An adaptive 4-week robotic training program of the upper limb for persons with multiple sclerosis

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Abstract

It is suggested that repetitive movements can initiate motor recovery and improve motor learning in populations with neurological impairments and this process can be optimized with robotic devices. The repetitive, reproducible and high dose motor movements that can be delivered by robotics have shown positive results in functional outcomes in stroke patients. However, there is little research on robotic neurorehabilitation for persons with multiple sclerosis (PwMS), more specifically there is lack of literature with focus on the upper extremity. Therefore, the purpose of this work was to use a robotic device to implement an adaptive training program of the forearm and wrist for PwMS. This approach is unique, as it incorporates real time learning from the robotic device to alter the level of assistance/resistance to the individual. This methodology is novel and could prove to be an effective way to properly individualize the therapy process with correct dosage and prescription. 7 individuals with varying levels of MS, placed their most affected limb (forearm) on a robotic device (Wristbot), grasped the handle, and using real-time visual feedback, traced a Lissajous curve allowing the wrist to move in flexion/extension, radial/ulnar directions. Robotic training occurred 3 times per week for 4 consecutive weeks and included 40 minutes of work. Robotic software was adaptive and updated every 3 laps to evaluate the average kinematic performance which modified the robotic assistance/resistance. Outcome measures were taken pre and post intervention. Improvements in performance were quantified by average tracking and figural error, which was significantly reduced from pre – post intervention. Isometric wrist strength and grip force endurance also significantly improved from pre to post intervention. However, maximum grip force, joint position matching, 9-hole peg test, and patient-rated wrist evaluation did not show any significant improvements. To our knowledge, this study was the first adaptive and individualized

robotic rehabilitation program providing two opposing forces to the hand/wrist for PwMS. Results of this 4-week training intervention, provide a proof-of-concept that motor control and muscular strength can be improved by this rehabilitation modality. This work acts as a stepping-stone into future investigations of robotic rehabilitation for an MS population.

Multiple sclerosis, robotics, rehabilitation, upper limb, biomechanics

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List of Abbreviations

MS – Multiple sclerosis

PwMS – Persons with MS

RRMS – Relapsing Remittent MS

SPMS – Secondary Progressive MS

PPMS – Primary Progressive MS

PRMS – Progressive Relapsing MS

EDSS – Expanded disability status scale

PRWE – Patient rated wrist evaluation

9-HPT – 9-hole peg test

MAS – Modified Ashworth's scale

CNS – Central nervous system

ROM – Range of motion

VR – Virtual reality

ADL – Activity of daily living

Chapter 1 – Introduction

1.1 Background

Multiple Sclerosis (MS) is a chronic, autoimmune and inflammatory disease affecting the central nervous system, musculoskeletal system and spine. Presently, there is no existing cure. MS affects approximately 77,000 individuals in Canada and 2.5 million worldwide (MS Society, 2020). Specific causes of this disease remain unknown but are understood to be genetic or related to environmental factors (Weiner & Stankiewicz, 2012). Symptoms of MS typically begin between the ages of 20-40 years and are up to 3 times more prevalent in females than males. It is the most common autoimmune disease affecting the central nervous system and also known as the most disabling chronic disease of young adults during their most productive years (Weiner-Blackwell, 2012). There are four types of MS that are all categorized by the way the disease acts upon the body. 1) Relapsing remitting is the most common form of the disease. Usually the first diagnosed showing temporary relapses or flare-ups followed by periods of partial to fully complete recovery which tends to progress over time. On average, relapses occur 1.1 times per year during early stages of the disease and increase with years (Weiner & Stankiewicz, 2012). 2) Secondary progressive symptoms also get progressively worse; however, individuals with this form of disease may show signs of progressing disease with or without relapses. Secondary progressive follows initial relapsing-remitting. 3) Primary progressive shows progressive worsening symptoms with no early relapses or remissions (Thompson et al., 2018). Despite significant research, pharmacological therapies are still unable to improve motor function. Pharmacological treatments either lessen the symptoms or delay the progression of the disease but do not fully eliminate all symptoms (Carpinella, Cattaneo, Bertoni & Ferrarin, 2012). Symptoms can appear in many forms such as numbness, tingling sensations, blurred vision,

slurring of speech, loss of coordination, muscle weakness, fatigue, loss of bowel/bladder control, paralysis and impaired cognitive functions (Weiner & Stankiewicz, 2012). The durations of these symptoms are chronic with recurrent episodes. Inflammation can accumulate on the brain and spinal cord, eventually resulting in neurodegeneration and demyelination of the efferent/afferent pathways and affects the motor capabilities of the upper limb (Weiner-Blackwell, 2012). Upper limb disability is present in 66% of individuals that are diagnosed with MS (Zhong et al., 2016). Aside from walking, loss of hand and wrist function is most disabling to one's quality of life. With lack of hand function, lack of dexterity and declining grip strength comes the inability to perform basic activities of daily living (ADL's) such as bathing, dressing and feeding. PwMS become dependent and require complete reliance on caregivers to help complete fine motor skills (Mekki, Delgado, Fry, Putrino & Huang, 2018).

The cost of this disease is substantial for both pharmaceutical and manual therapy, although medication is not guaranteed to slow the progression (Aminian, Ezeugwu, Motl & Manns, 2019). Manual therapy and activity-based rehabilitation are the main source of rehabilitation for patients acutely recovering from relapse in hospitals and preserving musculoskeletal function years after the injury (Zariffa et al., 2011). In order to promote motor learning and increase functionality of the forearm and hand, manual motor therapy is required in high repetitions, multiple times daily (Olek, 2005). This method is both costly and time consuming for PwMS and the physical or occupational therapist. Robotic rehabilitation is a relatively new innovation that can increase the amount of work per therapy session as compared to manual therapy and decrease the hands-on time required from the therapist. This may help reduce the financial costs of physical and occupational therapists. If the use of robotic rehabilitation improves neurological and hand function this may also help decrease the cost of a

