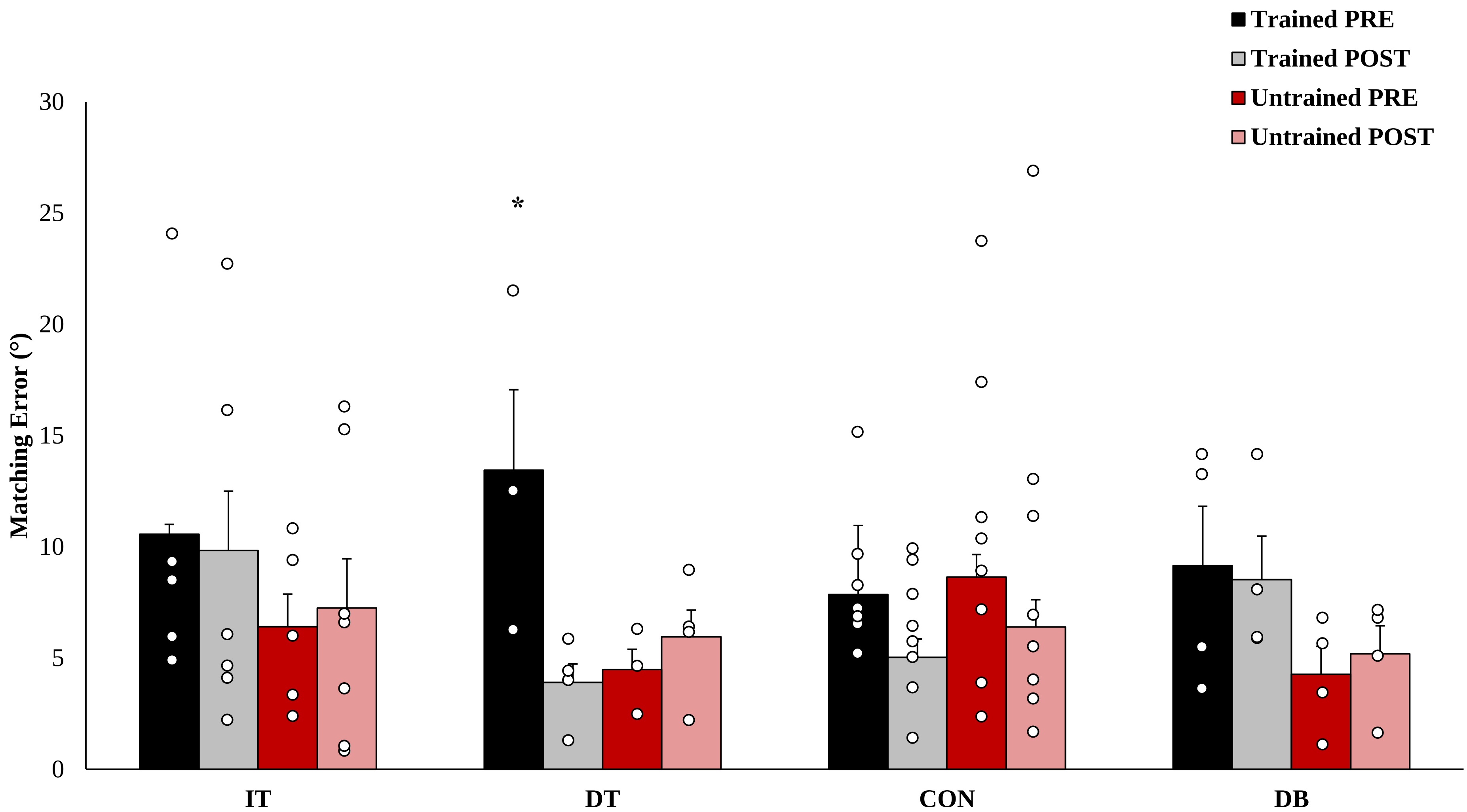


Figure 29. Matching error (degrees) of flexion across each group for the trained/untrained limb at PRE/POST. Data are represented as group means, individual data points and standard error bars. *denotes significance

Abbreviations: IT – indirect training, DT – direct training, CON – control, DB – double baseline

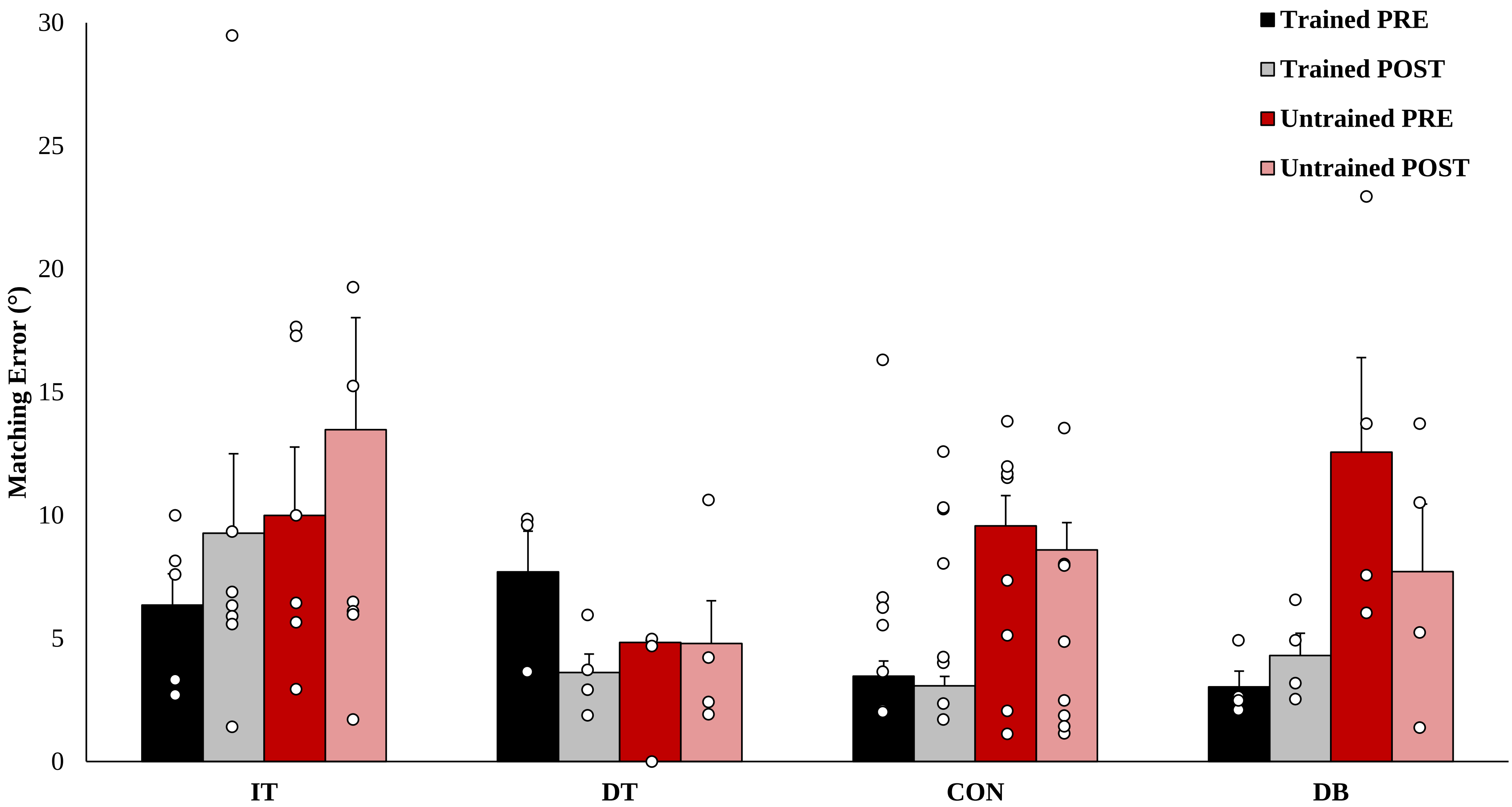


Figure 30. Matching error (degrees) of extension across each grip for the trained/untrained limb at PRE/POST. Data are represented as group means, individual data points and standard error bars

Abbreviations: IT – indirect training, DT – direct training, CON – control, DB – double baseline

Error Bias – Flexion

A 2 (trained/untrained x 2 (PRE/POST) x 4 (DT, IT, CON, DB) repeated measures ANOVA was conducted to assess changes in error bias (EB) PRE and POST across all participant groups. Analysis revealed no main effect of limb ($F_{(1,16)}$=2.546; p=.130; η^2=.137) or between groups ($F_{(1,16)}$=.310; p=.818; η^2=.055). There was a main effect of time ($F_{(1,16)}$=5.070; p=.040; η^2=.397).

A Bonferroni post-hoc analysis reported no significant changes in EB in the trained (PRE: 10.57±7.77; POST: 10.10±7.89; p=.980; η^2=.703) or untrained (PRE: 6.4±3.78; POST: 8.66±6.86; p=.499; η^2=.051) for IT. There were no significant changes in EB in the trained (PRE: 13.45±7.67; POST: 3.25±1.7; p=.053; η^2=.134) or untrained (PRE: 4.49±1.92; POST: 4.94±2.36; p=.476; η^2=.350) for DT.

For the control groups, there were no significant changes in EB in the trained (PRE: 8.26±3.08; POST: 8.53±3.89; p=.387; η^2=.154), untrained (PRE: 10.66±7.04; POST: 9.09±8.2; p=.221; η^2=.155) for CON. Lastly, there were no significant changes in EB in the trained (PRE: 4.27±2.52; POST: 8.53±3.89; p=.859; η^2.050) or untrained (PRE: 4.27±2.52; POST: 5.18±2.53; p=.499; η^2=.122) for DB.

Error Bias – Extension

A 2 (trained/untrained x 2 (PRE/POST) x 4 (DT, IT, CON, DB) repeated measures ANOVA was conducted to assess changes in EB PRE and POST across all participant groups. The analysis revealed no main effects for limb ($F_{(1,16)}$ = 3.568, p=.077, η^2 = .182), time ($F_{(1,16)}$=2.833, p=.112, η^2=.150), or between groups ($F_{(3,16)}$=2.838, p=.071, η^2=.347).

A Bonferroni post-hoc analysis indicated no significant changes in EB for the trained (PRE: 1.91±7.19; POST: -.33±12.21; p=.123; η^2=.104) or untrained (PRE: -3.52±11.82; POST: -16.35±14.75; p=.138; η^2=.172) limbs in IT. Similarly, there were no significant changes in EB for the trained (PRE: 6.47±4.65; POST: 4.19±1.57; $p=.337$; $\eta^2=.139$) or untrained (PRE: 2±5.85; POST: -3.37±6.64; $p=.436$; $\eta^2=.872$) limbs in DB.

No changes in EB were observed for the trained (PRE: -1.49±7.4; POST: -.63±8.16; $p=.684$; $\eta^2=.070$) or untrained (PRE: -4.89±8.39; POST: -2.53±6.4; $p=.482$; $\eta^2=.112$) limbs in CON. There were no changes in EB for the trained (PRE: 1±3.27; POST: 2.71±4.26; $p=.515$; $\eta^2=.091$) or untrained (PRE: -5.16±14.26; POST: -4.67±6.72; $p=.912$, $\eta^2=.051$) limbs in the DB group.

7.4.3. Follow-Up Assessments

Motor Control

Results show a small decrease POST/FU in Figural Error performance for the MS group in the trained (POST: 0.706±0.209°; FU: 0.637±0.237°) and a small increase in the untrained (POST: 0.724±0.194°; FU: 0.754±0.17°) limb (Figure 31). There was no change POST/FU in Tracking Error performance in the trained (POST: 2.628±2.379°; FU: 2.678±2.697°; p=1.00) and a slight increase in error for the untrained (POST: 1.938±1.349°; FU: 2.181±1.551°; p=.109) limb (Figure 32).

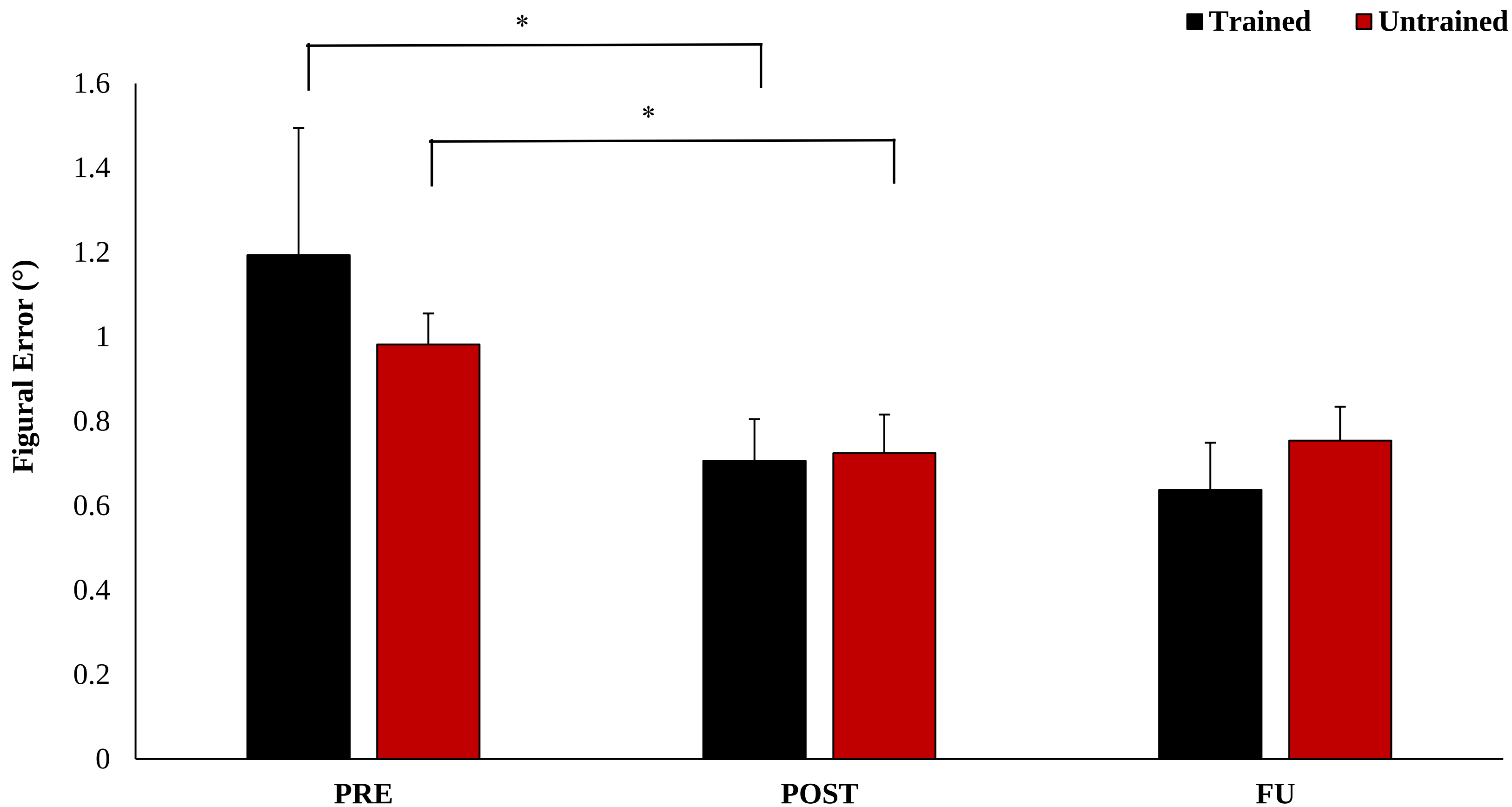


Figure 31. Figural Error of the MS Group (pooled Direct and Indirect) PRE, POST and FU. Data are represented as group means and standard error *denotes significance

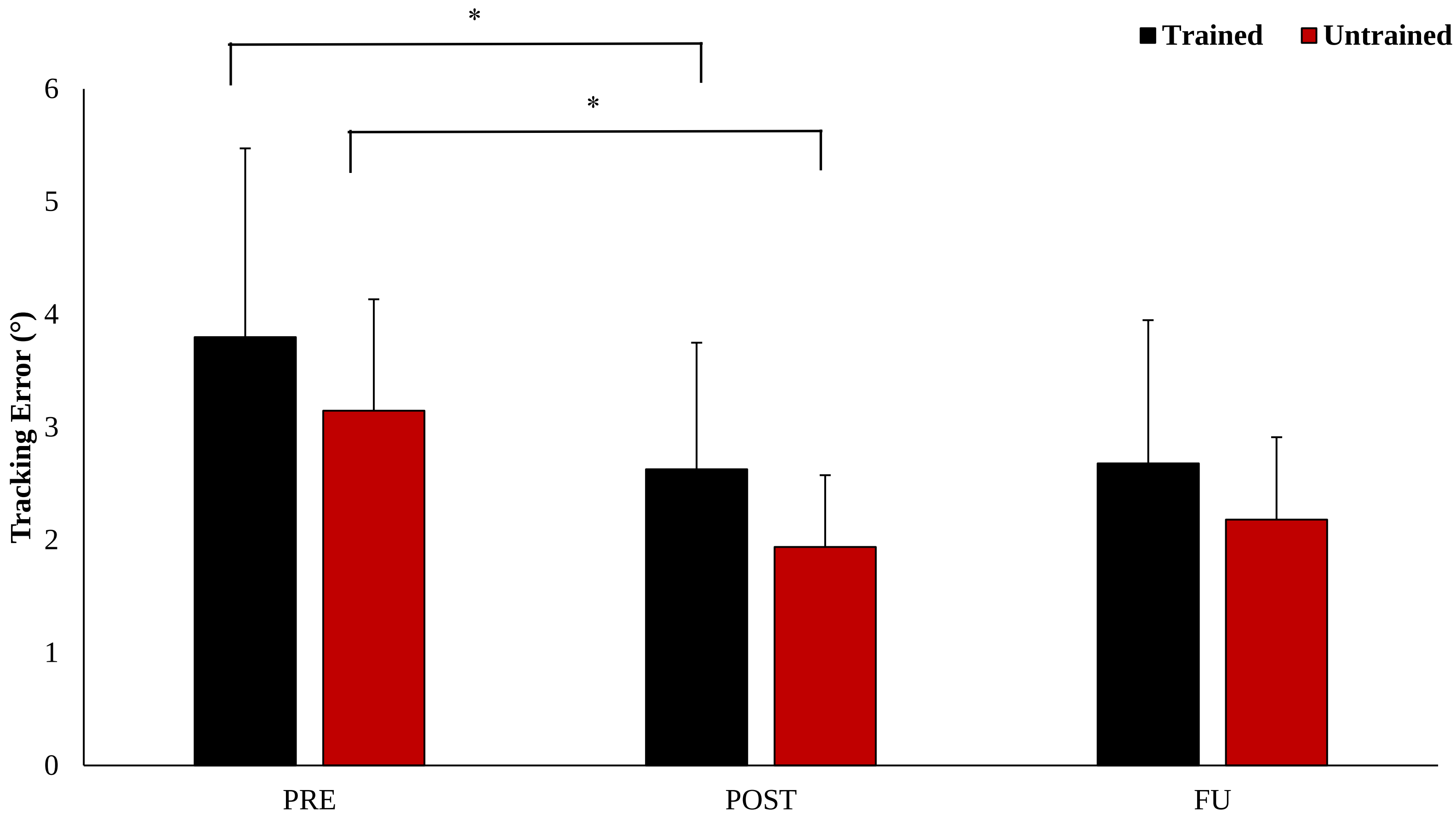


Figure 32. Tracking Error of the MS Group (pooled Direct and Indirect) PRE, POST and FU. Data are represented as group means and standard error *denotes significance

Results show little change POST/FU in Figural Error performance for the CON group in the trained (POST: 0.536±0.108°; FU: 0.601±0.189°) and untrained (POST: 0.676±0.109°; FU: 0.670±0.071°; $p=1.00$) limbs (Figure 33). Results also show a slight increase in error POST/FU in Tracking Error for the CON group in the trained (POST: 1.168±0.206°; FU: 1.568±0.595°) or untrained (POST: 1.147±0.248°; FU: 1.751±0.714°) limbs (Figure 34).