caregiver as these improvements lead to better performance of activities of daily living and therefore becoming less dependent. After injury, intensive task-specific therapy is needed to preserve function of the wrist and hand (Prasad, Aikat, Labani & Khanna, 2018). Robotics supports the theory that repetitive movements can initiate motor recovery when there is an absence of central nervous system innervation and perhaps stimulate central pattern generators which can produce rhythmic movement patterns (Sledziewski, Schaaf & Mount, 2012). There are multiple forms of robotics that have been introduced to neurological impairment populations, such as exoskeletons. An exoskeleton robotic device provides direct movement of the body segment, controlling each plane of motion. The control of the limb prevents any unwanted movements and forces the body segment through a specific motion (Weber & Stein, 2018). This often involves an interactive component on a monitor to add a visual element. Mar and colleagues found that the visual therapy results in a significant improvement in kinematics and proprioception, as well as movements such as smoothness and aim. Exoskeletons can imitate functional and daily activity tasks (Mar et al., 2013). Research to date uses exoskeletons with a combination of body weight supported treadmill training to improve gait for neurological conditions such as MS, spinal cord injuries and strokes (Díaz et al., 2011). Little research is available that includes the use of robotics for upper limb and hand function for individuals with MS and in addition, the few studies that have done upper limb robotic training could have implemented improved periodization and progress of the therapy. However, literature regarding upper limb robotic rehabilitation does exist. In one of the first pilot studies by Gijbels et al, they concluded that robotic enhanced rehabilitation is effective for upper limb functionality for PwMS. Using a handheld, exoskeleton, 10 subjects with an EDSS score of 7.0-8.5 trained 3x a week for 8 weeks. 4 subjects were able to complete functionality tests post experiment that they

were unable to do at the beginning of the 8 weeks (Gibels et al, 2011). Similarly, a more recent study using a mechatronic end-effector computer-assisted robotic device of the upper limb, subjects trained at a high-intensity (50-minute training sessions) 2 days per week for 5 weeks (Gandolfi et al, 2018). Out of 18 subjects, all showed significant improvements in the Action Arm Reach Test and the Fugl-Meyer Assessment Scale–upper extremity section. The limitations of these studies include finding the optimal dosage according to the degree of disability as well as the lack of implementation of periodization and progression of the therapy. Aside from therapy, robots can also be a tool used for assessment of sensorimotor control. The complex integrated systems provide a better quantitative assessment than standard subjective measures such as the EDSS to help better demonstrate adaptations that may occur over time due to treatment.

1.2 Research Gap

To date, there is little research on robotic neurorehabilitation for persons with multiple sclerosis. More specifically, there is a gap in research investigating the upper limb for this population. Current research of training interventions with the use of upper limb robotics shows significant benefits for those affected by neurological disorders such as ischemic stroke or cerebral palsy (Squeri et al, 2014; Mazzoleni et al, 2017). However, evidence supporting robotics for assistive/resistive therapy and the changes in neuroplasticity, improvements in motor control and manual dexterity are still lacking. The repetitive, highly reproducible and high dose motor movements made possible with robotics often demonstrate positive results for motor learning and are a promising steppingstone for developing new motor pathways (or restoring) and increasing muscular strength, which should translate into improved functionality of the forearm

and hand (Vergaro et al., 2010, Krebs et al., 2007, H. S. Lo & Xie, 2012). For these reasons, using robotics as a rehabilitation modality for PwMS for the purpose of improving functionality and motor skills of the hand and wrist is necessary to investigate. In this thesis, we proposed a unique approach, as the protocol incorporated real time learning from the robotic device to alter the level of assistance to the individual. This periodization and progression of the therapy is lacking in many studies, most robotic therapy studies that exist use the same dosage for the entire treatment, thus, no challenge or progressive overload is incorporated. Our methodology is novel and could prove to be an effective way to properly individualize the therapy process with correct training dosage and prescription.

1.3 Purpose

The purpose of this study was to use a robotic device to implement an adaptive, individually tailored, training program of the forearm and wrist for persons with multiple sclerosis. The overall goal of this work was to investigate changes in wrist and grip strength, motor control, spasticity and coordination of muscles in the trained limb compared to the control limb, to ultimately explore if this robotic training could improve overall hand function.

1.4 Research Questions

1. Will a 4-week robotic training program improve motor control at the wrist and hand in the trained limb compared to the control limb in PwMS?
2. Can a robotic training program increase isometric wrist strength, grip force and grip endurance (muscular fatigue) in the trained limb for an MS population?
3. Does an increase in wrist strength and an increase in maximum grip force correlate to an increase in hand dexterity/improvement in functional performance?
4. Will a robotic training program reduce the level of disabling spasticity/rigidity in the trained limb compared to the control limb?

1.5 Hypotheses

I. To address research question 1, we hypothesize that there will be a decrease in tracking and figural errors from pre to post-intervention in the trained limbs.

II. To address question 2, we hypothesize that participants will demonstrate a significant increase in maximum isometric wrist force for all directions (flexion/extension and radial/ulnar deviation) following the training program.

III. To further address question 2, we hypothesize that maximum grip force and grip endurance will increase from pre to post training in the trained limbs.

IV. To address question 3, we hypothesize that an increase in wrist strength will correlate with improved scores on functional tests and performance measures (e.g. 9-hole peg test and patient rated wrist evaluation).

V. To address question 4, we hypothesize that joint kinematic outcomes and overall tracking accuracy of performance will improve as a result of a decrease in disabling spasticity from week 1 compared to week 4 for each of the trained limbs.

Chapter 2: Literature Review

2.1 Background of Multiple Sclerosis

2.1.1 Neurological Impairments

Multiple sclerosis in layman's terms is defined as "multiple scars". MS is caused by the degeneration and demyelination of the nervous system. Nerve fibres of the brain and spinal cord are protected by a fatty protective coating known as the myelin sheath. The primary function of the myelin sheath is to insulate the axon and facilitate conduction of nerve impulses and signals to and from the brain and spinal cord. The "scars" refer to the development of scar tissue on the myelin sheath where there is a tear due to the demyelination. Degeneration of this sheath causes distorted, deaccelerated or interrupted signals (Weiner & Stankiewicz, 2012). The degeneration is a gradual and unpredictable process. The most aggressive form of this disease is progressive MS. Persons with progressive MS undergo attacks regularly where the signals are interrupted and affected which get gradually more severe and frequent with time. The second form of MS is known as relapsing-remitting MS where individuals may undergo relapses after a experiencing no symptoms. This indicates that attacks, tremors and slowed signals develop in inconsistent and unexpected spurts (Weiner & Stankiewicz, 2012). In both forms of MS, blood pressure and basic heart rate are increased compared to healthy age-matched individuals due to the lack of autonomic control of cardiovascular functions (Halabchi, Alizadeh, Sahraian & Abolhasani, 2017).

Neuropathic pain is often a painful symptom of neurodegenerative diseases. Approximately 66.5% of individuals living with MS suffer from this type of pain (MS Society, 2020). Pain is most likely to occur in the lower back, lower limbs and upper limbs. Neuropathic pain is caused by lesion or disease of the somatosensory system (Colloca et al., 2017) which is

responsible for touch, pressure, pain, temperature sensation, and vibration. Neuropathic pain can be reported as a burning, electrical pain or a discomfort from a non-painful stimulus (i.e. clothing, a light touch). Aside from this symptom being incredibly painful, it contributes to the decrease in quality of life. Pain can be associated with a loss of function, depression and impaired sleep (Colloca et al., 2017). There is no existing cure to completely eliminate the presence of neuropathic pain. Some therapy modalities such a mirror therapy can be suggested, along with disease modifying drugs (DMD's) or antidepressants. However, because pain effects each individual differently, there is no prescription that provides positive results for everyone affected. The integration of virtual reality (VR) and robotic devices with a goal-directed task can pose as a temporary distraction, contributing to a temporary relief of pain.

2.1.2 Functional Impairments

The primary sensorimotor cortex is mainly responsible for execution and coordination of simple voluntary movements. Functional and motor impairments are the most prominent and disabling symptoms of MS. 45% of PwMS report motor disability within the first month of diagnosis and 90% report motor disability within a year of diagnosis (Baird, Hubbard, Sutton & Motl, 2018). 75% of sensorimotor impairments are reported from the lower limb and 66% are reported for the upper limb (Bonanno, Russo, Bramanti, Calabro & Marino, 2019). A result of interrupted and deaccelerated signals from the motor cortex to the limbs is loss of function of fine and gross motor control of the distal upper limb. Of the 66% of PwMS that report upper limb dysfunction, 30.7% report sensory disturbance to the limbs and 8.9% report motor (subacute) disturbances. Lesions in the cerebellar pathways are a common source of disability. The cerebellar function regulates movements so that approach to the target is direct and accurate (Olek, 2005). With impairments to these pathways, movements are inaccurate and slowed. These

movements can be shown in delayed reaction times as compared to healthy controls, a lack of muscular strength, dysmetria and difficulty in performing coordinated actions. It has been reported that weakness in the upper limb is most prominent in the finger extensors and intrinsic hand muscles (Olek, 2005). Two of the most disabling symptoms of MS are ataxia and tremors (Carpinella, Cattaneo, Abuarqub & Ferrarin, 2009). Motor dysfunctions are commonly due to muscle weakness, spasticity and fatigue (Halabchi et al., 2017). Regardless of how this loss of motor function occurs, it is severely disabling to one's quality of life. In most cases rudimentary tasks such as bathing and feeding becoming increasingly more difficult. In more severe cases, turning a doorknob or picking up smaller objects become unmanageable. In addition to the functional impairments, the neuroinflammation and neurodegeneration cause CNS fatigue. Fatigue can present itself in two ways: 1) primary fatigue - this fatigue is caused by the pathology of the disease and the loss of connectivity of neurons. 2) secondary fatigue – is a result of impaired motor function or side effects due to drugs or pain (Patejdl et al., 2016). This too can cause impairments in one's quality of life with limitations in physical abilities.

2.1.3 Classifying Level of Disease

MS affects every individual differently; therefore, there are various levels for classification. The most common method to quantify disability of MS is the Expanded Disability Status Scale (EDSS) (See Appendix – A). 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 none symptomatic, 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. It is the most universally known measure used in clinical and

research aspects (MS Society of Canada, 2019). However, this test is not without its limitations. The scale is mostly related to the ability to walk a distance (m) with or without a walking aid. Therefore, a person may have little symptoms affecting gait, appearing as low level of disability but suffer from upper limb motor impairments. Additionally, symptoms of MS vary day-to-day due to time of day, fatigue, temperature, etc. Therefore, an individual may vary above or below 0.5 units.

Spasticity is a very prevalent symptom of MS. Spasticity or tremors can come in many forms: resting tremor, postural tremor, kinetic tremor and intention tremor (Bain, Navan & Aziz, 1992). Each of these tremors can be disabling in their own way. Clinicians often look for a classification scale to rate the degree of disability. Currently, one of the most popular clinical measures of muscle spasticity is the Modified Ashworth Scale (MAS) (Ansari, Naghdi, Arab & Jalaie, 2008). Although this scale is widely used amongst clinicians, there is no specialized training required to execute the test. The MAS has been tested to be more reliable for upper extremities as compared to lower extremities (Pandyan, Johnson, Price, Curless, Barnes & Rodgers, 1999). Ansari, investigated the reliability of the scale between trained physiotherapists and novice investigators. Results concluded that MAS is a reliable measure of spasticity for both professionals and novice users however, due to the nature of spasms, both limbs may not be consistent with scoring (Ansari et al., 2008). Reliability was more accurate when scoring the upper extremities than for lower limb. In order to complete the test, investigators are to ask participants to perform flexion/extension movements of targeted joints, refer to figure 1 and 2 below. They then rate the amount of spasticity on a scale of 0-4. Zero indicating no increase in tone and 4 indicating affected areas are rigid in flexion and extension (Bohannon & Smith, 1987).

0	No increase in tone
1	Slight increase in muscle tone, manifested by a catch and release or minimal resistance at the end of the ROM when the affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

Figure 1. MAS – Spasticity rating (Bohannon & Smith, 1987).