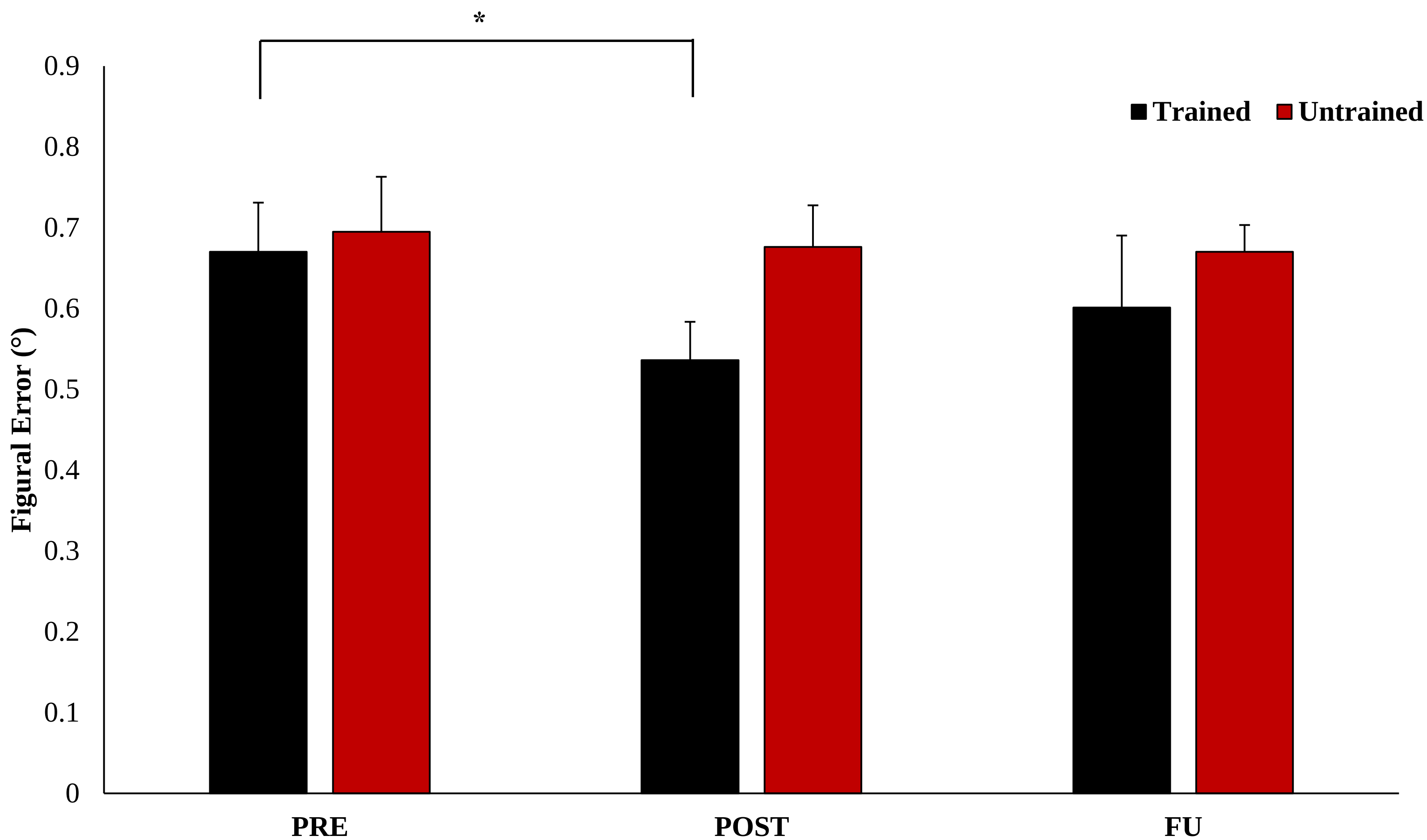


Figure 33. Figural Error of the CON Group PRE, POST and FU. Data are represented as group means and standard error
*denotes significance

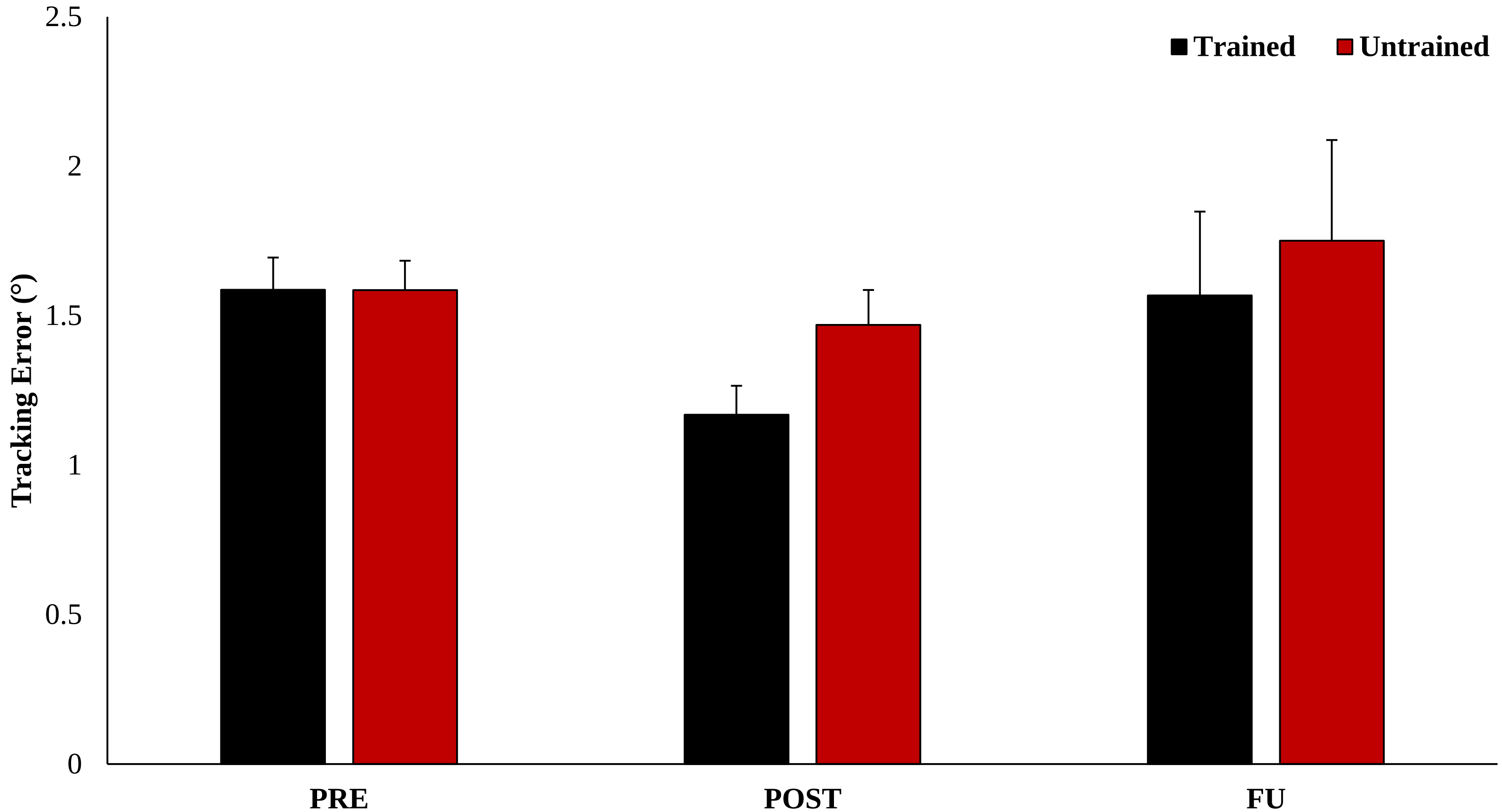


Figure 34. Tracking Error of the CON Group PRE, POST and FU. Data are represented as group means and standard error

Joint Position Matching

Overall trends for ME POST/FU show a small decrease for the MS group in flexion for the trained (POST: 11.081±10.121°; FU: 10.642±10.111°) or untrained (POST: 6.188±7.898°; FU: 3.996±1.31°) limbs. There was an overall decrease in ME POST/FU in extension for the trained (POST: 12.282±15.071°; FU: 5.681±3.190°) and untrained (POST: 3.198±2.408°; FU: 5.069±0.848°) limb.

There was an overall decrease in EB POST/FU for the MS group in flexion for the trained (POST: 3.058±11.459°; FU: -7.462±13.202°) and untrained (POST: 5.42±8.626°; FU: 1.154±4.597°) limb. Whereas there was a small increase in EB POST/FU in extension for the trained (POST: -4.837±8.626°; FU: -0.942±7.406°) and untrained (POST: -3.198±2.408°; FU: 1.498±5.489°) limb.

Results show an overall increase in error POST/FU for the CON group in ME in flexion for the trained (POST: 4.785±3.242°; FU: 7.471±5.459°) and a decrease in error for the untrained (POST: 6.681±4.86°; FU: 2.799±0.788°) limbs. Similar results for extension as there was a slight increase in error for the trained (POST: 2.764±1.321°; FU: 2.878±2.162°) and a slight decrease in error for the untrained (POST: 8.789±4.395°; FU: 6.208±5.928°) limb.

Results show an overall increase in error POST/FU for the CON group in EB in flexion for the trained (POST: -1.25±6.479°; FU: 4.837±7.646°) and a decrease in error for the untrained (POST: -5.898±6.098°; FU: -1.389±1.941°) limbs. As well as in extension, there was an increase in error for the trained (POST: 2.31±1.259°; FU: -1.108±3.607°) and a slight decrease in error for the untrained (POST: -5.541±9.439°; FU: -3.355±8.385°) limb.

Robotic Outcome Measures – Range of Motion

Results show no change POST/FU for the MS group in ROM in flexion for the trained (POST: 60.906±4.208°; FU: 61.493±5.027°) or untrained (POST: 54.396±4.537°; FU: 56.683±3.505°) limbs, or extension in the trained (POST: 53.082±2.538°; FU: 55.53±5.332°) or untrained (POST: 59.183±4.086°; FU: 58.215±5.886°) limbs, radial deviation in the trained (POST: 39.651±2.789°; FU: 39.246±.568°) and untrained (POST: 39.662±1.159°; FU: 39.222±2.274°) limbs, lastly in ulnar deviation in the trained (POST: 37.927±7.131°; FU: 35.055±4.556°) and untrained (POST: 36.917±11.89°; FU: 30.362±11.596°) limbs.

Results show no change POST/FU for the CON group in ROM in flexion for the trained (POST: 65.657±1.609°; FU: 63.002±3.12°) and untrained (POST: 63.654±2.533°; FU: 55.399±3.626°) limb. As well as extension in the trained (POST: 43.936±6.483°; FU: 53.254±2.162°) and untrained (POST: 52.728±7.951°; FU: 57.53±4.256°) limb. As well as in radial in the trained (POST: 33.391±2.425°; FU: 40.594°) and untrained (POST: 39.089±0.477°; FU: 39.502±5.647°) limb. As well as ulnar deviation in the trained (POST: 41.023±6.256°; FU: 35.502±7.129°) and untrained (POST: 36.959±4.361°; FU: 35.806±2.99°) limb.

7.5 Discussion

Following the eight-weeks of robotic training of the upper limb, this chapter focuses on the clinical and sensorimotor robotic assessments of the trained and untrained limb. Objective 4 of this dissertation was to evaluate cross-education effects of motor control from pre- post robotic training in the DT, IT, CON and an untrained DB group. Pre and post robotic training, participants completed a series of robotic assessments, including: a wrist tracking task, range of motion and proprioception. It was hypothesized (hypothesis 3) that motor control and therefore, robotic assessment performance would improve pre- post-training. In support of hypothesis 4, tracking and figural error improved following the eight-weeks of robotic training in the trained and untrained limbs suggesting cross-education effects. DT and IT significantly improved in in tracking and figural error in the trained and untrained limbs. CON did not significantly improve in performance/decrease in tracking error but did improve in figural error in the trained limb. There were no significant improvements in range of motion and proprioception for either group. DB group did not show significant changes between assessments and therefore, implicating that the improvements in performance for the other groups were not due to acute learning (from PRE assessment) and rather, was from an improvement in motor control as a result of the intervention. Lastly, the clinical assessments were contradictory in determining group severity of disease and lack sensitivity to performance changes following the training intervention.

<u>Clinical and Sensorimotor Evaluations</u>

Despite being used for decades; subjective clinical scales have been speculated to not be sensitive enough to small rehabilitative progressions or are mainly directed towards impairments in the lower limb or gait (Lamers & Feys, 2014). Most clinical scales are subjective, rather than objective, which could have clinician bias and they are also prone to ceiling effects. Our results support this speculation as no changes in the clinical scales (EDSS and ABILHAND questionnaire) were shown pre- post-training, but quantitative robotic measures of performance (tracking and figural error) were reported. If the scales used for prescribing therapies, predicting functional impairment and progress are not sensitive, this could lead to clinicians potentially prescribing incorrectly, difficulties implementing rehabilitation strategies and delayed progression for the client. For example, a clinician may think the individual could tolerate high load and frequency training, and in turn the client receives less care than optimal treatment. EDSS has been known to be restrictive to discrete changes (Holper et al., 2010) and results of the EDSS not demonstrating any changes in this work further emphasizes this. The ABILHAND questionnaire is self-reported by the participant, thus, there could be a sense of insecurity when completing the questions and as a result the reported responses are untruthful. The questionnaire also has large gaps between ratings, as in not able to hammer a nail (a score of 0) to being able to hammer a nail with no complications (a score of 2). Results of this work further support the argument that evaluations of functional performance and severity of disease need to be quantitative and performance-based scales to ensure the most accurate representation of disease and rehabilitation progressions.

Although there were no significant functional improvements according to the clinical based scales, there were significant improvements in performance on the robotic tracking task assessment. The MS groups (IT and DT) showed a greater decrease in error compared to the control group. However, the MS groups also had a greater error or decreased performance at PRE compared to the controls and thus, had greater room for improvement. This novel tracing task was selected to also evaluate transfer of learning. The given task allowed the user's wrist to move in two common wrist rotations (flexion/extension, radial/ulnar). For tasks to be functionally relevant it needs to include ROM that represent an activity of daily living (Gates et al., 2016). Thus, the wrist rotational tracking task can provide speculation that the task was functional and possibly transferable. Task learning is the process of improving at the task at hand whereas transfer of learning is also the ability to transfer what has been learnt to a new variant. Motor learning or motor skill acquisition is a process in which requires both principles (Seidler, 2010). The underlying mechanisms of learning and transfer may differ and be affected by aging (Tablerion et al., 2020). However, specificity of learning is also an important consideration, dating back more than 60 years, it has been suggested that learning is specific to the task performed (Bachman, 1961). In this work, we saw no improvements in proprioception PRE/POST intervention which may be explained by specificity of learning. Proprioception is often impaired in PwMS due to damaged white matter pathways as a result of the disease and thus, affecting processing of sensory feedback (Fling et al., 2014). This robotic training intervention lacked proprioceptive feedback. It can be suggested that because proprioception is such a complex sense, that to improve it, it may need to be directly trained. It has been shown that individuals with MS have decreased proprioception compared to non-affected adults, as measured by an ankle repositioning test by Ozkan et al., 2023, and has been contributed to balance and gait issues. However, most literature investigates deficits in proprioception and improving gait and less is known about proprioception and the functional deficits of the upper limb (Jamali et al., 2017). Similarly, there were no significant changes in active range of motion found between the MS and non-MS groups. Baseline ROM results for the MS groups identified as functional which was comparable to the non-MS participants, consequently, there was no obvious improvement from pre- to post-training. In addition, the training task was individually set to 80% of ROM, with relatively normative baseline ROM values, 80% ROM would not have stretched the tissues or actively challenged the users ROM and could have also contributed to the unchanged POST values. Lastly, this result could be a limitation and constraint of the mechanical device. If the starting positioning of the robot (participant's wrist) was not placed directly in the centre of the device before beginning the assessment, this could lead to possible starting inaccuracies or the device limiting any further movement. Future work should further investigate active ROM impairment without these constraints in MS compared to non-MS controls.

Cross-Education of Motor Control

In the current literature, CE is typically presented as adaptations in muscular strength in the contralateral or untrained limb despite evidence of motor control transfer effects (Manca et al., 2020). Tracking error and figural error outcome measures are both representative of motor control and learning. This work demonstrates improvements in a novel tracking task in the untrained limb for both MS groups as tracking and figural error decreased post training, indicative of an increase in performance. A systematic review by Tablerion et al., 2020, revealed investigations where PwMS transferred reaction time to the untrained limb/hand and performance of reaching movement tasks. Green & Gabriel, 2018, reported evidence of reproducing a target task more consistently and steadily in the contralateral limb. Results of our work and that of previous work suggests that transfer effects of motor control and learning is possible for PwMS. Although statistical analysis reported no main effects of group, general trends appear that the IT group (trained their less affected limb) showed greater improvements in tracking and figural error when compared to DT (trained their more affected limb). Despite training their less-affected limb, IT reported greater error or worse performance at baseline when compared to the DT. From previous results (Chapter 6), IT also showed greater increase in strength compared to the DT. However, IT showed greater error at baseline than DT and this could potentially explain why IT reported greater change in performance as there was greater capability to improve in performance.

There was an improvement in figural error from CON, but this group did not improve in other outcomes. Perhaps, similar to Chapter 6 – strength results, that the robotic training was not intense enough for a non-MS group and therefore did not elicit improvements in motor control. However, these robotic assessments are novel, and the CON results provide normative baseline results that can be referred to for future work or comparative to MS results. Statistics in this work showed no group effects, but general trends can be observed that DT and IT produced greater errors at baseline compared to CON, but produced similar ROM results to the CON. Perhaps the smaller sub-group sizes were a limitation to the statistical output and thus, no firm conclusions can be drawn. Perhaps this acts as a stepping stone for future work with larger sample sizes to investigate novel robotic assessments and performative quantitative outcomes between MS and non-MS controls to develop new assessments of progression or disease severity using robotics.

There was evidence of motor control retention as there were no significant decreases in performance in figural and tracking error, range of motion, and proprioception following a 14–16-week assessment for a sub-group of MS participants and Control participants. This suggests that improvements in performance and transfer of a task following the 8-weeks of robotic training remain persistence for up to 14-16 weeks post training. It is important to note that this was also the case for the untrained limb thus, cross-education performance also demonstrated substantial retention. However, the sub-groups of participants were small and future work should include a larger sample size to expand on these results.

7.6 Limitations

This study was limited by the ceiling effects of the chosen subjective questionnaires (EDSS, ABILHAND) and determining progression based on these scales was inconclusive. This study would have further benefitted from a typical functional task (i.e., Wolf Motor Function Task) to objectively measure functional progression. The study was also limited by the sample size of the sub-groups potentially affecting the statistical analysis and comparison of between group effects. Lastly, the robotic assessments used in this work were novel approaches to measuring progression of rehabilitation. More established and regularly used robotic assessments need to be developed for consistency between studies and allow for comparisons of outcomes between future works.

7.7 Conclusion

Cross-education, although very highly investigated for over a century, still have questions remaining surrounding the cross-over of motor control and the benefit of exploiting these effects in rehabilitation. Results of this work provide evidence that motor control can transfer to the untrained limb following eight-weeks of robotic training of the upper limb. Future work should include investigation of functional tasks similar to activities of daily living to directly aid in task completion. Lastly, as the clinical scales remained unchanged following the training although improvements in robotic assessments were reported, provides direct evidence that these subjective scales are not sensitive enough to capture changes in performance in PwMS. A call for better and more quantitative assessments of upper limb impairment or disease progression are required.

Chapter 8 – Investigating changes in corticospinal excitability in individuals with multiple sclerosis following an 8-week robotic training program

8.1 Introduction

Cross-education (CE) is a neurophysiological phenomenon whereby one limb is trained, and the opposing (contralateral) limb exhibits muscular strength and/or skill improvements (Carroll et al., 2006). CE has been highly researched in healthy adults (Scripture EW, Smith TL, Brown EM, 1894) and stroke survivors (Sun et al., 2018b) and effects are amplified in clinical populations with a 29% increase in strength compared to a 15% increase in healthy participants (Green & Gabriel, 2018). Although CE is not an established rehabilitation strategy (Russell et al., 2018), CE has the potential to train asymmetries following stroke, MS or neuromuscular damage (Farthing and Zehr, 2014) and evidence of validity and efficacy of CE for rehabilitative purposes is necessary. CE of strength is often attributed to neural mechanisms, since the phenomenon is observed without muscle hypertrophy (Farthing et al., 2007). However, the sites of neural mechanisms are complex and largely unknown. There is consensus that CE is driven by neural adaptations, but the extent of those adaptations being driven by cortical or spinal levels of the CNS remain in question. To investigate evidence of CE, transcranial magnetic stimulation (TMS) is a non-invasive and painless way to stimulate the motor cortex and can be used as a quantitative assessment tool for evaluating any neurophysiological adaptations or corticospinal excitability of the trained and untrained hemispheres. While TMS fails to provide clear insight into the level of CNS adaptation, considering that CE has largely unexplored in MS populations, it provides a great starting point to better understand the mechanisms of CE.

MS is a bilateral disease but there is often a more affected limb which creates functional asymmetries that can lead to disuse of the more affected limb (Larson et al., 2013). CE could initiate a safer option to successfully “train” a weaker or uncoordinated limb and user engagement would still be feasible. Manual therapy and exercise for the limb that is more spastic, weak, and paretic can be challenging to rehabilitate (Vergaro, Squeri, et al., 2010). To combat this, some have applied novel unilateral training approaches (Manca et al., 2017b). In clinical settings involving PwMS, the effects of CE have led to improvements in ankle strength and mobility in the untrained limb (Manca et al., 2017b) following isometric strength training in both peak moment (Nm) and maximal work (J) ($p>0.03$). However, less is known about CE in the upper limbs. It is hypothesized that neurological changes in the upper limbs are different than in the lower limbs due to a more direct monosynaptic connection within the corticospinal pathway to the upper limb. Literature suggests that high-intensity training (capable with robotics) can induce the neurophysiological changes of CE (Carroll et al., 2006).

TMS is a non-invasive and painless way to assess the integrity of one's central motor pathways, and single pulse TMS can measure cortical excitability (Stampanoni Bassi et al., 2017). When TMS is used on individuals with MS, it can also be an indicator of axonal damage represented by a decrease in MEP amplitude and prolonged central motor conduction time (time taken for neural impulses to travel through the CNS to the targeted muscle) (Stampanoni Bassi et al., 2017). Exercise or skill rehabilitation that results in training-induced adaptations in the CNS can affect the time it takes for the electrical signal generated by TMS to propagate along the corticospinal tract and reach the muscle of the upper limb and can be quantified by MEP onset (recorded in milliseconds) (Latella et al., 2017). Additionally, cortical silent period (CSP) is representative of intracortical inhibition and is displayed as a suppression of EMG or muscle activation following a MEP (Zewdie & Kirton, 2016). A decrease in CSP is indicative of inhibitory circuit activity within motor cortex (M1) (Boyd et al., 2014) and has been observed to decrease in the trained limb following unilateral resistance training in stroke (Lim & Madhavan, 2023; Sun et al., 2018a). Ultimately, TMS is a quantifiable measure of neurophysiological adaptations and can be a useful tool to investigate corticospinal excitability, corticospinal inhibition and disease progression in neurological disorders such as MS.

Very little research has focused on CE in PwMS, specifically in the upper limb and the exact mechanisms of CE have remained elusive, with some consensus that CE is caused by changes in neural activity involving the M1 (Carroll et al., 2006). Chapter 6 demonstrates evidence for CE of strength in the upper limbs of PwMS and given that the site of neural adaptation is unknown in CE, the purpose of this work was to evaluate corticospinal changes in excitability to the forearm muscles following a resistive and adaptive eight-week robotic training intervention.

8.2 Methods

8.2.1 Participants

For TMS measures, participant groups were smaller than Chapter 6 and 7, due to exclusion criteria. As a result, the IT and DT groups were combined for the analysis (MS Group) (Table 17). DT (N=3): Across the entire intervention, there were 7 participants in this group. Of the total 14 participants from Chapters 6 and 7, 4 participants were excluded from TMS for not being able to sustain the 10% contraction and a history of seizures. IT (N=5): Across the entire intervention, there were 7 participants in this group. 2 participants were excluded from TMS due to previous concussions. DB (N=3): Across the entire intervention, there were 5 participants in this group. 2 participants did not pass the safety checklist and were excluded. CON (N=6): Across the entire intervention, there were 8 participants in this group. 2 participants did not pass the safety checklist and were excluded. A one-way ANOVA was conducted to compare sub-group means of group demographics. For mean EDSS, the MS group and double baseline groups significantly differed from one another (MS/double baseline – p=.025). Mean years since diagnosis did not differ between groups (MS/double baseline – p=.742). Mean years of age did not differ between groups (MS/double baseline – p=.718, MS/control – p=.124, control/double baseline – p=.797).