Here are the positions usually used for the MAS.

Elbow. Start position: Elbow fully flexed, forearm neutral. **Movement:** Extend elbow from maximum possible flexion to maximum possible extension. (Triceps would be the same position, opposite direction.)

Wrist. Start position: Elbow as straight as possible, forearm pronated. **Movement:** Extend the patient's wrist from maximum possible flexion to maximum possible extension.

Fingers. Start position: Elbow as straight as possible, forearm neutral. All fingers are done at once. **Movement:** Extend the patient's fingers from maximum possible flexion to maximum possible extension.

Thumb. Start position: Elbow as straight as possible, forearm neutral, wrist in neutral. **Movement:** Extend the thumb from maximum possible flexion (thumb against index finger) to maximum possible extension (in anatomical position, "abducted").

Figure 2. MAS – Movements to be performed (Bohannon & Smith, 1987).

A gold standard functional test known as the 9-Hole Peg Test (9-HPT) has been designed in 1985 by Mathiowetz et al, primarily for the purpose of testing hand and arm function for PwMS. A 9-hole peg apparatus (see figure 3 – below) is secured to the table horizontally in front of the upper limb being tested. Participants are asked to perform the task as quick as possible by taking 9 pegs and placing them in empty holes on the other side of the apparatus, then remove the pegs and place them into a container. Trials occur twice on each arm and are recorded based off of time to completion from when the first peg is touched to when the last peg is placed into the container. Any circumstances in which could affect the participant's performance (i.e. subject forgot glasses and cannot see the pegs clearly) will be indicated on the appropriate recording sheets provided by the National MS Society (National Multiple Sclerosis Society, 2019).

Figure 3. 9-hole peg apparatus (National Multiple Sclerosis Society, 2019).

An additional commonly used indicator of how the disease affects the functionality of the individual on a daily basis is known as the patient-rated wrist evaluation (PRWE) (See Appendix – B). The PRWE is a 15 patient-reported questionnaire used to assess pain in the wrist joint and functional difficulties in ADL's. There are 5 main objectives to the PRWE: 1) to determine the degree of musculoskeletal disability 2) determine relevant treatment goals 3) predict prognosis of patient 4) report any clinically relevant changes 5) communicate the functionality and pain of wrist in a meaningful way. Pain is rated on a scale of 0 (no pain) to 10 (worst pain) (MacDermid & Tottenham, 2004).

Joint position sense or somatosensory feedback is a useful 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 because decreased proprioception in the absence of visual or auditory feedback, could increase postural sway and delayed postural response (Fling et al., 2014). Assessments of sensorimotor impairments and joint position sense are often subjectively measured with a clinician with poor sensitivity (Marini et al., 2016). Today, proprioception assessments can be conducted with the use of robotics to form a validated and quantifiable performance measure. With MS there is a slowed conduction of processing and executing movements (Marini et al., 2016). There is also a difficulty in organizing a movement in the absence of appropriate sensation. Therefore, bodily spatial awareness is hindered in spatially disseminating diseases such as MS. Proprioceptive feedback is principally supplied by muscle spindles and proprioceptive receptors however these deficits are likely not a result of inactive mechanoreceptors (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, outcome measures such as variability error (overshooting or undershooting) and error bias (how consistently and similarly the participant matched the target) can also be measured from performing one set of joint angle positions (Iandolo et al., 2020). Understanding the correlation between proprioceptive pathways and upper limb performance can help establish appropriate rehabilitative interventions to better one's performance of ADLs. In a study with MRI imaging following proprioceptive tasks at the ankle joint conducted by (Iandolo et al., 2020), showed that parietal regions of the brain are involved in processing of 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 kinesthetic sense. Likewise, performance in the absence of visual feedback was correlated with corpus collosum and damage to microstructural properties during bi-lateral proprioceptive tasks (Iandolo et al., 2020).

2.1.4 Prevalence and Economic Cost of Disease

There has been an increase in the number of cases of MS in Canada from 4051 to a speculated 100, 000 by the year 2031. Canada is among one of the highest prevalence of MS worldwide (Nana et al, 2017). Due to the progression of the disease, approximately 80% of PwMS find themselves unemployed (Nana, et al, 2017). The rising cases of this disease place a large demand on inpatient/outpatient care and therefore a large economic burden in Canada. 71% of PwMS reported pain as a result of their disease that related to poorer mental health and higher level of discomfort (Charles, 2007). Pain is often treated with pharmaceutical methodologies. In 2007, the 6-month mean total for treating pain in Canada was $79,444,888 and the average cost of overall treatment of MS was $112,881,741. The total sector of health costs is estimated to

reach $2 billion dollars within the next 20 years (Nana et al, 2017). From a systematic review conducted by Naci et al, 2010, confirmed that there is an increase in cost associated with an increase in severity (based on the EDSS scale). Naci also concluded that DMD's are the costliest form of health treatment for PwMS with a lower severity. As for PwMS with a high severity, inpatient/outpatient care is the highest expense.

MS also has large financial out-of-pocket requirements for PwMS and their families. Many people require disability leave, or a reduction in their level of employment as the disease progresses. This results in a lowered income or an early retirement may become necessary (De Judicibus & McCabe, 2007). 70% of spousal of an individual with MS reported financial strain as one of their highest ranked concerns. Along with a reduction in income, PwMS have a high expenditure on quality of life care aside from rehabilitation, psychological care and physician fees. This includes any home modifications such as doorway widening, bathroom remodeling, lifts for stairways and the need to install air conditioning due to heat sensitivity (De Judicibus & McCabe, 2007). Additionally, health care remedies such as dietary supplements, specialized foods, mobility equipment, nursing care and travel costs are all additional expenses.

2.2 Motor Learning

2.2.1 Cerebellar Deficits

As previously noted, common disabling symptoms of MS are coordination and motor control issues that generally occur due to pathology within the cerebellum (Wilkins, 2017). Cerebellum deficits contribute to tremors, mainly ataxia and can also contribute to cognitive disabilities such as speech and memory loss. Ataxia – the loss of motor control and coordination of voluntary movements are predominately present in progressive forms of MS and can inhibit

one's ability to perform ADL's. In relapsing remittent MS, cerebellum and brainstem damage occur during periods of relapse.

There are clinical tests available to determine cerebellar deficits. One of those tests being a 9-Hole Peg Test. This is a popular, fine motor skill test administered for PwMS as previously described above in section 2.1.3. The cerebellum is responsible for receiving information from the sensory systems as well as it is responsible for fine motor and motor learning skills. Hence, poor performance on this task could be associated with high level of damage to or lesions on the cerebellum. D'Ambrosio et al., 2017, reported a correlation with poorer performance on the 9-HPT and MRI measures of cerebellum involvement. Proprioceptive afferent inputs may also be affected with damage to the cerebellum. Thus, a clinical test of joint position of the upper limb can also be an assessment for cerebellar deficits (Wilkins, 2017). It is proposed that rehabilitation therapies such as with the use of robotics, can lessen the degree of ataxia and thus, lessening the severity and slow the progression of the deficits caused by the lesions/damage to the cerebellum.

2.2.2 Neuroplasticity

Neuroplasticity is associated with reorganization of the motor cortex which allows for recovery of motor abilities and is the main principle of motor learning. Neuroplasticity can be measured with the use of functional magnetic resonance imaging (fMRI), activity of the brain can be observed during rest and in an active or task dependent state. Neuroplasticity is best achieved via repetitive and high intensity movements (Lo, Stephenson & Lockwood, 2019). Furthermore, research has shown that brain plasticity is enhanced using task dependent or goal-oriented exercises. Bonanno, found that high-intensity and repetitive motor function training in the upper limb improved microstructural properties in corpus callosum which leads to growing evidence that training positively changes responses from the brain to the limbs (Bonanno, Russo,

Bramanti, Calabro & Marino, 2019; Duret, Mazzoleni & Krebs, 2017). Robotics are able to produce the highly repetitive, intensified and task specific exercises that have been proven to contribute to reorganization of the brain and promote positive changes in the neural motor networks (Duret, Mazzoleni & Krebs, 2017).

2.2.3 Corticospinal Tracts

Corticospinal tracts are white matter pathways that connect the motor cortex of the brain that transfers to the spinal cord and contributes to motor function of the trunk and limbs. Impairments to these tracts in neural degeneration diseases such as MS occur due to demyelination of long white matter fiber tracts resulting in spasticity, progressive loss of motor function of the upper and lower extremities. Muscle weakness is also a large impairment stemming from damage to the central nervous system limiting ability to recruit upper motor neurons in the spinal cord (Baird, Sandroff & Motl, 2018). Similar to changes in neuroplasticity, cortical re-organization can be improved and controlled with task specific practice (Duret et al., 2017). Messages are relayed from the cortex to the spinal tract via synapses. Research has shown that conventional rehabilitation has neurological changes in these tracts with repeated movement training in neurological disorders. These results can be used as evidence for incorporating robotic rehabilitation. Robotics may increase the repetitions of the training and stimulate regeneration of these pathways. Although increased repetitions are beneficial for motor learning, it is also important to avoid fatigue as a side effect of MS is increased fatigability in the motor units and in turn can become disabling to the individual (Duret et al., 2017). With the use of robotics, this goal can be achieved while also avoiding motor unit fatigue.

2.3 Rehabilitation Therapies

2.3.1 Currently Researched Rehabilitation Techniques

Upon diagnosis of MS, pharmaceutical therapies (DMDs) such as corticosteroid injections, are much more commonly prescribed and recommended than rehabilitation therapies often to reduce inflammation, slow progression of the disease or decrease the frequency of relapses (Bonzano et al., 2013). To date, there is no agreement on which specific rehabilitation is most beneficial. However, task specific exercises and emphasis on motor learning has been most commonly used. For healthy populations, active movement has demonstrated more significant improvements in motor function. This proved to remain true for PwMS as compared to passive exercises in order to maintain integrity of white matter and deaccelerate progression of the disease (Bonzano et al., 2013). Physiotherapy is a recommended rehabilitation tool from the MS Society of Canada. Stretching, range of motion (ROM) and strength training exercises are necessary to maintain function. The MS Society of Canada also recommends occupational therapy to maintain functional independence. Speech therapy is used for vocal and swallowing issues. Neuropsychologists and the use of cognitive rehabilitation are often recommended for psychological therapy (MS Society of Canada, 2019). Exercise promotes strengthening the musculoskeletal system as well as aids in building coordination and balance. The MS Society of Canada's physical activity guidelines for adults with MS includes a minimum of 150 minutes of moderate intensity aerobic activity per week (Kalb et al., 2020). Aerobic training can include, arm or leg cycling, walking and elliptical training. Guidelines also suggest strength training exercises for major muscle groups at least 2 times per week. This can include weight machines, free weights, resistance bands and cable pulleys (MS Society of Canada, 2019). Exercise as therapy has also been researched to lower the rate of depression and promotes a social

environment and flexibility exercises can reduce spasticity episodes (Halabchi, Alizadeh, Sahraian & Abolhasani, 2017).

Constraint-induced movement therapy has mostly been used with stroke populations to regain function of the affected limb. Some studies have also demonstrated that this therapy is also beneficial and effective for promoting positive neurological adaptations for MS (Duret et al., 2017).