Table 17. Participant Demographics

Group	Weeks Trained	Handedness	Limb Trained	Group Size	EDSS	MS Phenotype	Years Since Diagnosis	Years of Age	Training Sessions Attended
MS Group	8	4– Left 4 – Right	4 – Left 4 – Right	N=8	5.43 ± 1.94	4-RRMS 3-SPMS 1-PPMS	13 ± 10.61	54.71 ± 11.14	23.43 ± 0.49
Non-MS Control	8	1 – Left 7 – Right	1 – Left 7 – Right	N=7	0	N/A	N/A	45.57 ± 18.96	23.75 ± 0.43
Double Baseline MS	0	3 – Right	N/A	N=3	2	3 - RRMS	9.67 ± 7.32	41 ± 2.94	0

Abbreviations: RRMS – relapsing remittent MS, PPMS – primary progressive MS, SPMS – secondary progressive MS. Values are represented as group means ± standard deviation.

8.2.2 Experimental Procedures

Transcranial magnetic stimulation (TMS) was one experimental measure during the battery of pre and post assessments completed in this dissertation. TMS placed over the M1 of each contralateral hemisphere pre- and post- robotic training was used to assess changes in corticospinal excitability of the trained and untrained limbs. All participants were asked to complete a magnetic stimulation safety checklist before beginning TMS. If participants answered yes to the questions – they were not included in the neurophysiological measures.

Electromyographic (EMG) activity of the flexor carpi radialis (FCR) were recorded, bilaterally using disposable bipolar Ag-AgCl surface electrodes (Meditrace 130; Kendall, Mansfield, MA). Electrodes were placed over the muscle belly, in-line with fibre orientation, following previous placement guidelines (Mogk and Keir 2003; Forman et al. 2021). Before electrode placement, hair and epithelial cells were removed via a disposable razor, followed by sanitization with an isopropyl alcohol swab. EMG was band-pass filtered (10–1000 Hz) and differentially amplified (CMRR > 100 dB at 60 Hz; input impedance >10GΩ; AMT-8; Bortec Biomedical Ltd, Calgary, AB, Canada). EMG was sampled at 5 kHz using a CED 1401 interface and Signal 5 software (Cambridge Electronic Design, Cambridge, UK).

Standard lab procedures for EMG and stimulations were followed. Motor-evoked potentials (MEPs) were elicited via TMS of the contralateral motor cortex using a Magstim 200^2 and butterfly coil (Magstim, Dyfed, UK). Participants were seated in a chair, with their arm rested in a neutral position (folded into participant's lap). Participants wore a swim cap to ensure proper placement of the coil over the hotspot for FCR on the motor cortex. Firstly, the vertex was determined by the intersection of the midpoint between the participant's nasion and inion and the midpoint between the participant's tragi (Forman et al., 2016). This location was marked on the swim cap with a marker. Then, the coil was held 45° to the sagittal plane, tangentially to the skull, with the direction of current preferentially activating the correct limb (Figure 35) (Capozio et al., 2021). Stimulations were delivered over the primary motor cortex that corresponds to the motor representation of the FCR muscle, and the coil orientation adjusted based on the largest MEP response from FCR (see procedures below). The FCR muscle representation is located more medially and anteriorly. To ensure correct coil position, ‘hotspotting’ was conducted whereas the coil position was adjusted until a reliable MEP is elicited in the FCR muscle (Capozio et al., 2021). Once the position was determined, it was marked on the swim cap to ensure consistent positioning of the coil through the duration of the protocol. This ‘hotspotting’ procedure and swim cap marking occurred at during the initial pre assessment and occurred again at the post assessment sessions for each participant.

Next, participants were asked to produce maximal isometric wrist flexion against a force transducer (Model:BG500; Mark-10 Corporation, New York, USA) and the maximum voluntary contraction (MVC) force was recorded. 10% of this maximum was calculated and used as a submaximal isometric contraction target during all stimuli (Chapter 6 – section 6.2.4). TMS measures were collected bilaterally (contralateral to the trained limb and ipsilateral to the trained limb). Following coil placement, an active motor threshold (AMT) was determined as the lowest stimulator intensity required to elicit a clearly discernible MEP in 4 out of 8 trials, during a submaximal isometric wrist flexion contraction (10% maximum flexion) in FCR (Forman et al., 2019). Participants traced a target line on a computer screen (Signal 5, Cambridge Electronic Design, Cambridge, UK) set to 10% of their wrist flexion maximum in real time by exerting against the force transducer. MEPs recorded during the AMT were assessed to investigate activity-dependent changes in corticospinal excitability. Once the AMT was determined, a protocol was delivered to produce a stimulus-response curve. Three stimuli were delivered at each of the seven intensities in 10% increments as a percentage of maximal stimulator output (%MSO) between 90 and 150% of AMT (90, 100, 110, 120, 130, 140, 150% of AMT) (Chaves, Snow, et al., 2021).

Figure 35. Participant in TMS set-up

8.3 Data Analysis

Slope of the stimulus response curve (SRC) was identified following previous guidelines (Forman et al., 2019) and was compared PRE and POST training. Slope was manually calculated as the net change in MEP amplitude (normalized to MEP max) over the net change in stimulation intensity, made relative to active threshold (Forman et al., 2019) (Figure 36). To do this, average data for each intensity was graphed and the MEP threshold and MEP plateau were visually selected (Forman et al., 2019), and slope was calculated:

$$\text{Slope} = (\text{MEP}_{\text{plateau}} - \text{MEP}_{\text{threshold}}) / (\text{SI}_{\text{plateau}} - \text{SI}_{\text{threshold}})$$

Whereas $\text{MEP}_{\text{plateau}}$ is where the MEP amplitude begins to remain flat and $\text{MEP}_{\text{threshold}}$ is where the MEP amplitude was visually recognized. $\text{SI}_{\text{plateau}}$ and $\text{SI}_{\text{threshold}}$ represent the stimulus intensity at MEP plateau and MEP threshold.

Area under the curve (AUC) was calculated as a gross measure of corticospinal excitation (Figure 37) and to characterize the effects of the magnitude and duration of the recruitment curve PRE and POST intervention (Zewdie & Kirton, 2016). AUC was calculated using a trapezoidal integration equation outlined by (Chaves, Snow, et al., 2021):

$$\text{AUC} = \Delta X \times (Y1+Y2)/2$$

Whereas, X represents the stimulus intensities (90-150% active motor threshold), and Y values represent MEP amplitudes (µV).

The cortical silent period (CSP) measures cortical inhibition and change in CSP can examine changes in cortical excitability and inhibition of the motor cortex (Zewdie & Kirton, 2016). CSP was calculated as the time (milliseconds) from after the MEP to the point where muscle activity is visible as outlined by (Chaves, Snow, et al., 2021) (Figure 37). CSP at 150% stimulus intensity was compared between PRE/POST of both trained and untrained limbs and between groups (MS and Control).

MEP Onset is a measure of corticospinal excitability whereas shorter onset duration typically indicates a higher level of excitability (Zewdie & Kirton, 2016). MEP onset was measured as the time (milliseconds) between the stimulus artifact and the beginning of the MEP

(Figure 37). Onset at 150% stimulus intensity was compared between PRE/POST of both trained and untrained limbs and between groups (MS and Control).

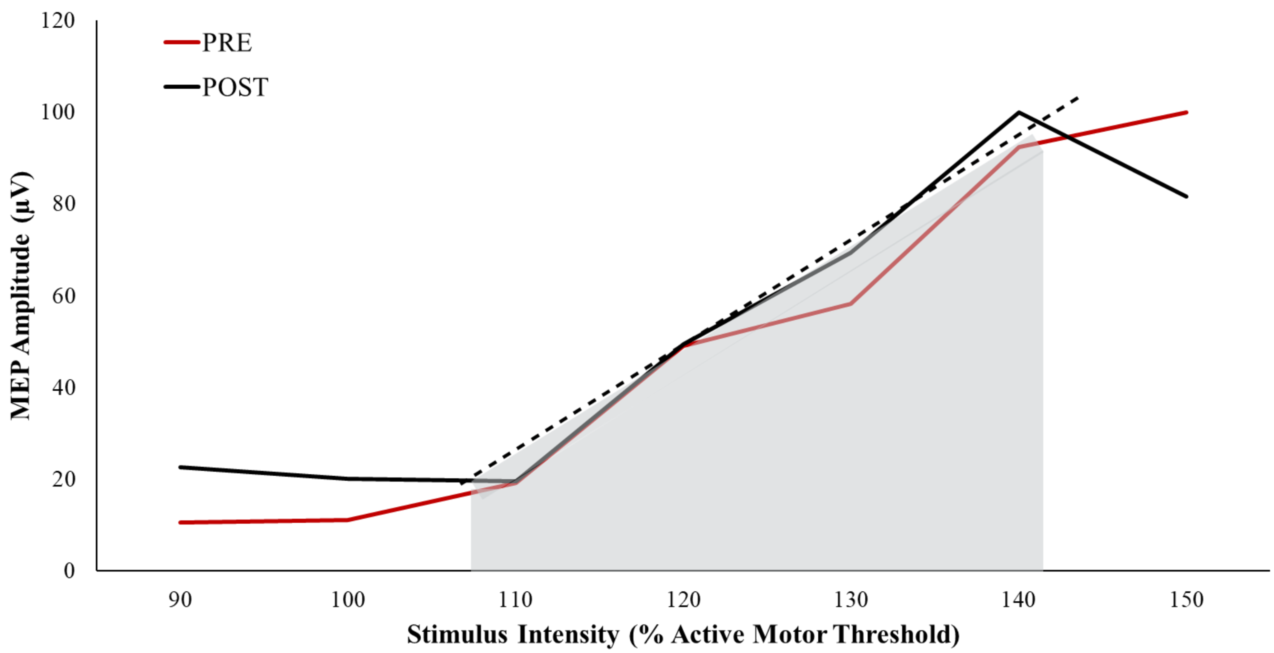


Figure 36. Raw data example of recruitment curve slope calculation, represented by a curve from one participant. Dotted line depicts the linear portion of the curve that was used to calculate the slope. The grey area represents the AUC

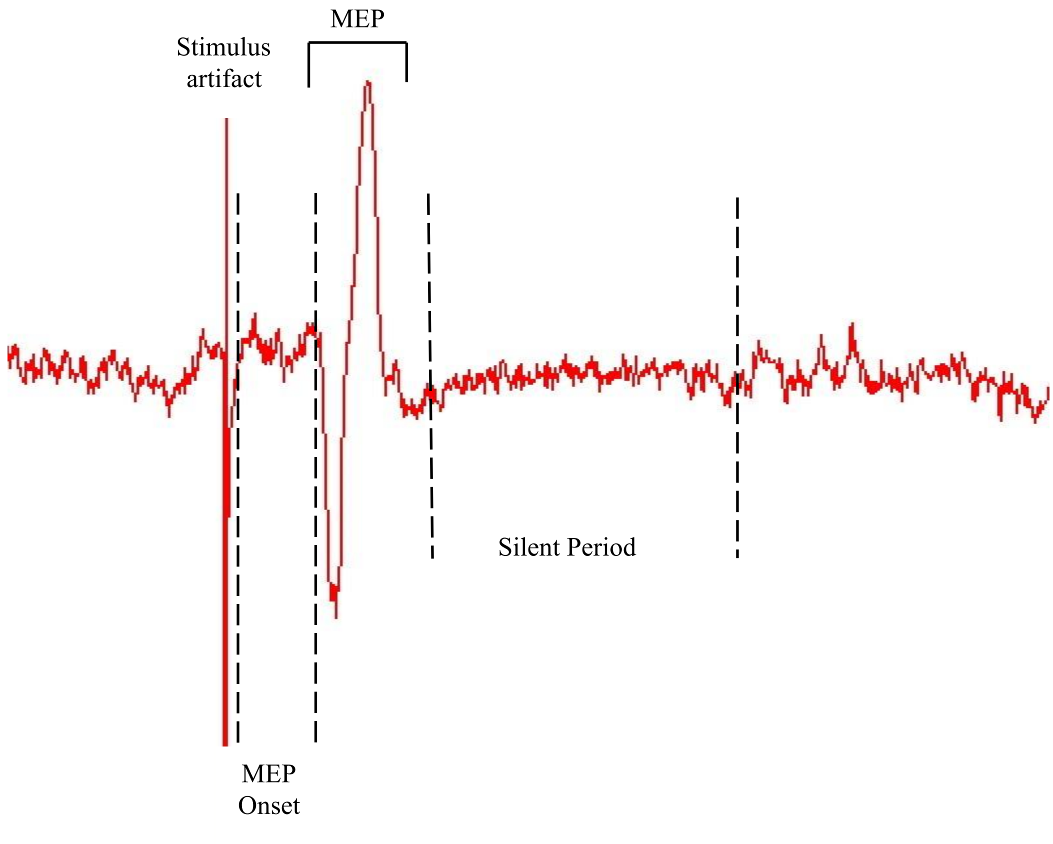


Figure 37. Measures of cortical silent period, MEP peak to peak amplitude and MEP onset

8.3.1 Statistical Analysis

Peak-to-peak MEP amplitudes, silent period and MEP onset were analyzed off-line (Signal 6, CED). The most linear portion of the curve (slope) and AUC were manually calculated in Excel (Microsoft Excel, 2021). A 2 (limb: trained/untrained) x 2 (time: pre/post) repeated measures ANOVA with between group effects (MS, CON, DB) was conducted to compare all outcome measures (slope, AUC, CSP, Onset) (SPSS Statistics for Windows, Version 26.0. IBM Corp.: Armonk, NY, USA). Whereby there was an interaction, a Bonferroni post-hoc was conducted. Significance was set to $p < .05$.

8.4 Results

8.4.1 Strength

Detailed strength results are presented in Chapter 6. However, it is important to mention the strength differences for the cohort involved in the TMS portion of this collection. The percent change scores PRE/POST intervention of the trained and untrained limb are presented in Table 18. The MS cohort increased by a range of 3.22 - 64.32% in the trained limb and 35.96 - 84.87% in the untrained limb. The non-MS control group presented a range of -5.77 - 61.79% in the trained limb and 8.6 - 44.25% in the untrained limb. The double baseline group presented a range from -1.86 - 22.17% in the trained limb and -2.98 - 23.92% in the untrained limb.

Table 18. Percent change scores of strength categorized by group

	Grip	Flexion	Extension	Radial	Ulnar
MS Group (trained)	3.22±13.32%	44.17±38.22	52.24±58.74	64.32±41.53	55.82±47.84
MS Group (untrained)	35.93±68.32	84.87±69.51	59.53±18.54	66.12±34.92	52.89±44.86
Control (trained)	-5.77±6.59	12.93±14.09	49.82±48.92	61.79±56.59	47.95±51.66
Control (untrained)	8.6±6.51	8.97±14.06	27.19±66.63	44.25±57.76	13.33±34.95
DB (trained)	-1.86±9.52	10.11±14.93	22.17±13.08	18.15±23.06	17.13±32.02
DB (untrained)	3.34±17.85	23.92±28.13	-9.11±4.88	-2.98±24.56	2.53±12.86

8.4.2 Recruitment Curves Slope

Slope: There was no limb*group ($F_{(2, 13)}$=.349; p=.712; η^2 =.094) or time*group ($F_{(2, 13)}$=.282; p=.759; η^2 =.085) interaction or limb*time interaction ($F_{(2, 13)}$=.123; p=.223; η^2 =.071). There was no between group ($F_{(2, 13)}$=1.97; p=.179; η^2 =.334) effect (Figure 38).

AUC: There was a limb*group ($F_{(2, 13)}$=4.726; p=.029; η^2 =.685) there was no time*group ($F_{(2, 13)}$=.5.83; p=.016; η^2 =.779) interaction or limb*time interaction ($F_{(2, 13)}$=.396; p=.540; η^2 =.090). There was no between group ($F_{(2, 13)}$=.602; p=.562; η^2 =.129) effect (Figure 38).

Slope and AUC: MS

No significant differences of group mean slopes (MEP amplitude (%max) / %MSO) PRE and POST training were observed in the trained limb (PRE: 1.39±0.56; POST: 1.42±0.43; p=.937; η^2=.051). No significant differences PRE and POST training were observed in the untrained limb (PRE: 1.11±0.57; POST: 1.34±1.17; p=.605; η^2=.078).

There was a non-significant increase in AUC (%MSO * MEP amplitude (%max)) PRE/POST intervention for the trained (PRE: 860.81±368.43; POST: 1174±500; $p=.105$; $\eta^2=.365$) and untrained (PRE: 471.72±264.16; POST: 560.91±433.42; $p=534$; $\eta^2=.091$) limb.

Slope and AUC: CON

No significant differences of group mean slopes (MEP amplitude (%max) / %MSO) PRE/POST training were observed in the trained limb (PRE: 1.02±0.45; POST: 1.46±0.7; $p=.250$; $\eta^2=.201$). No significant differences PRE/POST training were observed in the untrained limb (PRE: 1.74±0.64; POST: 1.74±0.88; $p=.994$; $\eta^2=.050$).

There was a decrease in AUC (%MSO * MEP amplitude (%max)) PRE and POST intervention in the trained (PRE: 1128.64±452.35; POST: 621.47±284.01; $p=.044$; $\eta^2=.541$) and untrained (PRE: 1219±413.74; POST: 832.23±349.79; $p=.047$; $\eta^2=.529$) limbs.

Slope and AUC: DB

No significant differences of slopes between the two assessment periods were observed in the dominant limb (PRE: 1.189±0.58; POST: 1.2±0.5; $p=.981$; $\eta^2=.051$). No significant differences of slopes PRE and POST training were observed in the non-dominant limb (PRE: 1.44±0.19; POST: 1.37±0.35; $p=.918$; $\eta^2=.050$).

There were no significant differences of the AUC (%MSO * MEP amplitude (%max)) PRE and POST intervention in the trained (PRE: 1128.64±452.35; POST: 621.47±284.01; $p=.570$; $\eta^2=.084$) and untrained (PRE: 1219±413.74; POST: 832.23±349.79; $p=.874$; $\eta^2=.053$) limbs.

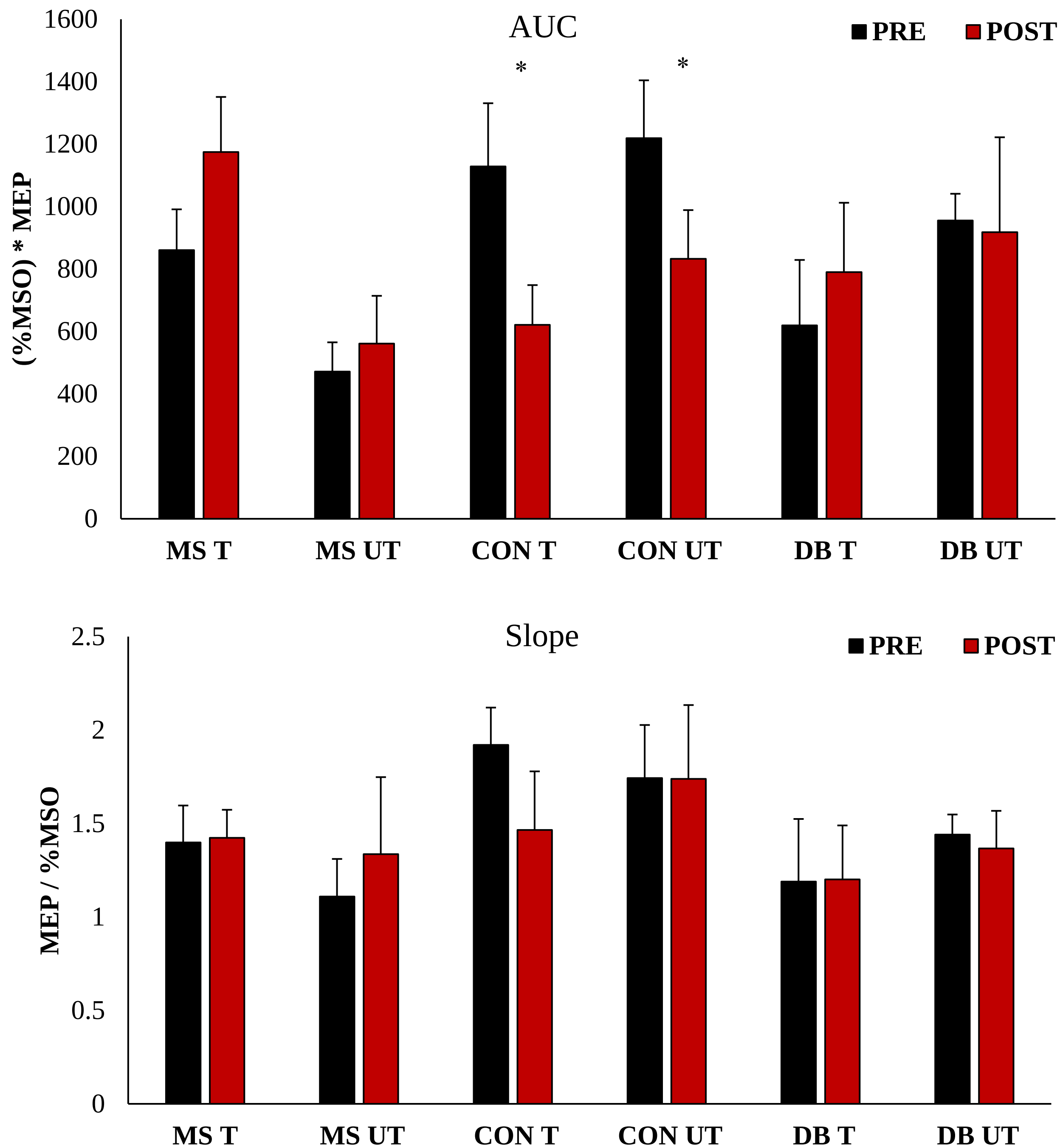


Figure 38. AUC (top), and gain – slope (bottom). Data are represented as group means and standard error. Abbreviations: MS T – T – trained, UT – untrained, MS – MS group, CON – control, DB – double baseline

*denotes significance

8.4.3 Cortical Silent Period

There was no limb*group ($F_{(2, 13)}$= .318; p=.734; η^2=.089) or time*group ($F_{(2, 13)}$= 1.61; p=.241; η^2 =.294) interaction or a between group ($F_{(2, 13)}$= 1.66; p=.230; η^2 =.283) effect (Figure 39).