2.3.2 Exercise with Multiple Sclerosis

The most common symptoms of MS are the inability to generate a maximal force and muscle fatigue that are both inherently linked to muscle weakness. This muscle weakness in turn affects one's motor or muscle performances which can be a result of either incomplete motor unit recruitment, decreased motor unit discharge rates or disuse atrophy (Taylor, Dodd, Prasad & Denisenko, 2006). Nearly two decades ago, it was thought that resistance training would be detrimental and increase the progression of this disease because subjects with MS are highly fatigable with high bodily temperatures. Healthy individuals are able to activate between 94% - 100% of their motor units and PwMS are able to activate only 47% - 97% (Patrocinio, Moreira, Carrion, Medina & De Paz, 2018). This was believed until Petajan and colleagues disrupted this theory in 1996 with a 15-week cardiorespiratory intervention that had significant improvements in VO_2 maximum, increases in muscular strength and endurance. In addition to aerobic exercise, resistance training improves muscle strength which can lessen fatigue, improve posture and gait and upper limb function (Petajan et al., 1996). However, resistance training improves muscle strength which can lessen fatigue, improve posture and gait and upper limb function. PwMS are prone to balance difficulties therefore, exercises should be completed when seated as much as possible. Due to the high bodily temperatures, appropriate rest of 2-4 minutes should be given

between exercises. This will also help eliminate any symptom flare-ups or pseudo exacerbations that are caused by over fatigue. It is recommended by the Canadian Society of MS that individuals participate in a minimum of 150 minutes of moderate intensity exercise per week (MS Society, 2020). More so, individuals with an EDSS of 0-6.5 are recommended to engage in aerobic exercise 2-3 times per week for 10-30 minutes, resistance training 2-3 per week consisting of 1-3 sets and 8-15 repetitions (60% - 80% of 1-repetition maximum) and neuromotor training 3-6 times per week for 20-60 minutes. Individuals with an EDSS score of 7.0-7.5 are recommended to engage in exercise for up to 20 minutes per day followed by breathing exercises (Manago, Glick, Hebert, Coote & Schenkman, 2019; Kalb et al., 2020). Progressions should exist to generate and increase muscle force. In previous literature, progressions have been determined using a Borg Scale or standard group averages. This has been proven unsuccessful when evaluating improvements in muscle strength when compared to studies that have made progressions based off an individual's isokinetic dynamometer maximum or 1 rep-maximums predications (Manago, Glick, Hebert, Coote & Schenkman, 2019). Rather, progressions should occur when the subject is fully capable of performing 12 to 15 repetitions of an exercise with full ROM. Resistance can then be added by 2% - 5%. It is recommended that when resistance training for this disease that focus is primarily on lower limb exercises as the lower body strength deficit is greater than that of the upper extremity (Halabchi et al., 2017). However, current research has placed an equal importance on upper body to improve dexterity, function and strength gains to improve ability to perform ADL's and become less dependent on caregivers.

2.4 Robotics for Rehabilitation

2.4.1 Primary Benefits

Hand functionality can drastically improve overall quality of life, allowing individuals to be less dependent on their caregivers. Manual therapy is necessary for rehabilitation; however, these populations require repetitive ROM therapy that is either too intensive for a single physical therapy session or too financially unsustainable for the individual affected to continue (Naci et al., 2010). Motor rehabilitation has been proven to reduce ataxia and tremors. The highly repetitive movements linked to robotics allows for much less hands-on association with a therapist. Most research to date includes robot-assisted training to improve upper limb function for populations affected by stroke with positive results in improvement of functionality. Robotics facilitate efficiency in a clinical setting, increasing the number of individuals that can be treated in a single day (Lo, Stephenson & Lockwood, 2019). Robotics for rehabilitation avoid the phenomenon of motor slacking during a therapy session. Motor slacking occurs when the human motor system finds the most efficient and economical way of performing the exercise in an attempt to avoid fatigue. This can also go hand-in-hand with a lack of motivation during therapy. With the use of robotics, the participant is not able to move off of the programmed ROM or intensity until the task and all repetitions are complete. As opposed to manual therapy, robotics are also able to quantify sessions and progressions of the exercise to allow clinicians to track progress and make advancements where necessary (Washabaugh, Treadway, Gillespie, Remy & Krishnan, 2018). Robotics are able to lock motors and allow for a single or minimal degree of freedom, better focusing on a particular important motor pattern such as flexion/extension, radial/ulnar deviation or pronation/supination. In addition to, they can be gravity assisting or gravity eliminating aiding movements for those with severe motor impairments. Extrinsic

feedback is crucial to the development of motor learning. Robotics are able to do so during a rehabilitation session as well as provide a goal driven movement thus, better engaging the participant to his/her treatment. Masiero et al., found that during upper limb therapy training, greater interaction resulted in greater opportunities for the nervous system to experience ADL tasks related to sensorimotor input (Masiero, Poli, Rosati, Zanotto, Iosa, Paolucci & Morone, 2014). An article written by (Livengood et al., 2011), reported a clinician's view on robotics. The clinicians noted that the use of robotics was easier for replication and adjustment of a rehabilitation session, that it provided real-time or delayed time, and the mechanisms provide haptic, visual and auditory feedback to enhance the therapy session.

A strict limitation to the introduction of robotics to a medical clinic or rehabilitation center is the primary capital upon first purchasing a robotic device. Additionally, robotics are not easily accessible and are not available in every clinic. A recent study compared the costs of a robotic system compared to the costs of a physical therapist to deliver equal quantities of treatment. The study showed that the purchase of a robot had a better economic outcome or was most cost effective when compared to conventional therapy. The robot also required less motor movement from the therapist, allowing the therapist to focus on multiple other factors important to rehabilitation such as posture, alertness etc. (Lo et al., 2019).

2.4.2 Types of Robots

Robotics for the use of neurorehabilitation is an innovative therapy based on the human-robot interaction. Human-robot interaction is an important instrument in motor recovery. Three main components to human-robot interaction are; induction, intention and feedback to the brain. Each of these components form a closed neuronal pathway (Yue, Zhang & Wang, 2017). Hand robotics for rehabilitation devices were first used over two decades ago. Studies have shown that

repeatable, flexible and high dose exercise training can modify brain organization and promote changes in neural motor networks (Duret et al., 2017). The first models were initially used for gross motor control and heavy labour work to reduce the work for human therapists and were mainly designed for the rehabilitation the upper limb for stroke patients (Yue et al., 2017). The first device developed known as the MIT-Manus was built in 1992, a 2 DoF apparatus that was created for the rehabilitation of the shoulder and elbow for post-stroke patients (Laut et al., 2016). Currently, the goal of robotics in neurorehabilitation of the upper limb is to 1) train (robot-aided therapies), 2) support (exoskeletons), or 3) replace (prosthesis). There are two main types of robotics used in rehabilitation used in all 3 of these methods: exoskeletons and end-effectors. Exoskeletons encase the limb and allow movement at each limb joint, mimicking the kinetic movement of the upper limb and acts directly upon specific joints. Exoskeletons offer assist-as-needed force fields or weight support to eliminate gravity (Laut et al., 2016). Existing exoskeleton robots include MEDARM, L-exos and CADEN-7, Figure 4 – below.