<u>Mean CSP: MS</u>

CSP at 150% stimulus intensity did not change PRE/POST for the trained (PRE: 35.04±15.61; POST: 32.52±25.41ms; p=.833; η^2=.055) and untrained (PRE: 18.43±17.06; POST: 25.5±27.94ms; p=.106; η^2=.363) limbs. These results suggest there are no changes of inhibition PRE and POST intervention.

<u>Mean CSP: CON</u>

CSP at 150% stimulus intensity did not significantly change PRE/POST for the trained (PRE: 15.15±8.12; POST: 16.93±13.24ms; p=.861; η^2=.053) and untrained (PRE: 23.17±24.94; POST: 14.44±.01ms; p=.444; η^2=.113) limbs.

<u>Mean CSP: DB</u>

CSP at 150% stimulus intensity did not significantly change PRE/POST for the trained (PRE: 35.15±8.11; POST: 31.39±11.86ms; p=.793; η^2=.057) and untrained (PRE: 44.19±12.33; POST: 46.78±16.57ms; p=.059; η^2=.485) limbs.

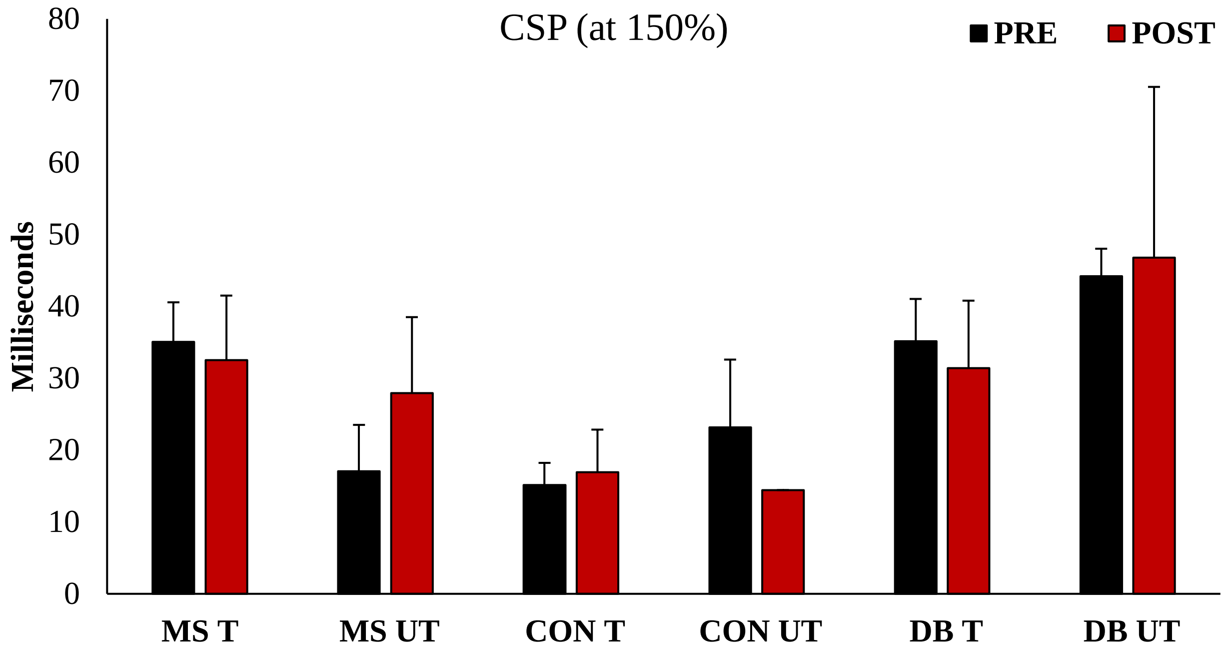


Figure 39. Cortical Silent Period (ms) at 150% stimulus intensity PRE/POST. Data are represented as group means and standard error. Abbreviations: T – trained, UT – untrained, MS – MS group, CON – control group, DB – double baseline

8.4.4 MEP Onset

There was a limb*group ($F_{(1, 13)}$= 6.16; p=.027; η^2=.632) and time*group ($F_{(2, 13)}$= 4.44; p=.034; η^2 =.656) interaction and a between group ($F_{(2, 13)}$= 7.48; p=.007; η^2 =.876) effect. Bonferroni post-hoc analysis revealed that the trained limb at POST for MS was different than the CON (p=.027), the MS was different than the DB (p=.016) but DB was not different than the CON (p=1.000) (Figure 40).

Mean MEP Onset: MS

There was no change in MEP Onset (milliseconds) at 150% stimulus intensity PRE/POST for the trained (PRE: 21.55±9.26; POST: 20.96±6.48ms; p=.814; η^2=.056) and untrained (PRE: 23.84±12.52; POST: 20.19±4.6ms; p=.787; η^2=.131) limbs.

Mean MEP Onset: CON

There was no change in MEP onset (milliseconds) for the CON in the trained limb (PRE: 16.02±1.37; POST: 16.75±3.18ms; p=.786; η^2=.058). There was a significant increase in MEP onset of the untrained limb (PRE: 6.53±5.29; POST: 16.62±1.56ms; p=.041; η^2=.984).

Mean MEP Onset: DB

There was no change in MEP onset (milliseconds) for the DB in the trained limb (PRE: 16.64±4.02; POST: 17.61±3.02ms; p=.392; η^2=.984). There was no change in MEP onset of the untrained limb (PRE: 6.53±5.29; POST: 16.62±1.56ms; p=.816; η^2=.056).

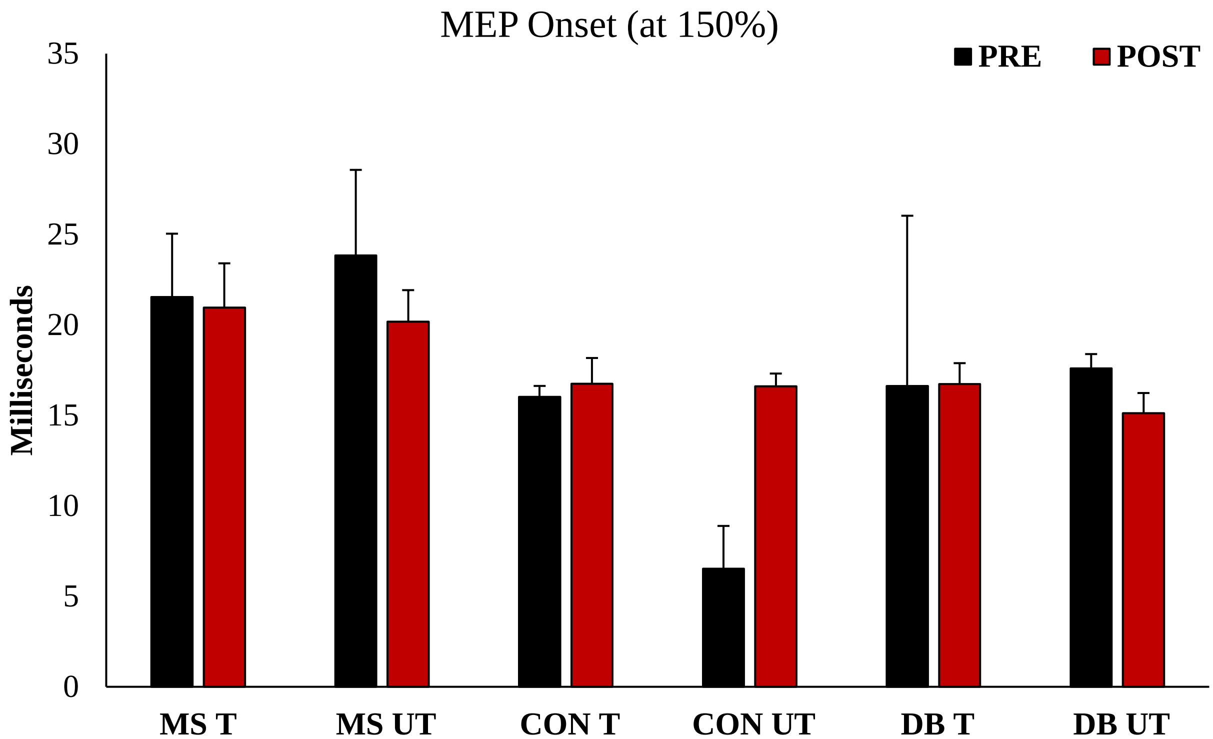


Figure 40. MEP onset at 150% stimulus intensity PRE/POST. Data are represented as group means and standard error. Abbreviations: T – trained, UT – untrained, MS – MS group, CON – control group, DB – double baseline

8.5 Discussion

TMS was conducted as a gross measure of corticospinal excitability. Strength data from this dissertation (Chapter 6) revealed clear evidence of CE of strength in the trained and untrained limbs of PwMS following our 8-week robotic intervention. Considering that CE has been largely unexplored in MS populations, this chapter attempts to provide a starting point for some clarity on corticospinal excitability PRE/POST intervention and what the focus of future neurophysiology studies should be. Contrary to hypothesis 2, there were predominantly no significant changes from pre to post for most of the measures assessed. However, there were some inconclusive changes in corticospinal excitability for the MS and control groups, reported as a non-significant change in slope and AUC pre- and post-intervention. Overall trends report a longer duration in MEP onset and CSP for the MS group compared to the control group. Recognizing the small sample size, this could be suggestive of a decrease in corticospinal excitability and decreased inhibition for the MS group compared to controls.

Examining recruitment curves provides an in-depth analysis of neuronal availability and neurotransmission as a result of stimulus intensity and MEP amplitude correlation (Chaves, Snow, et al., 2021). Parameters of overall excitation are examined using slope and AUC. Slope was measured as the most linear portion of the SRC and represents motor neuronal recruitment and AUC was defined as the area under the most linear portion of the curve. There was no significant change in corticospinal excitability (slope and AUC) from pre- to post-intervention for the trained and the untrained limb for both the MS and CON. This is likely due to the limitation of solely stimulating M1. Stimulations of M1 provides information of the corticospinal pathway without differentiating from supraspinal and spinal adaptations (Pearcey et al., 2021). For example, there may have been enhanced excitability occurring at the spinal level, but reduced or inhibited excitability at other levels of the corticospinal tract that were not objectively measured with this protocol. However, intervention studies with walking, cardiovascular exercise 3x per week for 10 weeks have reported increased MEP amplitudes and decreased CSP in progressive MS measured from the first dorsal interosseous hand muscle, alongside improvements in gait walking tasks, strength and performance (Chaves, Devasahayam, Riemenschneider, et al., 2020). Corticospinal excitation is mediated by glutamate and its activity on NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and cardiovascular training or therapies directly treating D-aspartate (such as theta burst stimulation) have shown to increase MEP amplitudes (Chaves, Devasahayam, Riemenschneider, et al., 2020). The effects of resistance training and boosting NMDA is more complex. The training intervention applied in this work resulted in a wide range of strength changes for these individual cohorts demonstrated as percent change score form PRE/POST intervention. The MS cohort ranged from 3.22-64.32% in the trained limb and 35.96-84.87% in the untrained limb and the non-MS control group presented a range of -5.77-61.79% in the trained limb and 8.6-44.25% in the untrained limb. It could be suggested that the resistance training paradigm from this methodology did not boost NMDA or AMPA receptors as there is evidence that corticospinal neurons are unaltered with acute (3-12 weeks) resistance training in a MS population (Carroll et al., 2002).

CSP and MEP onset were a secondary analysis in addition to the objective of this study. A few suggestions can explain the lack of findings in relation to both outcomes. A systematic review including 30 studies, investigated TMS as a potential biomarker for MS (Snow et al., 2019). Results report that 11/30 studies were at high risk of bias as the experimenter was not blinded to the study and thus creating a bias in favour of the interest. None of the stages in this protocol were blinded to the experimenter, and the same experimenter conducted the protocol both PRE and POST assessment. While this reduces the risk of inter-rater reliability, it does put the study at risk for potentially favoring the outcome. Secondly, there are confounding factors that that can influence silent period and MEP onset. These confounding factors include the level of attention of the participant during the testing, medication usage and overall fatigue (Snow et al., 2019). As these outcomes were part of a secondary analysis, this work did not control for these named factors. It is specifically difficult to control for medication usage for a MS population as there are a wide variety of drugs used and vastly differs upon individual symptoms, as well as it would be deemed unethical to ask the participants to not participate in drug use prior to the testing period. Lastly, sex-differences in MS have been reported when measuring MEP latency and CSP (Chaves, Kenny, et al., 2021). Results report that in the weaker hand, males demonstrated lower AMT and longer MEP latency compared to females, whereas females tended to show more asymmetry, lower corticospinal excitability as represented by lower MEP amplitudes and a longer inhibition period (CSP) (Chaves, Kenny, et al., 2021). These aforementioned covariates were not controlled for during this work and as such, future work should control should take appropriate measures to control for one or more of the suggested factors. It is important to highlight that results of this work should act as a starting point to the investigation of CE in MS, as TMS has considerable inter- and intraindividual variability in TMS findings, more literature needs to exist for comparative findings and to form any firm conclusions (Chipchase et al., 2012).

Cross-education

The objective of this work was to investigate mechanisms of CE following a robotic training program for a MS cohort and a non-MS control cohort. Although there was a wide range of percent strength change across cohorts, there was an evident increase in strength in the untrained limb for the MS cohort. These results can loosely suggest evidence of CE of strength following the intervention. However, the findings are not consistent with the results of the TMS protocol in this work as there was no evidence of CE from the neural adaptations as there were no significant changes in overall corticospinal excitability between the trained and untrained limb for the MS nor the Control Group. A systematic review by (Colomer-Poveda et al., 2021), concluded that adaptations underlying CE may be a result of changes in motor planning or changes to M1 structures that are unable to be identified with single-pulse TMS and MEP amplitude. Current mechanisms of CE are debatable and a deeper insight into M1 neuroplastic changes and spinal excitability are necessary to explore in future research.

MS Group vs. Control Group

It is important to compare the MS group to the Control group to understand the effect of the disease. Results of this study show no between-group affects (of AUC, slope, CSP and onset) indicating that the MS group did not differ from CON. These results are contrary to previous literature that also demonstrated decreased MEP amplitudes when compared to controls (Bridoux et al., 2015; Pisa et al., 2021). Although not statistically significant, results of this work showed an overall trend of a prolonged CSP and MEP onset in the MS group compared the Control. This trend does align with literature comparing MS CSP and MEP onset (Stampanoni Bassi et al., 2020). Delayed MEP onset may be representative of a prolonged evoked potential period compared to controls (Neva et al., 2016) whereas CSP abnormalities may be a result and a measure of the cortical inhibitory interneurons as they are an important role in producing a CSP (Tataroglu et al., 2003). Prolonged CSP may also be indicative of cerebellar dysfunction and overall altered balance between cortical excitation and inhibition in MS when compared to non-MS (Stampanoni Bassi et al., 2020). Following the robotic training intervention, results of this study showed no significant changes in CSP or MEP onset from pre- post-training. Both healthy and stroke literature have reported reduce short intracortical inhibition (as measured by CSP) following a single bout of cardiovascular exercise (Abraha et al., 2018) and that a prolonged CSP has been directly related to a inferior cardiorespiratory fitness (Chaves et al., 2019). Similar results were found following 5 weeks of maximal wrist extension training for stroke survivors. Sun et al., (2018) reported a CSP decrease of 12% in the less-affected limb from PRE/POST training. As previously described as a limitation to this study, assessments were collected greater than 96 hours following the final training and could not have captured direct effects of the training and excitatory or inhibitory processes.

8.6 Limitations

Due to exclusion criteria and thus, a small sample size of participants with MS, the direct and indirect training groups were combined to form one MS cohort. The limitation lies where one group trained their less-affected limb and one trained their more-affect limb. This could impact the results. For example, for the strength training results, although not a statistical significance between groups, there was an overall observed trend that the indirect training group (training their less-affected limb) resulted in larger percent change scores of strength in the trained and untrained limbs post-intervention. This can suggest that training the more or less symptomatic limb does have an effect on overall strength and perhaps contributing to corticospinal excitability and can affect results in this work. However, even with combining the MS groups, sample size including the control group size was still low and could be underpowered.

Lastly, it is important to report that final TMS assessments were completed on average 4.07 days after the participant's final training. Studies that have investigated MEP amplitudes and CE have conducted TMS within the hour of completing exercise (Colomer-Poveda et al., 2021) or 24-95 hours after the final training (Carroll et al., 2002). Therefore, it is recommended for future studies to measure spinal and nerve stimulations to investigate where these adaptations may occur and that the final assessments occur within 24 hours of the training to record all direct and immediate changes.

8.7 Conclusion

Changes in corticospinal excitability pre- and post-robotic training remain elusive. Results show a non-significant change in gross corticospinal excitability in both the MS and non-MS groups. Consistent with previous literature, this study found that PwMS have prolonged CSP, and delayed MEP onsets compared to non-MS controls. This study focused on stimulating the contralateral hemisphere and motor cortex; therefore, it is recommended that future research explore inter-hemispheric outcomes (e.g., SICI, IHI) to further investigate the mechanisms of corticospinal excitability and identify neural adaptations following robotic training interventions.

Chapter 9 – A 4-week robotic training intervention for individuals with multiple sclerosis

9.1 Introduction

Robotic rehabilitation has gained popularity over the past decade, and the literature provides sufficient evidence that robotic based rehabilitation can improve upper limb function in MS. However, a gap in the literature remains surrounding appropriate therapy duration, load and frequency of the training (Lamers et al., 2016). A robotic treadmill intervention study for PwMS reported using as little as two-week training (Lyp et al., 2018) whereas a robotic arm and functional electrical stimulation intervention for PwMS reported ten-weeks of training (Sampson et al., 2016). Both durations of training have reported improvements in motor control, muscular strength, or coordination, but it is still unknown what the optimal duration intervention should be. As discussed in Chapter 6, this work began with an eight-week training intervention. Eight total weeks of training was determined based off previous upper limb robotic rehabilitation literature demonstrating that between six to eight weeks of training resulted in the greatest improvements in motor control, performance, or strength (Lamers et al., 2016). In addition, our battery of assessment tests was time consuming and complex. It was challenging to ask our eight-week study participants to commit to a mid point assessment with an already busy 3x/week commitment to the study. As such, the purpose of this study was to investigate objective five and evaluate a four-week training intervention using the same robotic intervention of the upper limb that was previously used for eight-weeks. This allowed for a new participant pool and comparisons of strength, robotic assessments and clinical evaluations were evaluated pre- post an eccentric robotic training intervention of the upper limb for PwMS. It was anticipated that the results of this work could add to the literature in this field surrounding the question of optimal duration and prescription of therapy. This work could provide direction for robotic rehabilitation prescription and help facilitate a better understanding of robotic training intervention usage.

9.2 Methods

9.2.1 Participants

A total of nine individuals with MS participated in four-weeks of the robotic training with a pre/post assessment study design (Figure 41). A detailed rationale for robotic parameters are outline in Chapter 5 – section 5.2. Group demographics are outlined in Table 19. Participant reported pharmaceuticals were recorded and categorized based on inhibitory, excitatory, disease modifying or recreational drugs and are reported in Table 19. Participants with MS were required to have a medical diagnosis of MS and were required to have active use of at least one upper limb as the robotic protocol did not offer assistance. Participants were excluded if they were currently undergoing a relapse or suffered from any trauma to the upper limb other than impairments due to MS related symptoms (i.e., broken bones).

Participants participating in the four-week training intervention were placed into two groups based on participant demographics:

1) **Indirect training group (IT):** Participants with MS (N=4) visited the lab three times a week for four- consecutive weeks for approximately a 25-minute training session using their self-reported less affected limb, regardless of hand-dominance.

2) **Direct training group (DT):** Participants with MS (N=5) visited the lab three times a week for four- consecutive weeks for approximately a 25-minute training session using their self-reported more affected limb, regardless of hand dominance.

Paired t-tests were conducted to report statistical significance between groups for mean EDSS, years since diagnosis and years of age. Mean EDSS, did not differ between groups (direct/indirect – p=.088). Mean years since diagnosis did not differ between groups (direct/indirect – p=.558). Mean years of age did not differ between groups (direct/indirect – p=.616.

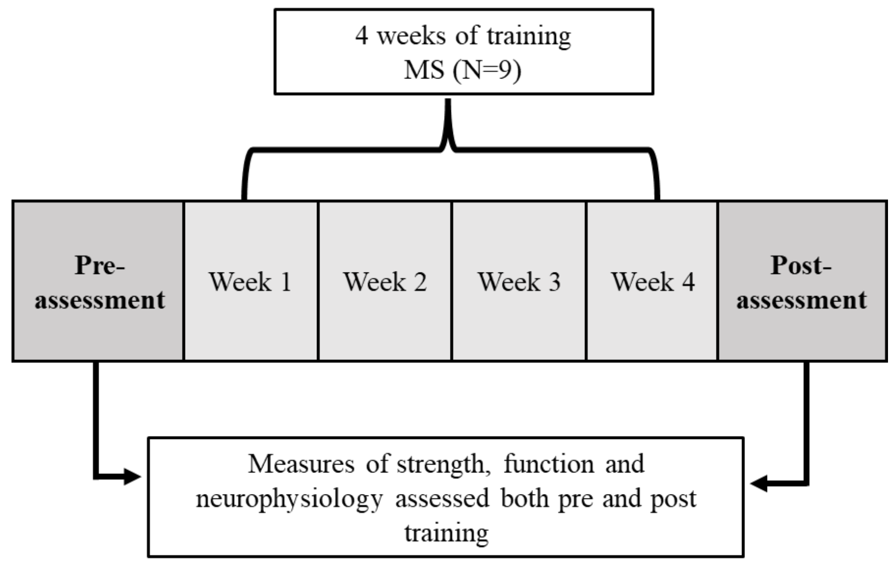


Figure 41. Training intervention timeline

Table 19. Participant and group demographics

	Completed Sessions	Handedness	Limb Trained	EDSS	MS Phenotype	Years Since Diagnosis	Years of Age	Drug Use
Indirect Training								
Participant 1	10	Right	Right	2	RRMS	5	51	Inhibitory
Participant 2	12	Left	Left	8	SPMS	22	58	N/A
Participant 3	12	Right	Right	6	RRMS	2	43	DMD
Participant 4	12	Right	Left	6	PPMS	4	59	Inhibitory/DMD
Group Mean ± SD	11.5 ± 0.86	1 – Left 3 – Right	2 – Left 2 – Right	5.5 ± 2.18	2-RRMS 1-SPMS 1-PPMS	8.25 ± 8.01	52.75 ± 6.42	
Direct Training								
Participant 1	12	Right	Left	4.5	RRMS	3	39	DMD
Participant 2	12	Right	Left	4.5	SPMS	9	50	N/A
Participant 3	12	Left	Right	4	RRMS	10	69	DMD
Participant 4	11	Right	Left	8	PPMS	29	68	N/A
Participant 5	12	Right	Left	6	SPMS	4	59	Inhibitory
Group Mean ± SD	11.8 ± 0.4	1 – Left 4 – Right	3 – Left 2 – Right	5.5 ± 1.51	2-RRMS 2-SPMS 1-PPMS	16 ± 10.88	57.8 ± 11.58	

*Abbreviations: RRMS–relapsing remittent MS, SPMS–secondary progressive MS, PPMS–primary progressive MS, DMD–disease modifying drug

9.2.2 Intervention and Experimental Protocol

This study was designed as a training program. Training intervention and robotic parameters are the same as outlined in Chapters 6 and 7. The goal of this Chapter was to examine the outcomes on strength, sensorimotor, clinical and evidence of cross-education following half the duration of training (four weeks).

9.2.3 Assessment Sessions

Assessment sessions consisted of a combination of assessments as performed in Chapter 6, section 6.2.4 and Chapter 7, sections 7.2.2 and 7.2.3. In addition, the Wolf Motor Function Test (WMFT) was uniquely added to this Chapter and details are expanded on below:

<u>Wolf Motor Function Test (WMFT)</u>

The WMFT is a time-based evaluation of upper limb performance of joint-specific (proximal and distal) and total limb movements (Wolf et al., 2001). Tasks 1-6 involved joint-segment movements and tasks 7-15 involved functional movements and were rated on a scale of 0 = does not attempt, 1 = upper limb being tested does not participate functionally, 2 = requires assistance of the upper limb not being tested, 3 = movement is influenced by some degree of synergy, 4 = movement is close to normal but lack precision and 5 = movement appears to be normal. The WMFT is a quantitative functional assessment where performance is measured based on physical completion of daily tasks. It was necessary to add a functional assessment in addition to the previously included questionnaire (ABILHAND) to eliminate bias or overcome the limitations of participant reported questionnaires. It has been established that the minimal clinically important difference (MCID) for the WMFT can be determine by calculating the percent change score from pre to post scores, and a minimum of 17-20% change would be indicative of clinically meaningful (established from stroke participants) (Lang et al., 2008).

9.3 Data Analysis

9.3.1. Statistical Analysis

Muscular Strength: Assessments of grip force and isometric wrist flexion, extension, radial and ulnar deviation force were collected PRE/POST as described in Chapter 6 – section 6.2.4. Due to the small sample size and abnormal distribution of data, a non-parametric Friedman test (SPSS Statistics for Windows, Version 26.0. IBM Corp.: Armonk, NY, USA) was conducted to evaluate change in strength of the trained and untrained limbs for IT and DT groups. Wilcoxon Signed-Rank Tests were used as a post-hoc analysis. Significance was set to ($p < .05$). Percent change scores were also conducted to PRE/POST training and evaluate clinically meaningful adaptations. Percent change scores were calculated using the equation below:

$$\frac{(V_2 - V_1)}{|V_1|} \times 100\%$$

Whereas v_1 depicts muscular strength (N) at PRE and v_2 depicts muscular strength (N) at POST.

Clinical Assessments: Friedman tests were used to compare mean group scores (IT and DT) of the ABILHAND, EDSS and WMFT PRE/POST intervention. Wilcoxon Signed-Rank Tests were conducted as a post-hoc analysis and significance was set to $p < .05$. For the WMFT, a percent change score was calculated using the equation above to categorize the MCID as per previous literature (Lang et al., 2008; Shirley Ryan Ability Lab, 2016).

Robotic Assessments: Friedman Tests to compare robotic outcome measures (tracking, proprioception, and ROM) means of IT and DT group at PRE and POST for the trained and untrained limbs were conducted. Whereby an interaction was found, Wilcoxon Signed-Rank Tests were conducted as a post-hoc analysis. Significance was set to $p < .05$.

9.4 Results

9.4.1 Strength

A Friedman test was conducted to evaluate change in strength PRE/POST intervention of the trained and untrained limbs for both IT (Table 20) and DT (Table 21).

IT results showed no differences of grip strength ($X^2(3)=4.03$, $p=.258$) in the trained limb (PRE: 179.55±62.4 POST: 208.01±70.59) nor untrained limb (PRE: 235.18±30.94; POST: 225.44±30.33). There were no differences in flexion ($X^2(3)=.931$, $p=.818$) of the trained (PRE: 36.5±13.44; POST: 58.25±37.48), and untrained (PRE: 46±14.14; POST: 44.33±5.66). No changes in extension ($X^2(3)=5.3$, $p=.145$) in the trained (PRE: 17±8.49; POST: 41.25±21.21) and untrained (PRE: 35±2.83; POST: 44.67±2.12). No changes in radial deviation ($X^2(3)=4.48$, $p=.248$) in the trained (PRE: 36±10.61; POST: 62±53.74) and untrained (PRE: 49±12.02; POST: 53.33±1.41). Lastly, a significant interaction was reported in ulnar deviation ($X^2(3)=.966$, $p=.047$). A post-hoc analysis revealed no changes in the trained (PRE: 34.25±16.97; POST: 47.5±14.85; $p=.068$) and untrained (PRE: 39.33±8.48; POST: 54.67±22.63; $p=.109$) limbs.

DT results showed no significant differences of grip strength in the trained limb (PRE: 192.78±34.09; POST: 248.52±11.72) nor untrained limb (PRE: 200.98±23.49; POST: 228.69±23.44) ($X^2(3)=5.1$, $p=.165$). There were no significant differences in flexion of the trained (PRE: 60.25±11.31; POST: 72.25±17.68), and untrained (PRE: 74±18.39; POST: 82.25±36.77) ($X^2(3)=5.7$, $p=.127$). A significant interaction in extension was found ($X^2(3)=7.8$, $p=.05$). A post-hoc analysis revealed no changes in the trained (PRE: 46.25±4.95; POST: 60.75±15.56, $p=.068$) or untrained (PRE: 58.25±14.5; POST: 71±4.12; $p=.066$) limb. A significant interaction in radial deviation was found ($X^2(3)=7.8$, $p=.05$). Post-hoc analysis revealed no changes in the trained (PRE: 59.5±51.62; POST: 82.25±16.26; $p=.068$) and untrained (PRE: 72.5±60.1; POST: 95.5±43.84; $p=.068$). Lastly, a significant interaction in ulnar deviation strength was found

($X^2(3)=10.8$, $p=.013$). Post-hoc analysis revealed no changes in the trained (PRE: 50±23.33; POST: 71±12.02; $p=.068$) and untrained (PRE: 50±23.33; POST: 71±12.02; $p=.068$) limb.

IT demonstrated a non-significant but clinically meaningful increase in strength (MCID) of the trained limb in flexion (59.59%), extension (142.65%), radial (72.22%) and ulnar deviation (38.69%). IT also demonstrated a non-significant but clinically meaningful increase of strength in the untrained limb in extension (27.62%), and ulnar (38.98%) (Figure 45). DT demonstrated a non-significant but a MCID in strength of the trained limb in grip (28.91%), flexion (19.92%), extension (31.35%), radial (38.42%) and ulnar deviation (42%). DT also demonstrated a non-significant but MCID of strength in the untrained limb in extension (21.89%), radial (31.72%) and ulnar (38.98%). Although not statistically different, IT showed a larger percent change in strength PRE/POST intervention when compared to the DT group (Figure 42).

Table 20. Indirect Training group – mean strength results (± standard deviation)

	Grip	p-value	Flexion	p-value	Extension	p-value	Radial	p-value	Ulnar	p-value
Pre trained	179.55 ± 62.4	.564	36.5 ± 13.44	.149	17 ± 8.49	.021*	36 ± 10.61	.248	34.25 ± 16.97	.058
Post trained	208.01 ± 70.59		58.25 ± 37.48		41.25 ± 21.21		62 ± 53.74		47.5 ± 14.85	
Percent Change		15.85 ±14.23%		59.59 ±10.88%		142.65 ±12.13%		72.22 ±13%		38.69 ±6.63%
Pre untrained	235.18 ± 30.94	.827	46 ± 14.14	.827	35 ± 2.83	.127	49 ± 12.02	.658	39.33 ± 8.48	.376
Post untrained	225.44 ± 30.33		44.33 ± 5.66		44.67 ± 2.12		53.33 ± 1.41		54.67 ± 22.63	
Percent Change		-4.14 ±4.87%		-3.62 ±0.84%		27.62 ±4.84%		8.84 ±2.17%		38.98 ±7.67%

*denotes statistical significance and red denotes clinical significance as defined by a minimal increase of 16%

Table 21. Direct Training group – mean strength results (± standard deviation)

	Grip	p-value	Flexion	p-value	Extension	p-value	Radial	p-value	Ulnar	p-value
Pre trained	192.78 ± 34.09	.248	60.25 ± 11.31	.564	46.25 ± 4.95	.248	59.5 ± 51.62	.248	50 ± 23.33	.386
Post trained	248.52 ± 11.72		72.25 ± 17.68		60.75 ± 15.56		82.25 ± 16.26		71 ± 12.02	
Percent Change		28.91 ±27.87%		19.92 ±6%		31.35 ±7.25%		38.24 ±11.38%		42 ±10.5%
Pre untrained	200.98 ± 23.49	.386	74 ± 18.39	.773	58.25 ± 14.85	.384	72.5 ± 60.1	.468	41.25 ± 7.78	.149
Post untrained	228.69 ± 23.44		82.25 ± 36.77		71 ± 6.36		95.5 ± 43.84		90 ± 6.36	
Percent Change		13.79 ±13.86%		11.14 ±4.13%		21.89 ±6.34%		31.72 ±11.5%		118.18 ±24.34%

*denotes statistical significance and red denotes clinical significance as defined by a minimal increase of 16%

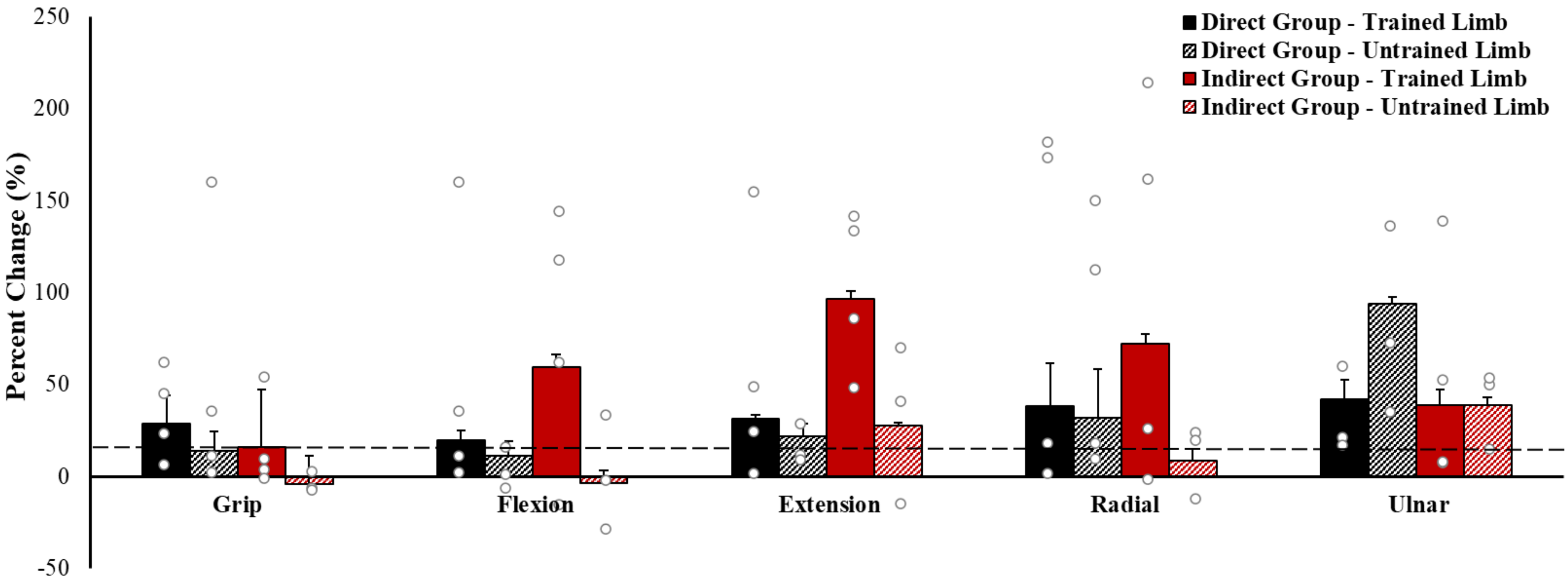


Figure 42. Maximal strength represented as percent change scores, PRE/POST training of the trained and untrained limb for the Direct and Indirect group. Data are represented as percent change and standard errors. Dashed black line represents minimal clinical significance threshold.

9.4.2 Clinical Assessments

Clinical assessments were conducted PRE and POST training. All assessments were conducted and reported by the same examiner to decrease inter-rater variability.

Expanded Disability Status Scale

DT and IT had the same mean score (5.5) indicating that both groups were at the same severity of disease (Table 22). There were no between group effects ($X^2(1)=1.0$, $p > .05$) and there was no change in EDSS scores did not significantly change PRE/POST training for IT or DT ($p=1.00$).

Table 22. Group mean EDSS

Group	EDSS PRE (group means ± SD)	EDSS POST (group means ± SD)
Direct PRE	5.5 ± 1.51	5.5 ± 1.51
Direct POST	5.5 ± 1.51	5.5 ± 1.51
Indirect PRE	5.5 ± 2.18	5.5 ± 2.18
Indirect POST	5.5 ± 2.18	5.5 ± 2.18

ABILHAND Questionnaire

DT had less severe upper limb impairment (80.76±5.71%) compared to IT (64.84±14.43%) at baseline (Table 23). There were no between group differences ($X^2(1)=2.667$, $p=.102$). The ABILHAND scores did not significantly change PRE/POST training ($p>.05$).

Table 23. Group means of ABILHAND scores

Group	Participant Measure PRE (group means ± SD)	Participant Measure POST (group means ± SD)
Direct PRE	74.66 ± 7.92%	74.66 ± 7.92%
Direct POST	80.76 ± 5.71%	80.76 ± 5.71%
Indirect PRE	64.75 ± 12.69%	64.75 ± 12.69%
Indirect POST	64.84 ± 14.43%	64.84 ± 14.43%

Wolf Motor Function Test

The WMFT was an additional functional test added to this work. As such, two participants completed the training prior to the addition of the assessment. Therefore, the WMFT has a smaller sample size of N=3 for IT and N=4 for DT.

The WMFT was conducted at PRE and POST assessments in both the trained and untrained limb. A Friedman Test was run to predict WMFT performance of the trained limb and untrained limb from PRE/POST training for IT and DT. There were no significant changes in performance score PRE/POST for IT in the trained ($X^2(2)=4.3$, $p=.102$) or DT ($X^2(2)=5.1$, $p=.180$) groups. (Table 24).

IT trained did not significantly change in performance in the trained (PRE: 45.7±20.93; POST: 48.7±21.84, 6.56% change) and untrained (PRE: 25.3±20.33; POST: 27.33±23.34, 8.02% change) limbs. DT did not significantly change in performance in the trained (PRE: 61.25±8.17; POST: 68.5±6.17, 11.84% change) and untrained limbs (PRE: 70.5±3.86; POST: 75±0, 6.38% change) (Figure 43).

Table 24. Group means of Wolf Motor Function Test performance

Group	Trained PRE	Trained POST	Untrained PRE	Untrained POST
Indirect Training (N=3)	45.7 ± 20.93	48.7 ± 21.84	25.3 ± 20.33	27.3 ± 23.34
Direct Training (N=4)	61.25 ± 8.17	68.5 ± 6.17	70.5 ± 3.86	75 ± 0

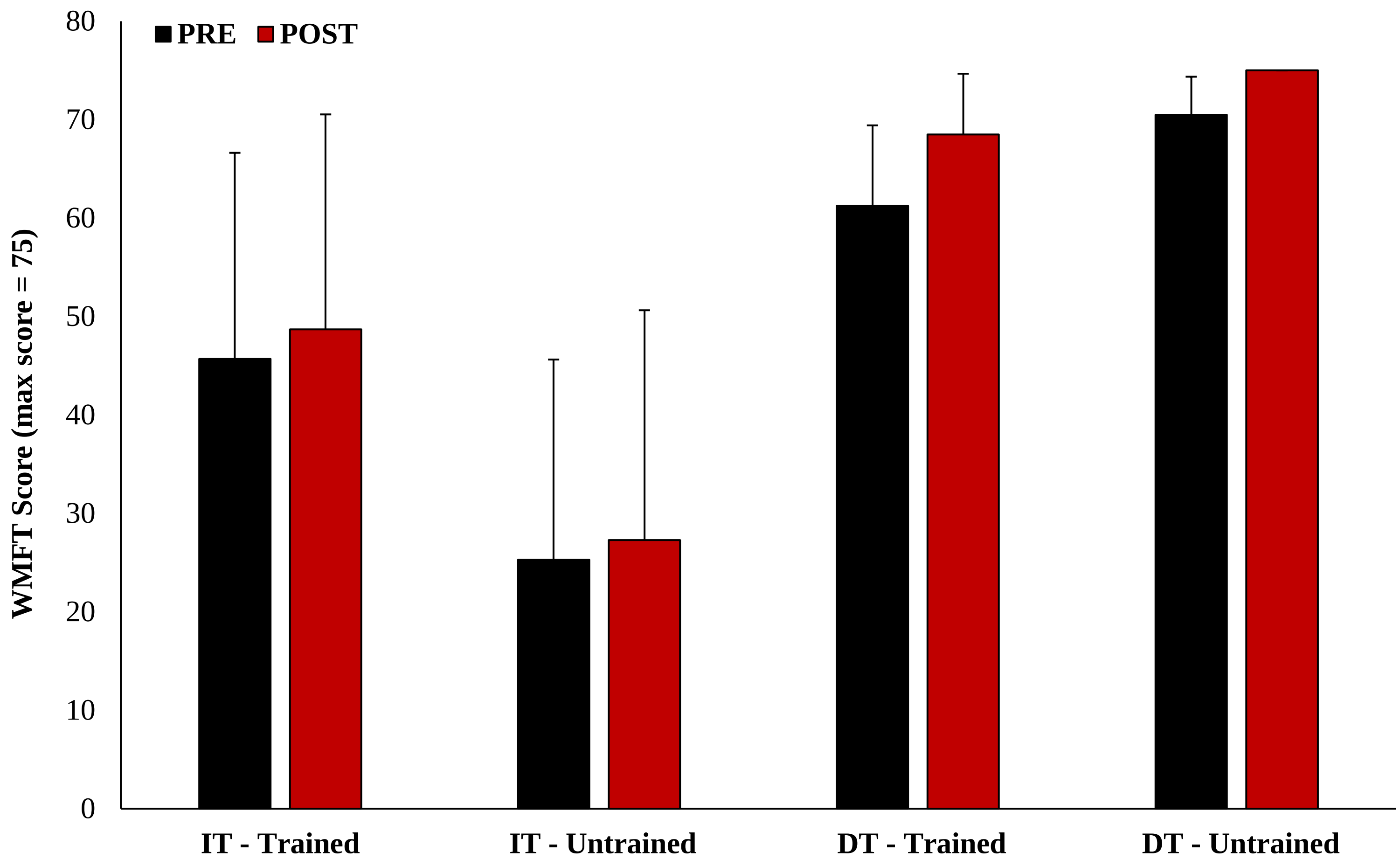


Figure 43. Wolf Motor Function Test scores PRE/POST training in the trained and untrained limb for the Direct and Indirect groups. Data are represented as group means and standard error

9.4.3 Robotic Assessments

ROM

A Friedman Test was conducted to measure active ROM in flexion, extension, radial and ulnar deviation for the trained and untrained limbs in the IT and DT (Figure 44 and 45, respectively). Whereby a significant interaction was found, Wilcoxon Signed-Ranks Test were performed as a post-hoc analysis.

For IT, there were no differences in flexion ($X^2(3)=4.8$, $p=1.87$) for the trained (PRE: 54.74±5.86°; POST: 60.29±3.84°) untrained (PRE: 50.211±2.25°; POST: 57.27±3.35°) limbs. There were no changes in extension ($X^2(3)=4.2$, $p=.241$) for the trained (PRE: 54.32±6.22°; POST: 47.07±8.71°) and untrained (PRE: 54.18±10.28°; POST: 52.22±7.53°) limb. No changes in radial deviation ROM ($X^2(3)=6$, $p=.112$) for the trained (PRE: 33.74±6.22°; POST: 37.99±.65°) or untrained limb (PRE: 32.55±1.07°; POST: 30.89±1.07°). There were no changes in ulnar deviation ROM ($X^2(3)=.000$, $p=1.00$) for the trained (PRE: 36.21±2.23°; POST: 30.89±4.24°) and untrained (PRE: 31.48±2.27°; POST: 30.16±6.46°) limb.

For the DT group, there were no significant differences in ROM PRE/POST in flexion ($X^2(3)=4.5$, $p=.212$) for the trained (PRE: 53.05±6.47°; POST: 58.56±3.83°) or untrained (PRE: 48.65±14.55°; POST: 58.02±4.28°). No changes in extension ($X^2(3)=7.5$, $p=.058$) for the trained (PRE: 40.34±15.95°; POST: 58.56±13.28°) and untrained (PRE: 57.12±10.23°; POST: 54.27±6.67°). No changes in radial deviation ($X^2(3)=3.00$, $p=.825$) for the trained (PRE: 36.75±4.75°; POST: 37.45±7.15°) or untrained (PRE: 30.12±12.04°; POST: 40.66±2.01°). No changes in ulnar ($X^2(3) = .900$, $p=.825$) for the trained (PRE: 31.36±6.04°; POST: 33.3±11.12°).or untrained (PRE: 34.43±8.96°; POST: 31.73±8.13°).