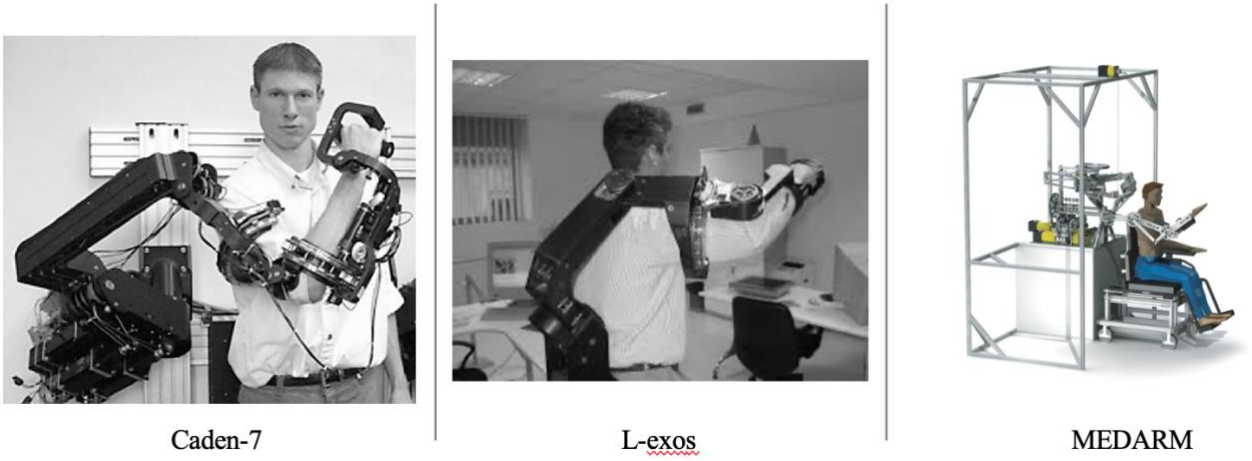


Figure 4. Existing exoskeleton robotics.

End-effectors attach to the end of the robot and manoeuvre only extremities of the limbs such as the hands and feet and are external to the human body (Lo et al., 2019). End-effectors

typically provide a force without the consideration for individual joint movement patterns because the interaction is only at a single interface. End-effectors are most commonly used for rehabilitation of the lower extremities rather than the upper limb. Each type of robotic device is powered by a different motor or transmission. As seen in Figure 5, end-effector robotics can have linkage or cable transmissions. Linkages, the most popular form of transmission for hand robotics, are easily controllable. Whereas a cable transmission includes a pulley system.

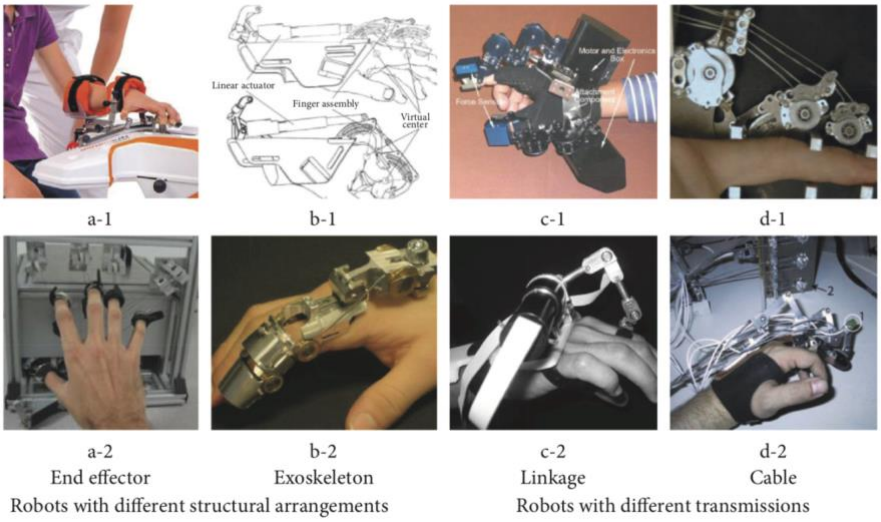
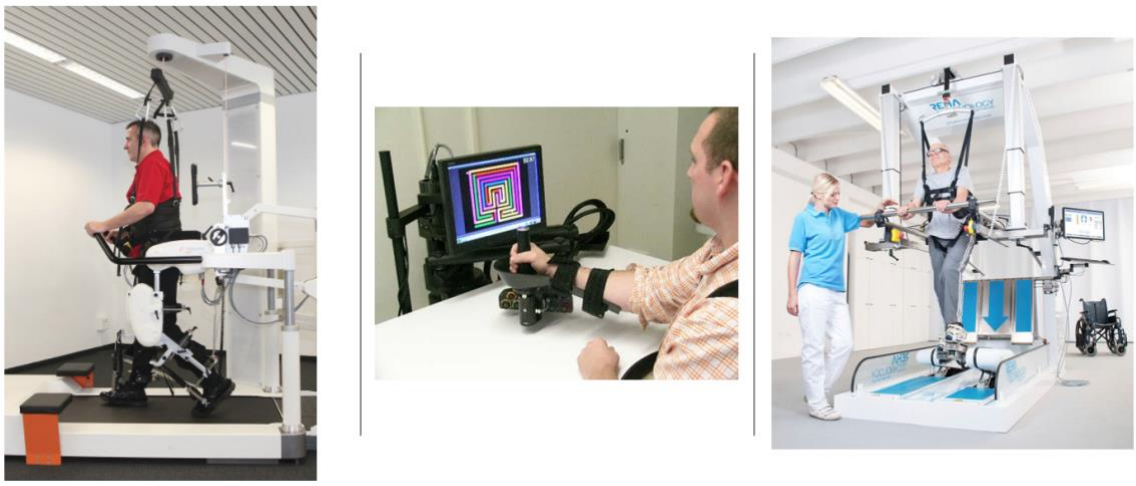


Figure 5. Examples of hand robotics, linkage vs. cable (Yue, Zhang & Wang, 2017).