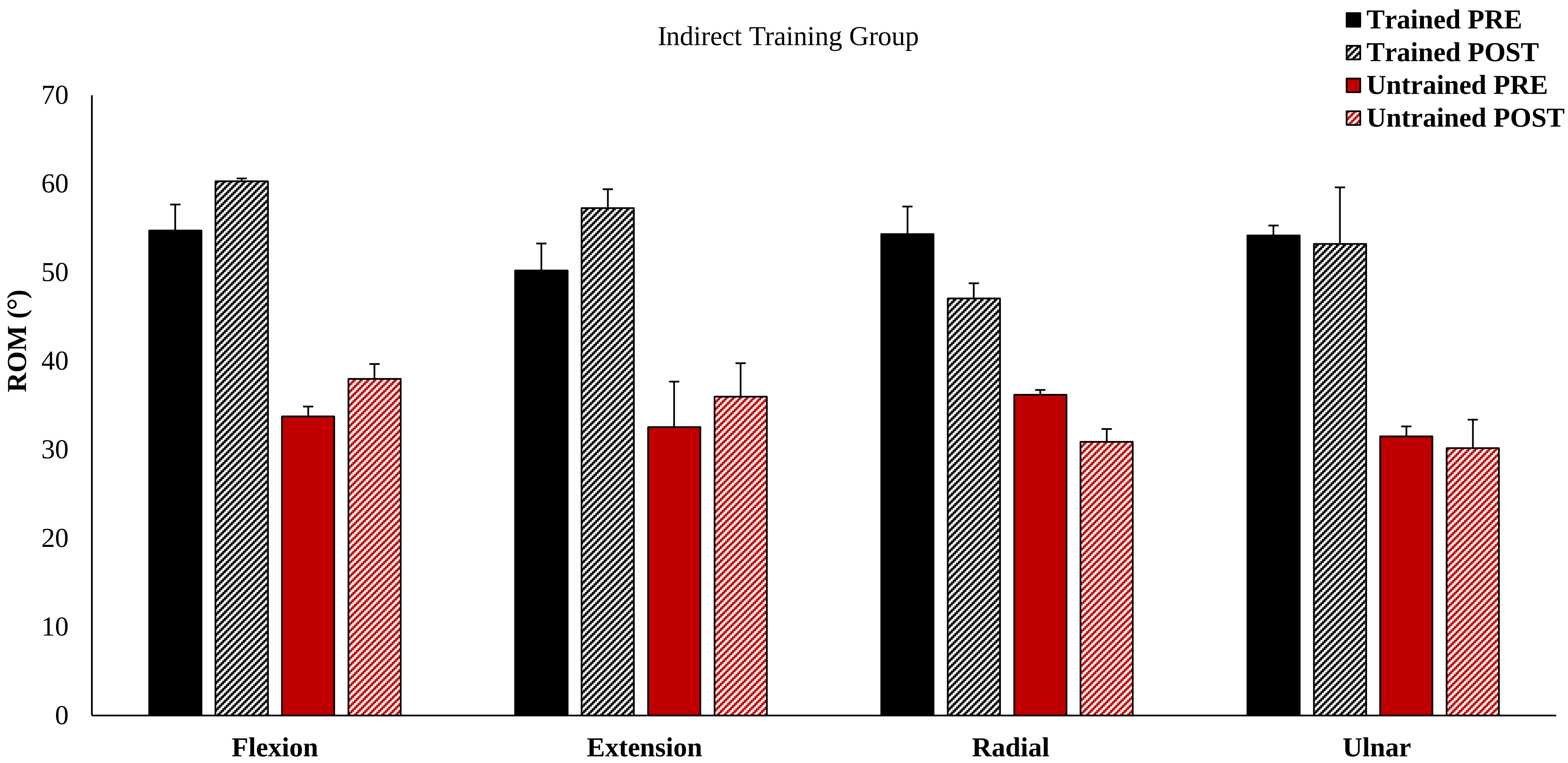


Figure 44. Active ROM for the Indirect Training group of the trained and untrained limbs PRE and POST intervention. Data are represented as group means and standard error

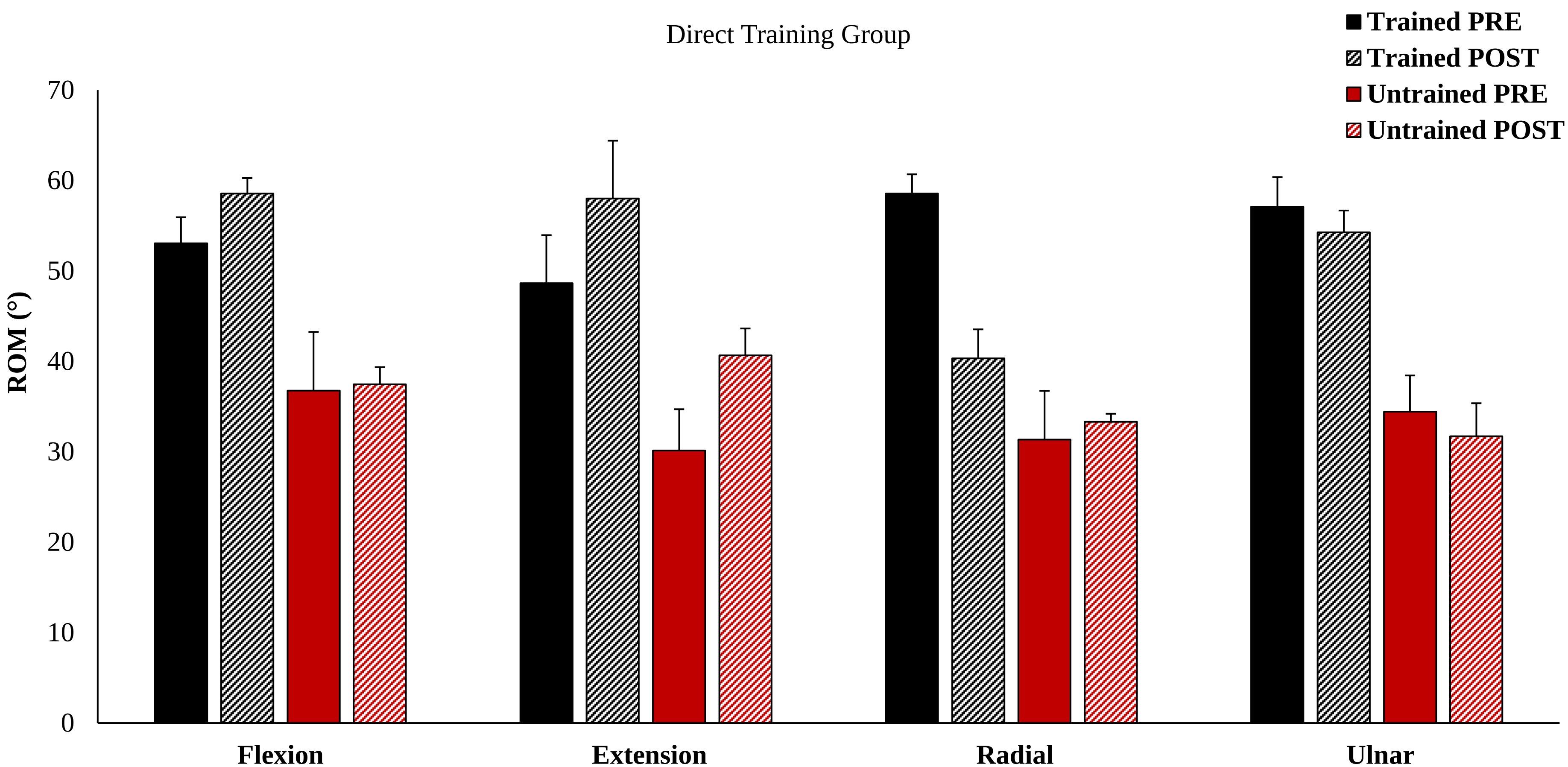
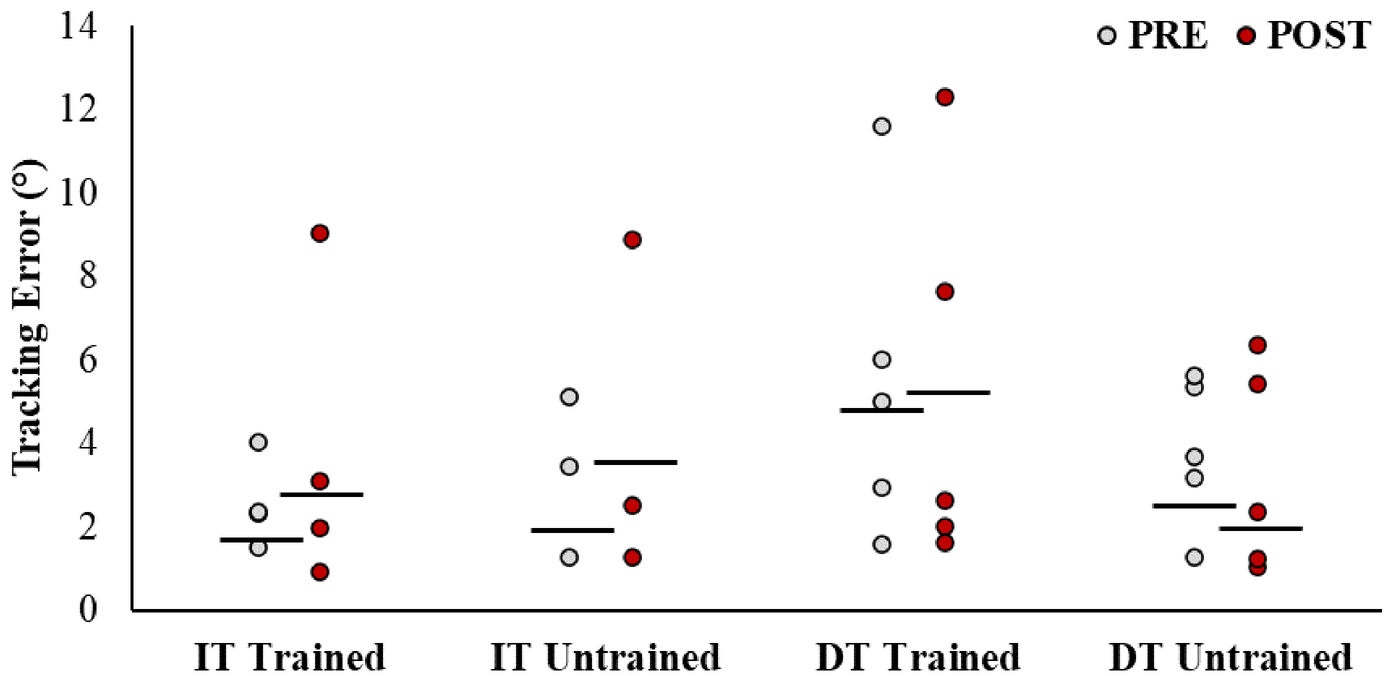


Figure 45. Active ROM for the Direct Training group of the trained and untrained limbs PRE and POST intervention. Data are represented as group means and standard error

Tracking & Figural Error

A Friedman Test was conducted to observe differences PRE/POST in tracking and figural error for the trained and untrained limbs. When interactions were found, Wilcoxon Signed-Ranks Test was conducted as a post-hoc analysis. For the IT group, there were no changes in tracking error ($X^2(3)=1.00$, $p=.801$) for the trained (PRE: 0.99±0.47°; POST: 0.774±0.37°) and untrained (PRE: 7.06±11.98°; POST: 0.77±0.27°) limb. There were no significant changes in figural error ($X^2(3)=7.00$, $p=.072$) for the trained (PRE: 2.55±1.06°; POST: 3.77±3.63°) and untrained (PRE: 11.92±17.32°; POST: 4.25±4.08°) limb.

For the DT group there were no changes in tracking error ($X^2(3)=1.56$, $p=.668$) for the trained (PRE: 5.43±3.86°; POST: 5.25±4.64°) and untrained (PRE: 3.82±1.77°; POST: 3.28±2.46°). There were no changes in figural error ($X^2(3)=6.36$, $p=.095$) for the trained (PRE: 2.35±2.7°; POST: 1.83±2.42°) and untrained (PRE: 1.19±0.38°; POST: 0.86±0.28°) limbs (Figure 46).


PRE
POST
Tracking Error (°)
0
2
4
6
8
10
12
14
IT Trained
IT Untrained
DT Trained
DT Untrained

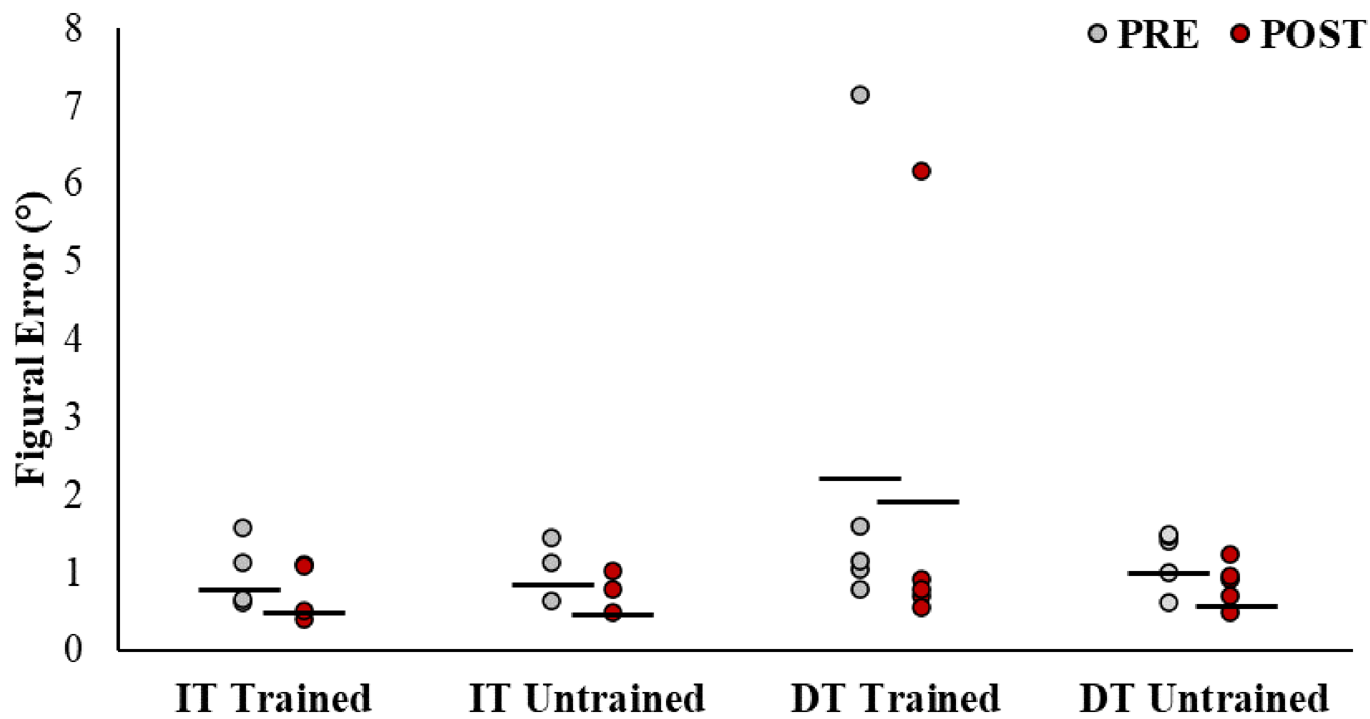


Figure 46. Tracking (top) and figural (bottom) error PRE/POST intervention in the trained and untrained limb in the direct and indirect training groups. Black lines represent group mean, grey dots represent individual data points at PRE and red dots represent individual data points at POST Abbreviations: IT – indirect training group, DT – direct training group

Joint Position Matching

A Friedman Test was conducted to observe differences PRE/POST in matching error and error bias for the trained and untrained limbs. When interactions were found, Wilcoxon Signed-Ranks Test was conducted as a post-hoc analysis.

For the IT group, there were no changes in matching error - flexion ($X^2(3)=5.86$, $p=.122$) for the trained (PRE: 8.61±5.35°; POST: 4.59±2.29°) or untrained (PRE: 10.66±56.10°; POST: 10.74±5.05°). No changes in matching error – extension ($X^2(3)=5.4$ $p=.145$) in the trained (PRE: 15.02±11.13°; POST: 8.15±7.72°) or untrained (PRE: 14.25±7.37°; POST: 4.01±2.12°) (Figure 47).

For error bias - flexion, IT group reported no changes ($X^2(3)=3.4$ $p=.334$) for the trained (PRE: 8.61±5.35°; POST: 0.49±11.27°) or untrained (PRE: -1.46±4.77°; POST: -6.27±8.17°). No changes in error bias – extension ($X^2(3)=1.00$, $p=.802$) for the trained (PRE: -9.73±6.85°; POST: -8.85±17.89°) and untrained (PRE: -7.82±8.14°; POST: -0.36±18.94°).

For the DT group there were no changes in matching error - flexion ($X^2(3)=4.8$, $p=.187$) for the trained (PRE: 13.21±10.64°; POST: 4.80±3.08°) and untrained (PRE: 13.87±3.91°; POST: 3.41±2.58°). There were also no changes in matching error - extension ($X^2(3)=.600$, $p=.896$) in the trained limb (PRE: 11.19±3.28°; POST: 8.57±7.75°) and untrained (PRE: 8.71±6.59°; POST: 9.21±8.37°) (Figure 47).

For error bias - flexion, DT group showed no changes ($X^2(3)=5.4$, $p=.145$) for the trained (PRE: -12.82±11.23°; POST: -1.95±4.99°) and untrained (PRE: 7.55±14.77°; POST: 1.89±4.09°). No changes in error bias – extension ($X^2(3)=1.2$, $p=.753$) for the trained (PRE: 2.01±9.64°; POST: 1.11±12.49°) and untrained limb (PRE: -2.59±11.88°; POST: -1.91±13.13°).

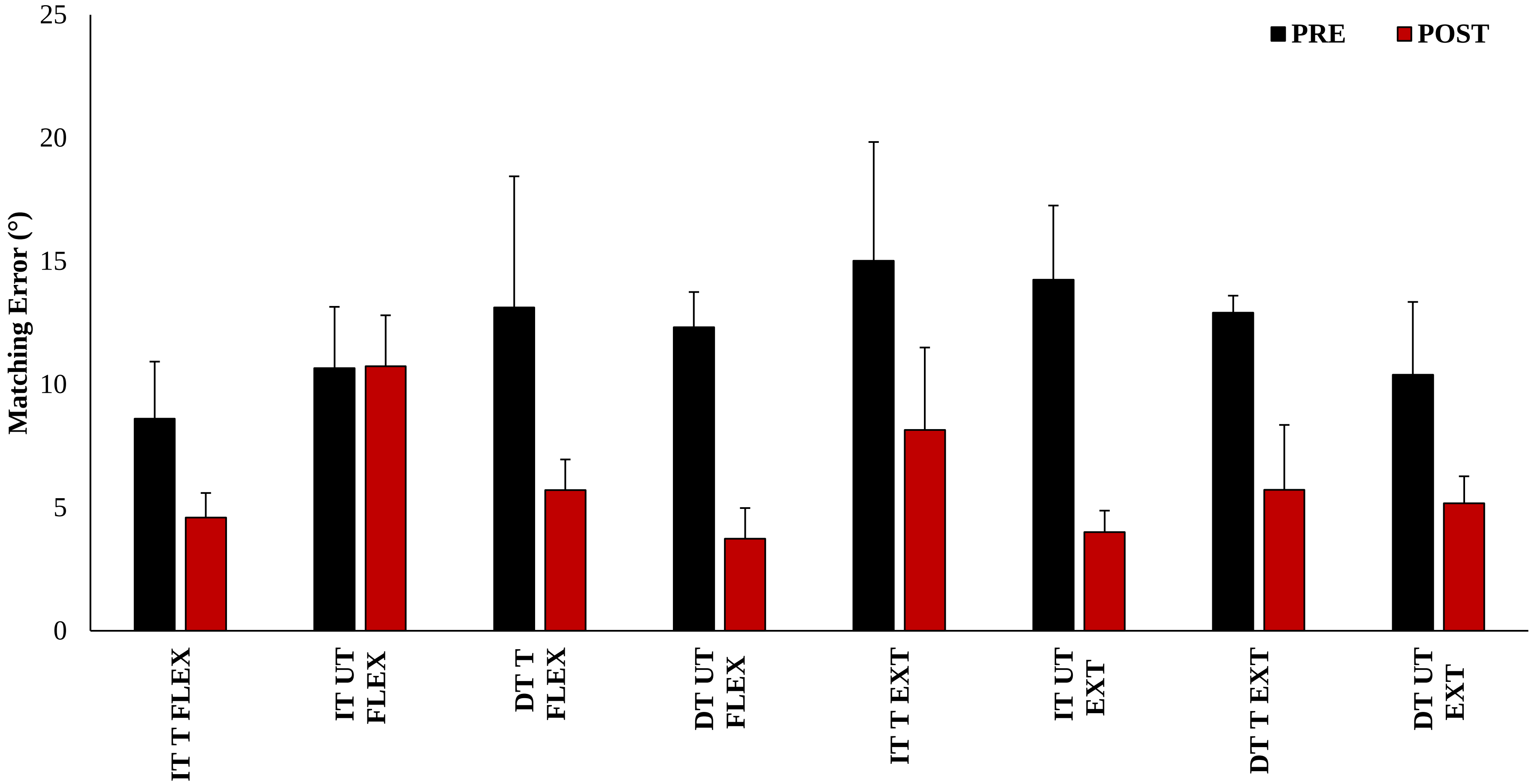


Figure 47. Matching error PRE/POST for the indirect and direct groups. Data are presented as group means and standard error. Abbreviations: IT – indirect training, DT – direct training, FLEX – flexion, EXT – extension, T – trained limb, UT – untrained limb

9.5 Discussion

Following an adaptive four-week robotic training intervention, participants with various phenotypes and severity of MS demonstrated a non-significant but rather a clinically or functionally meaningful increases in strength. In support of hypothesis 4, IT group averaged a percent change score increase in strength (grip, flexion, extension, radial, ulnar) of 65.8% in the trained and 13.54% in the untrained limb. DT group reported an average increase of 32.08% for the trained and 34.51% in the untrained limb. However, robotic assessments did not provide evidence of motor control adaptations as there were no significant improvements in performance measures as quantified by robotic measures. There were no improvements in performance quantified by tracking and figural error of a hand tracking task, no change in proprioception (matching error, error bias) or active ROM PRE/POST intervention. Lastly, the clinical assessment questionnaires (EDSS, ABILHAND) showed no change PRE/POST intervention, and the functional assessment (WMFT) reported a non-significant increase in overall performance scores PRE/POST intervention. This is further explained below.

Muscular Strength

Participants trained using the robotic device at a frequency of three times per week for four consecutive weeks, totalling 12 training sessions. Participants trained at 40% of their maximal and had the chance to train up to 65% of their maximum, depending on the adaptive algorithm. After four weeks of training, participants increased in isometric wrist strength regardless of training their less-affected limb (IT) or more-affected limb (DT). While the resistance training paradigm of this study did not include heavy loads, it has been proven that lighter loads also promote increases in strength, particularly in untrained subjects (Schoenfeld et al., 2017). Similar to the findings of our eight-weeks of robotic training, IT show a general trend of an overall greater increase in strength when compared to DT. As an interesting result, not only the trained limb demonstrated increased strength, but also did the contralateral or untrained limb. In addition to statistical significance, it is important to also evaluate the minimal clinically important difference (MCID). The MCID helps in deciding if a treatment effect is large enough to be considered beneficial in a clinical setting, used to assess the practical, real-world impact of a treatment. The MCID of grip strength and upper limb isometric force has been suggested in stroke and can be used as a reference for MS work and have been established as a minimum of a 16-30% change score would be needed to be considered clinically meaningful for the strength measures (Lang et al., 2008). IT reported a meaningful increase in strength of the untrained limb in extension (27.62%) and ulnar deviation (38.98%). The DT group reported a meaningful increase in strength of the untrained limb in extension (21.89%), radial (31.72%), and ulnar deviation (93.94%). This can be explained by the phenomenon known as CE and is further explained below.

Robotic Assessments

Participants were asked to perform novel upper limb assessments with the robotic device (i.e., not conducted during the training) to assess transfer or learning and motor control adaptations. Participants performed a tracking task which required moving an icon along the monitor in a Lissajous fashion by moving the robotic manipulandum. Two calculations from this task were computed to assess performance. A decrease in either error is indicative of an improved performance. There were no significant adaptations in tracking or figural error PRE/POST intervention for both groups (direct and indirect). The second novel task was an assessment of proprioception and again, both groups did not demonstrate adaptations or changes in performance PRE/POST intervention. Lastly, range of motion was assessed PRE/POST intervention and again, no significant results were observed.

These results were surprising based on previous work with the same robotic training but for eight-weeks. During the eight-week intervention, our MS groups significantly improved in performance of tracking and figural error which was representative of increased motor control. Results of this four-week intervention can confirm that the length of robotic training can impact rehabilitation results. In addition to, the eight-week intervention increased the by two sets from weeks five to eight. This can also speculate that the number of sets and repetitions (intensity) can impact results. This can act as leverage for future work to investigate the optimal prescription for robotic rehabilitation for MS.

Similar results in proprioception were reported following the eight-week intervention. Both four- and eight-week results demonstrated no change in proprioception performance. Proprioception is commonly impaired in PwMS and it can be speculated that to improve proprioception, it needs to be directly trained. These results are meaningful to clinicians and therapists alike, where PwMS should be directly training a specific task to help their ADLs. Lastly, the four-week of training reported no significant improvements in range of motion at the wrist. Range of motion at baseline was close to normative or non-MS ranges (comparative to the eight-week non-MS control). Thus, the starting point of our participant's level of impairment could create a ceiling effect with no room for further improvements post-training. Although, it is important to note that the training protocol had users working at 80% of their maximally recorded daily ROM and was chosen for safety. Perhaps training at 80% was not challenging one's ROM and an increase in ROM would not have been expected.

Interestingly, previous work Mannella et al., 2021, consisted on four-weeks of robotic training and demonstrated increases in strength and tracking error performance. It is important to note that is training was adaptive assistance/resistance protocol with a motor learning aspect. Whereas this training, was resistance only, with the goal to induce CE. It can be speculated that the overall goal or passive/assistance/resistance of the robotic protocol may also have an influence on performance POST intervention. Perhaps when establishing prescription guidelines, it is important to be tailored to the type of control strategy of the robotic device. Such as, high-level control considerations including assistance or challenge-based devices.

Cross-Education of Strength and Motor Control

The phenomenon of CE has been well explored but exploiting the advantageous effects in rehabilitation has not yet been well understood. In a recent systematic review by Voskuil et al., 2022, results showed a similar magnitude of CE in the upper and lower limbs as well as in both dominant and non-dominant limbs. This indicates that regardless of hand dominance and limb trained, effects of IT and DT would still be visible. In this work, there were clinically meaningful increases in strength of the untrained limb for wrist extension, radial and ulnar deviation for the DT and IT, and this can suggest some level of CE. When comparing the untrained limb strength results to that of the eight-week training, there was a greater percent change of strength following in the untrained limb following eight-weeks of training compared to these given four-week results. The eight-week IT group had an average percent change of 53% (between grip, flexion, extension, radial, ulnar) whereas the four-week training IT group had an average of 13.54% for the untrained limb. The eight-week DT group had an average percent change 27.32% for the untrained limb whereas, the four-week DT group had an average percent change score of 34.51% for the untrained limb. This indicates that four-weeks of robotic training may be sufficient to stimulate CE, but eight-week shows greater effects.

CE is often reported as muscular strength adaptations in the untrained limb, although there is evidence that CE of motor control and motor learning are evident (Carroll et al., 2006). To measure this, robotic assessments or proprioception, ROM and a novel tracking task were performed. Following four-weeks of this robotic training program we did not observe evidence of cross-education of motor control as there were no significant improvements in performance in the listed robotic assessments PRE/POST training in the untrained limbs. These results are suggestive that four-weeks of robotic training was not enough total training sessions to elicit transfer to the contralateral limb. Similar results are presented in the literature, following a Delphi consensus by Manca et al., 2020, the authors concluded that a minimum of 13-18 sessions or 4-6 weeks is necessary to elicit changes in maximal strength in healthy controls and there was no minimum conclusion for motor control or functional adaptations. In our previous work, these adaptations were evident following eight-weeks of the same robotic training. This provides further emphasis on establishing guidelines on optimal intensity, frequency, and load in this type of rehabilitation.

Clinical Assessments

When determining severity of disease for MS, motor impairments or therapeutic progressions, clinical scales of questionnaires or clinician evaluations are typically used. However, these scales often endure poor inter-rater variability or are too subjective to have a real glimpse at the progressions or changes occurring. This was further emphasized in this work as there was an increase in strength, but the clinical assessments showed no changes pre- and post-intervention. Two of the clinical assessments used were subjective (EDSS and ABILHAND) and were not sensitive enough to changes in performance but also too difficult to improve (i.e., being able to hammer a nail). The third clinical assessment used was a performance-based measure of functional tasks (WMFT) and reported improvements in performance were evident pre- post training. Lang et al., 2008, investigated the MCID for the Wolf Motor Function Test (WMFT) of stroke survivors and determined and overall change score of 1.0 for the dominant (17% change score) and 1.2 points (20% change score) for the non-dominant limb on the WMFT can determine clinically important changes (Shirley Ryan Ability Lab, 2016). Results in this work demonstrate no clinically relevant changes in WMFT performance as IT had a percent change score range of 6.38-11.84% and DT from 5.56-8.02%. Overall, this calls for future work to develop novel and quantitative assessments to measure severity of disease or disease impairment to ensure accuracy and true measures of disability specifically for upper limb function.

9.6 Limitations

Sample size and sub-group sizes of this study were small and included four participants in the indirect training group and five participants in the direct training group. The small sample groups limited the statistical analysis and may have skewed results. Outliers were included in the data and may have also contributed to skewing the results. In addition to, some robotic data was missing due to an error in extracting the data from the robotic device. As such, that created unequal and smaller sample sizes per outcome. Results should be interpreted with caution.

9.7 Conclusion

There was an evident gap in the robotic rehabilitation literature surrounding robotic rehabilitation prescription including, length and frequency of training (Lamers et al., 2016). Therefore, the purpose of this study was to evaluate four-weeks of an upper limb robotic intervention for PwMS and compare to existing work exploring eight-weeks of the same robotic intervention. Results of this work report that four-weeks of training elicited increased strength PRE/POST, however, there were no significant adaptations in motor control or clinical assessments. This is contrary to the eight-weeks of training, which reported improvements in motor control and transfer learning/cross-education effects (in addition to strength). Conclusively, if the goal is to improve strength, four-weeks of robotic therapy is efficient and effective, however, greater magnitudes of strength were found following 8-weeks of training. Similarly, if the goal is to improve in other aspects (i.e., motor control or functional evaluations), a minimum of eight-weeks of training is suggested. Future work should evaluate twelve weeks and beyond of training comparative to eight-weeks to confirm optimal prescriptive length of robotic rehabilitation of the MS population.

Chapter 10 – Study Contributions and Relevance

The overall purpose of this dissertation was to examine the effects of an adaptive upper limb robotic training program on clinical and functional outcomes in both the trained and untrained limbs of PwMS. The work had five main objectives. Chapter 4 provided a critical scoping review of existing literature in this field to analyze robotic rehabilitation prescription, training frequency and adaptable algorithms (objective 1). Chapter 5 outlined the development of an evidenced based adaptive robotic intervention based on knowledge of previous literature (objective 2). Chapters 6 and 7 of this dissertation were completed as one large longitudinal (eight-week) data collection that implemented the robotic intervention (objectives 3 and 4). The overall goals of the eight-week intervention were: 1) to implement an adaptive robotic training program, and 2) to investigate the outcomes of the program on the upper limb for PwMS. These outcomes were broken down into strength (Chapter 6) and motor control (Chapter 7) adaptations with our research design splitting participants into direct and indirection training groups, to explore effects of cross-education with consideration to training the more or less affected limb (objective 4). Results of this intervention provides knowledge for clinicians to help decide on best treatment using direct training of the more affected limb or to focus treatment on the less-affected limb. In addition to a battery of robotic and neuromuscular assessments PRE/POST, we also conducted neurophysiology evaluations to peel back the curtain and provide some insights into neural mechanisms of CE in PwMS (Chapter 8). Finally, in a secondary longitudinal data collection (four-weeks) we aimed to provide further insight into optimal training times for robotic rehabilitation for the upper limb (Chapter 9; objective 5).

The objectives of this dissertation collectively achieve the current research goals of investigating the effects of cross-education in a MS population. To our knowledge, this is one of the first studies to investigate cross-education in the upper extremity in PwMS. Objective 2 contributes to the robotic rehabilitation field by proposing a novel adaptive approach. Assist-as-needed adaptive robotic approaches have been well understood and are the most used paradigm. This approach suggests a challenge-based paradigm that adapts to the level of performance of the user. Results provide evidence that robotic training three times per week for eight-weeks is effective and safe for increasing strength and motor control for MS.

Objectives 4 explored the phenomenon of CE. CE is well understood and explored in both healthy participants and stroke survivors but has yet to be well understood for persons with MS. This work is unique as our adaptive robotic training program demonstrated an ability to influence both strength and motor control. This was due to the resistance and exercise parameters, but also due to the innovative tracking requirements of the adaptive program. Results of this work demonstrate that training the less-affected limb was more beneficial for CE than training the more-affected limb. While training the less-affected limb, we found greater PRE/POST percent increases in strength, motor control and CE. Results also conclude that to induce CE effects, a minimum of eight-weeks of training is needed as our four-week intervention showed some evidence of CE for strength, but greater and more meaningful changes were found after eight-weeks. Perhaps therapy should focus on both limbs to emphasize this result. Results of this work can be of use to clinicians. The possibility to treat the least affected limb to aid an immobile or most affected limb to a place where it can be directly trained can be crucial for this population. A conclusive decision-making tree has been developed to help clinicians make an informative decision on robotic rehabilitation for PwMS based on results of this dissertation (Figure 48).

Objective 5 explored the effects of the adaptive robotic rehabilitation training paradigm for four-weeks of training. Results of this work help fill the gap currently existing in the literature surrounding prescription of appropriate duration, frequency, and load for robotic rehabilitation. Considering our minimal changes in strength and motor control and a lack of evidence for CE, this work supports robotic rehabilitation being longer than four weeks for PwMS.

The above objectives collectively contribute to the field of robotic rehabilitation and the rehabilitation of individuals with MS. This dissertation can be useful to inform clinicians of optimal parameters for implementing robotic rehabilitation protocols into their programs. This dissertation also provides evidence for the need of robotic devices to provide quantifiable and valuable scales to measure level of impairments. Understanding the link between robotics, neuroplasticity, and CE in PwMS would be useful for clinicians to optimize the rehabilitation process with individualized care that greatly impacts quality of life, and this thesis provides a step forward.

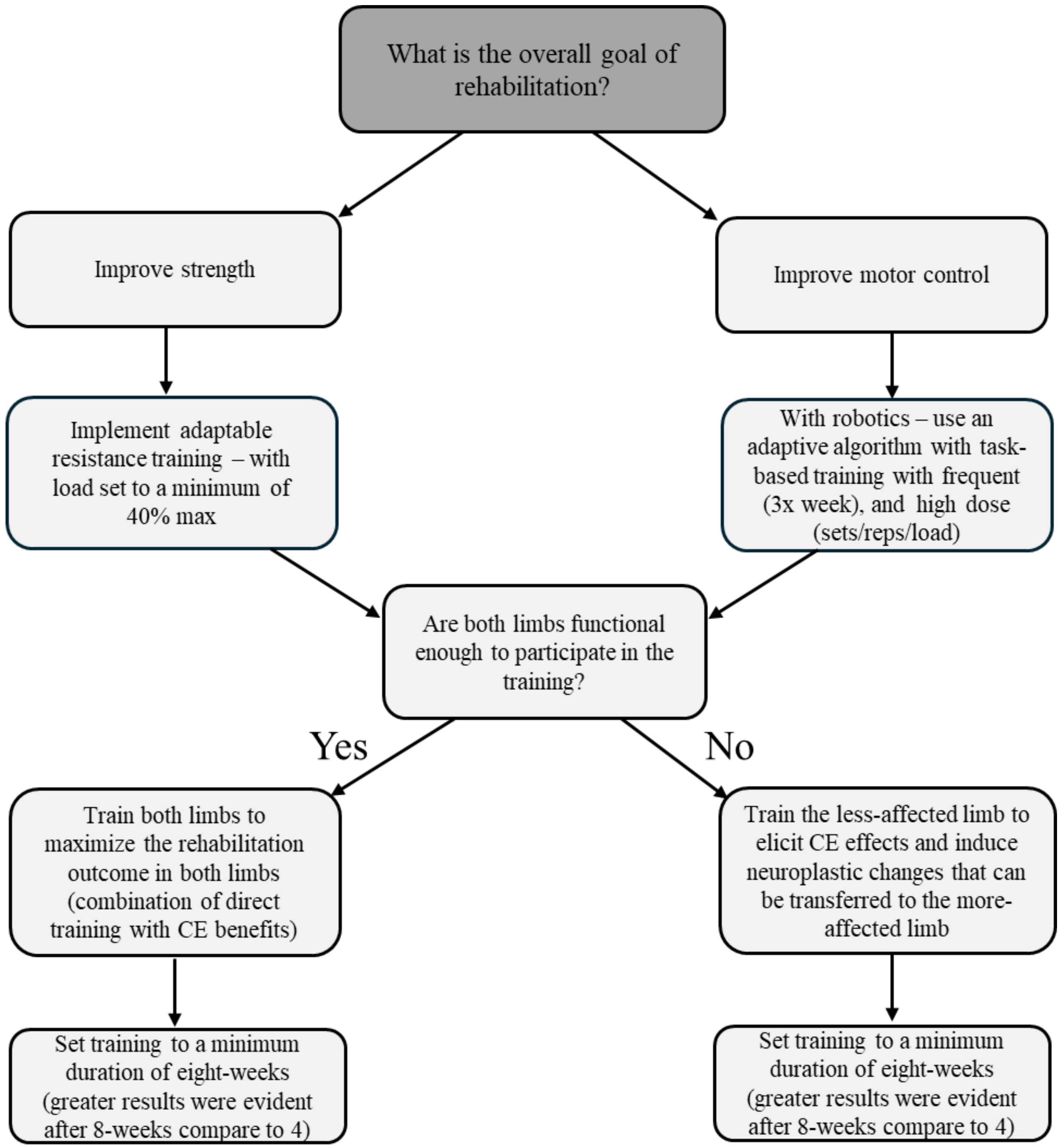


Figure 48. Decision making tree for robotic rehabilitation for individuals with MS

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Appendix

Appendix A – Informed Consent

Informed Consent

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Date: June 1, 2022

Project Title: **Does an adaptive robotic training program of the upper limb improve in muscular strength in the untrained limb for individuals with MS?**

Principal Student Investigator:

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INVITATION

You are invited to participate in a research study. Our hands are constantly being used throughout the day. They are used in complex tasks that require coordination and precision such as typing or doing up buttons or in more rudimentary tasks requiring strength like holding a cup or propping yourself up to get out of bed. Most people do not realize how valuable their hands are until they sustain an injury (short or long-term) to their hand or arm that inhibits their strength, range of motion or coordination. Without optimal function of the upper extremity, activities of daily living are increasingly more difficult to perform, and some tasks may not be able to be successfully completed at all.

Regardless of how wrist and arm dysfunction occur, it is commonly present in those with MS, making activities of daily living challenging and limiting independence. Robotic rehabilitation is a relatively new innovation that can increase the amount of work per therapy session as compared to manual therapy. The highly repetitive, high dose and reproducible movements from robotic devices promotes motor learning and an increase in muscle strength that over the course of a few weeks can increase and forearm muscle strength. Manual therapy and exercise for the limb that is more spastic, weak, and paretic can be challenging to rehabilitate. To combat

this, some have applied novel unilateral training approaches. Unilateral training (of the less affected limb) can affect neural pathways at the spinal and cortical levels, bilaterally and is known as cross-education (CE). CE is a neurophysiological phenomenon whereby one limb undergoes a training protocol, and the opposite/untrained limb exhibits muscular strength and skill improvements.
Therefore, the purpose of this proposal is to examine the effects of an adaptive robotic training program on hand function and strength in both the trained and untrained (CE) limbs in MS. This proposal has three objectives: 1) Building on our preliminary work, develop an adaptive robotic training program for the hand and wrist. By exploiting a novel haptic wrist robot (the only one of its kind in North America) as the repetitive therapy modality. 2) Complete a training study with pre/mid/post robotic and neurophysiological assessments to fully understand the adaptations of CE in this population. There is only one study where CE was explored in individuals with MS (while some in stroke and abundant in healthy populations) and this work will contribute greatly to MS rehabilitation research. 3) Link quantitative measures (robotic sensorimotor assessments) to subjective clinical scales for improved functional assessment. Findings from this proposal will provide new knowledge and encourage robotics research in MS (which lacks compared to other neurological disorders).

ELIGIBILITY
We aim to recruit 30 participants with MS for this study and 30 healthy age-matched controls. To be eligible you must be between the ages of 18-65, at least one-year post-diagnosis and have either relapsing remitting or secondary progressive MS, with an Expanded Disability Status Scale (EDSS) score between 4 and 8. You are unfortunately, not eligible to participate if you have experienced any significant trauma to the upper limb other than symptoms of MS (i.e. breaking a bone in the last 6-months), such as musculoskeletal injury. You are also unable to participate if you are taking any anti-seizure or anti-psychotic drugs listed in the Magnetic Safety Checklist. For the control group you must be between the age of 18-65 with no neurological disease or significant trauma to the upper limb. Anyone willing to participate must pass a safety checklist screening for possible contraindications that would prevent you from safely undergoing magnetic stimulation.

WHAT'S INVOLVED
As a participant, you will be asked to visit Dr. Mike Holmes' laboratory at Brock University (TH 141) 3 times per week for 8 weeks with sessions approximately 48 hours apart. During the first visit you will perform tasks that will test the strength, functionality, proprioception (knowing where your hand/arm is in space) and coordination of your hand and wrist. During the training visits, you will trace a figure on a computer screen using a robotic device. These visits will take approximately 35 minutes. The following paragraphs explain each of the tasks that will be tested pre, mid-way and post training as well as the training protocol. They will be repeated in the same order (see below) for each of your visits, and you will be able to rest for two minutes between each task.

EXPERIMENT PROTOCOL
Upon arrival to the lab, the investigators will explain and demonstrate all the tasks to you. We will also familiarize you with the equipment being used and answer any questions you may have. On the training days, you will complete *Task 7 (Tracing Task) – see below* only. This task will take approximately 35 minutes. Three times during the experiment (pre, mid, end – week 1, 4, 8), you will complete all of the tasks listed below and this session will take approximately 1 hour each.

INSTRUMENTATION

Haptic wrist device

The experimental device used for this study is a hand-held wrist robot (Figure 1). It is a mechanical system that can deliver forces to the human hand that is interacting with the device and has a virtual reality environment and computer display. The device allows for movements in the same way your wrist naturally moves. The device is controlled by custom programs.In each experiment, you will sit in front of the robot and hold the handle with both your dominant and non-dominant hand. The device is also equipped with a manual stop button that can be pressed by the participant or administrator if at any time the participant feels uncomfortable using the device.

Figure 1: The wrist robot that will be used in these studies. You will rest your arm on the device and hold the handle.

During the “Assessment Sessions” you will perform the following tests (Week 1, 3, 6).

Task 1 (Fugl-Meyer Upper Extremity Assessment)

You will be seated comfortably in a chair and asked to voluntary move your upper extremity into flexion and extension positions at the elbow and wrist without aid from the examiner. The FuglMeyer Upper Extremity Assessment is one of the most widely accepted clinical tests used to assess reflex activity, movement control and muscle strength in the upper extremity. It is based on a scoring system of 0=cannot perform to 2=performs fully. There are five subscale domains are assessed independently. For the purpose of this study, motor function and sensation domains will be assessed.

Task 2 (Grip Force and Isometric Strength):

You will be asked to place your forearm in the wrist robot, gripping a custom-built handle/joystick that is able to measure grip force. The device will be adjustable such that your elbow is flexed to 90 degrees. You will then grip the handle to your maximum capability and the device will record how hard you squeezed. This test will be performed twice (with 2 minutes rest between trials) and your highest score will count as your maximal grip strength. Similarly, you will grip the handle and push or pull maximally in 4 directions (up, down, left and right).

Task 3 (Passive and Active Range of Motion)

The robotic device will slowly move your wrist in up, down, left, right and a combination. When you believe that your maximum range of motion (before experiencing any pain) has been achieved, you will press a button with your free hand. The robot will then stop the motion and return the wrist to a neutral position. For safety reasons, the task can be stopped at any time by pressing the button. The same test will be performed manually by the researcher before every training session to ensure the safety of your wrist joint as well, will determine the appropriate size of the tracking image that will be used in the training session.

Task 4 (Position sense):
You will be seated with your dominant forearm attached to the wrist device (see below for details). You will hold a handle connected to the device and the haptic device will move your hand to a predetermined wrist joint angle, hold for three seconds and then return your hand to the starting (neutral) position. You will then be asked to move the device yourself (exerting mild muscle activity and effort) to the angle that the device previously completed. You will be blindfolded during the trials and will wear noise cancelling headphones. There will be two tasks of proprioception or joint angle position matching tasks. Including: 1) moving in just wrist left, 2) moving in just wrist right. You will perform 12 repetitions to randomly selected joint angles, with the robot positioning the hand at a speed of 15 degrees per second. All wrist joint angles will be randomized. These joint angles are much less than maximal for the wrist and thus, the risk of injury during this test is negligible.
The haptic device will record joint angles and we will be able to calculate how accurate you were at matching the target. The device is also equipped with a manual stop button that can be pressed by you or the test administrator if at any time you feel uncomfortable using the device.

Task 5 (Tracing Task):
Using the haptic device, you will trace a figure 8 shape on the monitor by tracking a dot on the computer screen as it moves around the shape. You will be asked to follow the dot to the best of your abilities using your dominant and non-dominant hand. The figure 8 shape allows the wrist to move in flexion, extension, radial and ulnar directions. The tracing dot moves at a mean speed of 20 degrees per second. You will be asked to perform as many repetitions of the completed shape as possible in 15 minutes with increase or decreasing assistance/resistance provided by the robotic device. As previously stated, the parameters of the shape that you are asked to track will be 75% of your daily maximum range of motion for your safety and will be determined by your manual range of motion task (see above).

Figure 2: The image you will be asked to track for 35 minutes.

On the "Training Sessions", 3 times per week for 8 weeks you will be asked to perform the following tracking task:

You will be seated with their forearm placed on the wrist robot, grasping the handle with your least affected hand. You will hear a ‘go’ sound (beep) and will begin to track a yellow circle on the monitor as it moves along different directions. You will be asked to follow the dot to the best of your abilities. The robot will help you in an adaptive, patient-tailored way. You will be asked to perform as many repetitions as possible within the 35-minute period. The device is also equipped with a manual stop button that can be pressed by you or researcher if at any time you feel uncomfortable using the device.

Transcranial Magnetic Stimulation (TMS)
These stimulations are common in this line of research and are safe. We will make sure that you are comfortable with the stimulations by slowly introducing them at lower intensity levels. The testing session procedures are as follows.

Instrumentation:

- Upon arrival, the skin overlying a forearm muscle and will be shaved and cleansed with rubbing alcohol by a research investigator. This shaving and cleansing is so that the surface electromyography (EMG) electrodes can be adhered to a surface with minimal interference through dead skin cells or hair. These electrodes are coated with an adhesive similar to a disposable bandage. A new disposable razor will be used and discarded after shaving. EMG will be collected throughout each session using this bipolar electrode, with a ground electrode placed on the clavicle. The placement of these electrodes can be seen on the diagram below.

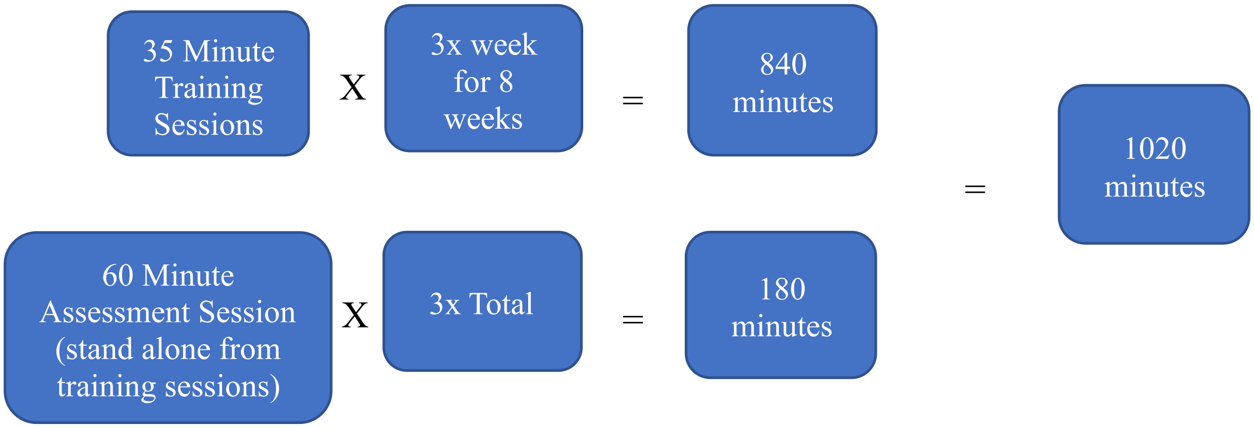
Procedures:

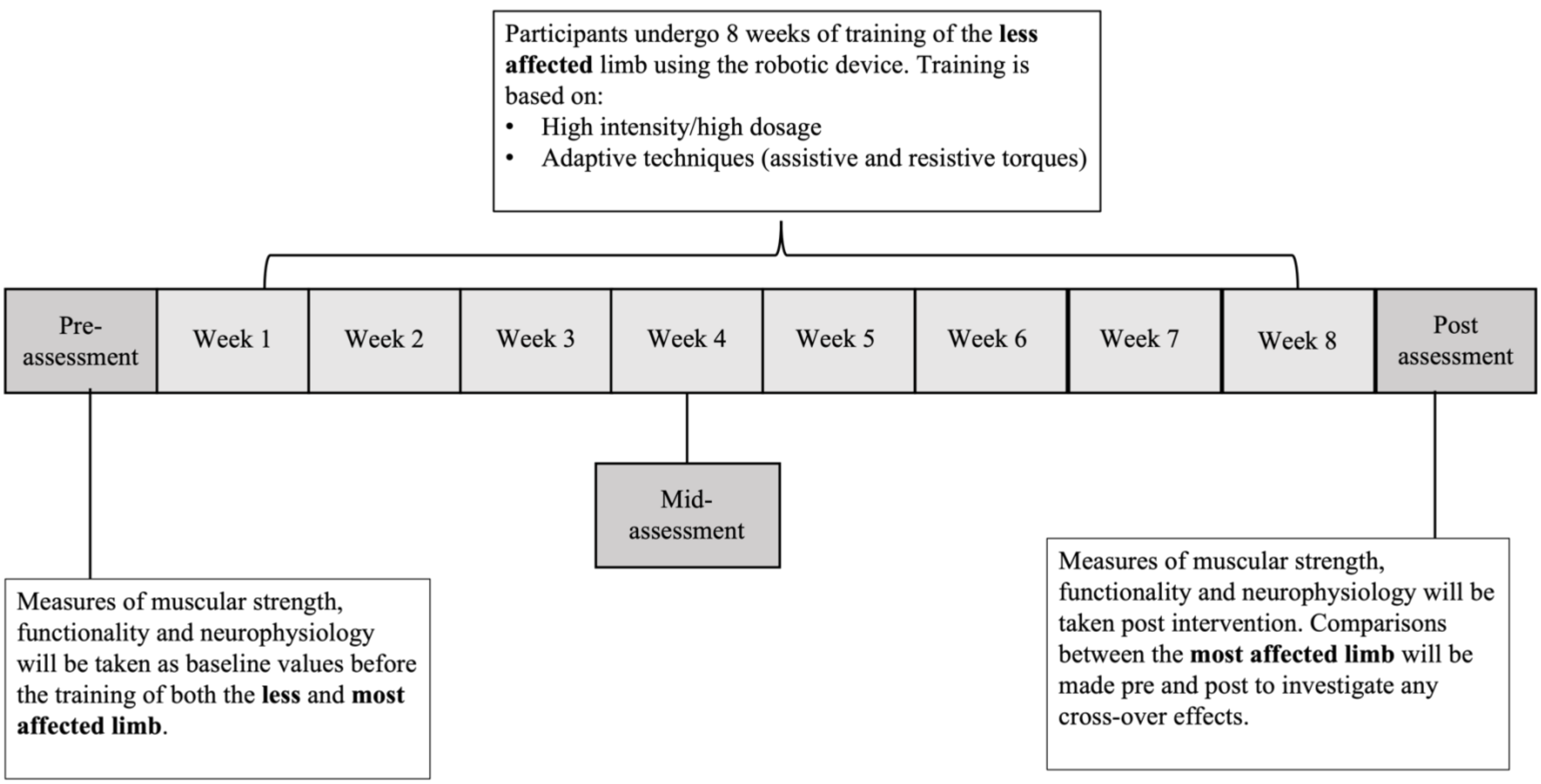
- Following application of the surface electrodes stimulation intensities that we will use for this experiment will be determined while you are at rest. One stimulation technique will be used in this study, called transcranial magnetic stimulation, or TMS. TMS is applied to the top of the head, activating the motor cortex. This technique is non-invasive and safe to use and is comparative to a light tap on the head. This is a well-tolerated technique that involuntarily activates a large group of muscles (your muscles will twitch without you telling them to). This sensation is novel to those who have never experienced it before, but we always start these techniques at very low intensities to allow people to acclimate to the sensation. You may choose to end the experiment at any time if you feel uncomfortable.

TIMELINE
Including instrumentation and experimental setup, it is expected that you will be in the laboratory for 24 “training” sessions” (35 minutes for each session) separated by at least 48 hours. This will occur 3x/week for 8 weeks. The tracking task used for “training” sessions, will be performed for approximately 35 minutes on the most affected arm.

There will be three additional data collection days in which all tasks will be performed. These are the “assessment sessions”. Pre, mid and post assessment days will be approximately 60 minutes in length.

Time Commitment:





POTENTIAL BENEFITS AND RISKS
You may experience an increase in muscle strength and improved dexterity in the upper extremities after the training program. Improvements in muscle strength and dexterity have the potential to increase functionality of the limb and performance of activities of daily living. You will be given a progress sheet to take home every week to show any improvements as a result of the training. Secondly, it will expose you to the research environment and also to a number of different research technologies. At the end of each session, you will be given an opportunity for 'debriefing' where one of the researchers will answer any questions you may have about the protocol or results obtained in your data collection session.

Results from this study will contribute to the scientific community by providing knowledge of upper limb robotic rehabilitation for a MS population. Such that, there is currently very limited research with this population and the implementation of robotics to initiate motor recovery.

The risk of injury during the training sessions is very minimal. The range of motion capable of the robot will be capped such that wrist rotations will be nowhere near end range of motion. Further, wrist rotations will be no faster than voluntary wrist motion. You may feel the typical, mild muscle soreness the day after training sessions, but if so, the soreness will not be enough to affect your activities of daily living and it will resolve within approximately 24 hours. However, these risks are very low, and we will mitigate them to the best of our ability. If needed, we can extend the number of days between sessions.

As a Power Cord member, we realize that you may feel obligated to participate and complete this study. However, we would like to remind you that you are in no way obligated to participate in this study, and declining will not affect your relationship with Dr. Ditor or jeopardize your ability to exercise at Power Cord.

CONFIDENTIALITY
Any information that is obtained in connection with this study and that can be identified with you will be disclosed only with your permission. Your information will be kept confidential through the following process. Once you are enrolled in the study you will be assigned a number, and all of your data will be labelled with that number, rather than your name. The code relating your name to your corresponding number, will be kept in an Excel file on Dr. Holmes' password protected office computers. All data will be confidential; hardcopy data will be kept in a locked filing cabinet in Dr. Holmes' research office. Digital data will be recorded on Dr. Holmes' computers that are password protected and only available to the researchers in a locked and secure room. The data will remain at this institution. The data will not be linked with any other data set and the data will not be sent outside of the institution where it is collected. Your identity will never be revealed in any reports regarding this study. The results of this study will appear in Scientific journals and be presented in scientific conferences, but your name will never be mentioned. The final scientific publication will indicate the average age, and years' post-diagnosis of all the participants of the study. It will also indicate the number of males and females. No individual personal information will be provided at all (just averages for the sample), and participant numbers will be used in the publication rather than names.

We will be asking you a few medical information questions but only to determine your age, your type of MS, and number of years since diagnosis as this information will be needed to describe the participant pool when we publish the data in a scientific journal.

Access to this data will be restricted to Dr. Holmes and the graduate student (Kailynn Mannella) involved in this work. After 1 year, the master list containing personal identifiers will be destroyed, so you will no longer be able to request personal data after this time. At times, deidentified data will be required by a journal for scientific publication. We assure that no identifying markers will ever be made available on data provided.

PARTICIPATION AND WITHDRAWAL
You can choose whether to be in this study or not. You indicate your voluntary agreement to participate by signing the consent form that is part of this letter. If you volunteer to be in this study, you may withdraw at any time without consequences of any kind, and your relationship with any of the researchers in the study will not be harmed nor will your opportunity to exercise in Power Cord be jeopardized. You may exercise the option of removing your data from the study. You may also refuse to answer any questions you feel uncomfortable answering and still remain in the study. The investigator may withdraw you from this research if circumstances arise which warrant doing so (e.g., if there are any safety concerns). Any data collected prior to withdrawal will be not be used for analysis purposes unless you wish it to be analyzed.

If you do feel the need to withdraw from the study for any reason, please contact the student investigator (Kailynn Mannella) whose contact information is located on the first page of this document.

COMPENSATION FOR PARTICIPATION
You will be compensated for travel to Brock University. Millage and parking will be compensated via cash reimbursement. You will also obtain a Lab T-Shirt upon completion of the study.

PUBLICATION OF RESULTS
Results of this study may be published in professional journals and presented at conferences. Any images and videos we release publicly will remain confidential by blurring out any identifying factors of any of the participants involved. This includes the blurring of participants faces. Feedback about the details of this study and your participation will be available to you by contacting Dr. Holmes at the address at the top of the form or completing the attached feedback letter after your participation has been completed or after you withdraw from the study if you wish to. Results should be made available approximately 6 months after your completion of the study. The results will be group data about the main findings of the study.

FEEDBACK
As previously mentioned, you will be receiving weekly feedback of your tracking task and wrist joint kinematics. At the conclusion of the study, you will have access to your own data, and you will be able to ask questions and get further clarification if desired. You will also have access to a summary of the total findings, although no names will be disclosed and all data will be anonymous. If you are interested in these options, contact Dr. Holmes at any time. We anticipate that the study findings will be available approximately 6 months after the start of data collection.

CONTACT INFORMATION AND ETHICS CLEARANCE
If you have any questions about this study or require further information, please contact Dr. Holmes using the contact information provided above. This study has been reviewed and received ethics clearance through the Research Ethics Board at Brock University (File #   ). If you have any comments or concerns about your rights as a research participant, please contact the Office of Research Ethics at (905) 688-5550 Ext. 3035, reb@brocku.ca.

Thank you for your assistance in this project. Please keep a copy of this form for your records.

INFORMED CONSENT

I have read the "Informed Consent", have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction. I also understand that I will receive a cash reimbursement for my millage and parking to Brock University.

I understand that I may withdraw from this study at any time without consequences of any kind, and my relationship with the researchers in the study will not be harmed nor will my opportunity to exercise in Power Cord or Hotel Dieu Shaver (or any other institution) be jeopardized.

____
Name (Please print)

____________________________________ __________________
Signature (Date)

____
Person Obtaining Informed Consent (Please print)

____________________________________ __________________
Signature of Person Obtaining Informed Consent (Date)

Appendix B – Expanded Disability Status Scale

Kurtzke Expanded Disability Status Scale (EDSS)

- ☐ 0.0 - Normal neurological exam (all grade 0 in all Functional System (FS) scores*).
- ☐ 1.0 - No disability, minimal signs in one FS* (i.e., grade 1).
- ☐ 1.5 - No disability, minimal signs in more than one FS* (more than 1 FS grade 1).
- ☐ 2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).
- ☐ 2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).
- ☐ 3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
- ☐ 3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).
- ☐ 4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters.
- ☐ 4.5 - Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.
- ☐ 5.0 - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
- ☐ 5.5 - Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0).
- ☐ 6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).

- ❑ 6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).

- ❑ 7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone).

- ❑ 7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+).

- ❑ 8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems).

- ❑ 8.5 - Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems).

- ❑ 9.0 - Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+).

- ❑ 9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, almost all grade 4+).

- ❑ 10.0 - Death due to MS.

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*Excludes cerebral function grade 1.

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step number is defined by the Functional System score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in Functional Systems scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS.

Sources: Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 Nov;33(11):1444-52.

Haber A, LaRocca NG. eds. Minimal Record of Disability for multiple sclerosis. New York: National Multiple Sclerosis Society; 1985.

Appendix C – Handedness Questionnaire

Handedness Questionnaire

Instructions

For each of the activities below, please indicate:

Which hand you prefer for that activity?
Do you ever use the other hand for the activity?

Which hand do you prefer to use when:		no pref		Do you ever use the other hand?
Writing:	Left ◯	◯	◯ Right	☐ Yes
Drawing:	Left ◯	◯	◯ Right	☐ Yes
Throwing:	Left ◯	◯	◯ Right	☐ Yes
Using Scissors:	Left ◯	◯	◯ Right	☐ Yes
Using a Toothbrush:	Left ◯	◯	◯ Right	☐ Yes
Using a Knife (without a fork):	Left ◯	◯	◯ Right	☐ Yes
Using a Spoon:	Left ◯	◯	◯ Right	☐ Yes
Using a broom (upper hand):	Left ◯	◯	◯ Right	☐ Yes
Striking a Match:	Left ◯	◯	◯ Right	☐ Yes
Opening a Box (holding the lid):	Left ◯	◯	◯ Right	☐ Yes

items below are not on the standard inventory:

Holding a Computer Mouse:	Left ◯	◯	◯ Right	☐ Yes
Using a Key to Unlock a Door:	Left ◯	◯	◯ Right	☐ Yes
Holding a Hammer:	Left ◯	◯	◯ Right	☐ Yes
Holding a Brush or Comb:	Left ◯	◯	◯ Right	☐ Yes
Holding a Cup while Drinking	Left ◯	◯	◯ Right	☐ Yes

(https://www.brainmapping.org)

Appendix D – ABILHAND Questionnaire

ABILHAND Questionnaire

Instructions

The activities given below normally use both hands, and we would like to know if you can do them. For each question please indicate whether you can do the activity using your hands:

N/A = not an activity you attempt
0 = Not at all
1 = Only partially or with great difficulty and slowly
2 = Fully and easily

Can you:	N/A	0	1	2	Weight
Hammer a nail					1.72
Thread a needle					1.68
Peel potatoes					1.53
Cut all your finger nails					1.49
Wrap up gifts					1.28
File all your finger nails					1.12
Cut up meat					1.11
Peel onions					0.73
Shell nuts					0.47
Open a jar					0.28
Fasten a zip on a jacket					0.22
Open a packet of crisps					0.11
Button up a shirt					-0.18
Sharpen a pencil					-0.33
Spread butter on bread					-0.71
Fasten a snap					-0.72
Button up trousers					-0.72
Take the cap off a bottle					-0.75
Open an envelope					-1.33
Squeeze toothpaste out of tube					-1.58
Zip up trouser zip					-1.59
Unwrap a bar of chocolate					-1.63
Wash both hands					-2.18

References:

Penta et al, 2001; Penta et al, 1998

Appendix E – Wolf Motor Function Test

General Description of the WMFT

All tasks are performed as quickly as possible and are truncated at 120 seconds.

1. **Forearm to table (side):** Subject attempts to place forearm on the table by abduction at the shoulder.

2. **Forearm to box (side):** Subject attempts to place a forearm on the box by abduction at the shoulder.

3. **Extend elbow (side):** Subject attempts to reach across the table by extending the elbow (to the side).

4. **Extend elbow (to the side), with weight:** Subject attempts to push the sandbag against outer wrist joint across the table by extending the elbow.

5. **Hand to table (front):** Subject attempts to place involved hand on the table.

6. **Hand to box (front):** Subject attempts to place hand on the box.

7. **Reach and retrieve (front):** Subject attempts to pull 1-lb weight across the table by using elbow flexion and cupped wrist.

8. **Lift can (front):** Subject attempts to lift can and bring it close to lips with a cylindrical grasp.

9. **Lift pencil (front):** Subject attempts to pick up pencil by using 3-jaw chuck grasp.

10. **Pick up paper clip (front):** Subject attempts to pick up paper clip by using a pincer grasp.

11. **Stack checkers (front):** Subject attempts to stack checkers onto the center checker.

12. **Flip cards (front):** Using the pincer grasp, patient attempts to flip each card over.

13. **Turning the key in lock (front):** Using pincer grasp, while maintaining contact, patient turns key fully to the left and right.

14. **Fold towel (front):** Subject grasps towel, folds it lengthwise, and then uses the tested hand to fold the towel in half again.

15. **Lift basket (standing):** Subject picks up basket by grasping the handles and placing it on bedside table.

Functional Ability Scale

0 – Does not attempt with upper extremity (UE) being tested.

1 – UE being tested does not participate functionally; however, attempt is made to use the UE. In unilateral tasks the UE not being tested may be used to move the UE being tested.

2 – Does, but requires assistance of the UE not being tested for minor readjustments or change of position, or requires more than two attempts to complete, or accomplishes very slowly. In bilateral tasks the UE being tested may serve only as a helper.

3 – Does, but movement is influenced to some degree by synergy or is performed slowly or with effort.

4 – Does; movement is close to normal *, but slightly slower; may lack precision, fine coordination or fluidity.

5 – Does; movement appears to be normal *. (*) For the determination of normal, the less-involved UE can be utilized as an available index for comparison, with pre-morbid UE dominance taken into consideration.