Additionally, bioelectrical signals can be used where the signal from an EMG electrode provides movement to the robotic device (Yue et al., 2017). Currently researched end-effector robotics include MIT-Manus, The G-EO System and The Haptic Walker, Figure 6 – below.



The Haptic Walker MIT-Manus The G-EO System

Figure 6. Existing end-effector robotics.

Regardless of the type of robotic device, the goal is to allow the limb to move naturally for specificity of learning so that motor tasks practiced can be translated to functional tasks. Robotics can assist/resist movement of the human limb in various ways, including, passively, active non-assist mode, active assist mode, resistive mode and bimanual exercise (Masiero et al., 2014). In some cases, robotics are implemented with more than one of the movements listed.

2.4.3 Virtual Reality and Robotics

As previously discussed, robotics can promote positive changes in neuroplasticity, motor learning and rehabilitation. The addition of a virtual reality (VR) component can further augment these results. VR can be defined as "an approach to user-computer interface that involves real-time simulation of an environment, scenario or activity that allows for user interaction via multiple sensory channels" (Adamovich, Fluet, et al., 2009). The goal of rehabilitation is to improve one's functional performance by means of recovery of lost motor skills. VR in

combination with robotics delivers relevant stimulation to the nervous system with a goal-directed task and thus, promoting the learning of these motor skills (D'Ambrosio et al., 2017). The VR adds a visual feedback as the human-robot interacting adds a haptic feedback thereby strengthening the stimulation to the nervous system. Additionally, the drive behind the theory of robotics is the overabundance of repetitions of practice – VR can increase this potential. Providing more augmented feedback, VR can aid in consistent task repetition (Cheung et al., 2014). Augmented feedback received from a sensory system (in this case, visual) is a major supporting factor in motor learning (Schmidt & Lee, 2011). Another main component of motor learning that has been highly researched is attentional focus. For individuals with Parkinson's or older age adults, it has been demonstrated that the learning of a motor task is most effective with an external focus of attention as compared to an internal focus (Wulf et al, 2009). The use of VR alongside a goal directed task acts as an external focus cue, which one can assume this theory would remain true for additional neurological disorders such as MS. Aside from the motor learning aspect, VR aids in keeping the user entertained and engaged in the task. For tasks of high repetition this is very important for motivation levels in order to produce the best results possible. A proof of concept study was conducted by (Mirelman et al., 2007) and demonstrated that robot-aided neurorehabilitation has more positive impacts in reducing impairments in stroke patients as compared to robotics alone. Although this study was investigating the improvements in gait, these results have the potential to be transferred to the upper limb as well.

2.5 Researched Evidence

2.5.1 Evidence – Robotic Rehabilitation

Robotic rehabilitation of the upper limb is a newly explored topic for PwMS however, there is some evidence to support the benefits of robotics. Carpinella and colleagues confirmed after an 8-session treatment, robot-based training significantly improved upper limb coordination, functionality and dexterity for 22 subjects with MS (Carpinella, Cattaneo, Bertoni & Ferrarin, 2012). Using an apparatus that consists of planar robotic manipulandum, participants made significant improvements in the velocity, smoothness and linearity of their reaching movements. Participants performed 8 therapy sessions of 160 movements with a duration of 30-45 minutes each. Participant's wrists were secured to an exoskeleton robot, leaving the hand and fingers free. They were asked to perform a dual task. Subjects were to reach with their forearm and wrist to match a dot located on an LED monitor in front of them while their hands were grasping physical objects with the free hand. This occurred in 2 conditions; null phase and perturbed. These results suggest improvements in the use of robotics for upper limb muscle coordination and dual task performance. Magnetic resonance imaging (MRI) shows that robotic rehab in PwMS show positive effect on neural pathways. A case study of a 47-year-old woman with relapsing remitting MS was conducted. The participant underwent a total of 40 high-intensity repetitive upper limb robotic training sessions (5 times a week for 8 consecutive weeks). MRI's were taken pre and post training. Results showed significant improvement in microstructural properties of the corpus callosum. The primary role of the corpus callosum is to integrate motor, sensory and cognitive performances. Therefore, these results show improvements in functional connectivity as well as musculoskeletal improvements (Bonanno et al., 2019). Similarly, Feys et al, completed a study of 17 participants with MS, with an EDSS

score of 3.5-8.5. Participants performed 30-minute sessions, 3 times a week for 8 weeks. The robotic device used was both an output device - providing haptic feedback, as well as an input device – allowing navigation within a virtual learning environment. Results showed that robotic training led to better efficient movement and reaching execution and improvements in spatial domain. Surveys from participants also indicated improvements in everyday life (Feys et al, 2015). These results suggest positive improvements using robotics as a therapy modality in muscle activation and motor learning for MS and improvements in overall functionality of the upper limb. There is lack of robotic rehab therapy for PwMS however, there is significant research for stroke patients to validate the idea. Hsief et al, conducted a 4-week robotic rehab intervention for persons affected by ischemic stroke. A high-intensity group underwent 600 to 800 repetitions a day, 5 days a week. A lower-intensity group underwent the same protocol with half the amount of repetitions and lastly, a control group that did not undergo any robotic therapy training sessions. Researchers found that the higher-intensity group made the most significant improvements. The lower-intensity group still made significant improvements compared to the control group, but not as substantial as the high-intensity group. These results suggest that intensity is the most important parameter of robot-assisted therapy (Hsief, Wu, Lin, Yao, Wu & Chagne, 2012). A noteworthy importance of each of these studies is that all positive results were shown without any muscular damage, fatigue or adverse effects. These results suggest that robotic rehabilitation is a safe and effective method to improve motor skills without altering muscle form or contributing to an increase in spasticity (Cortes et al., 2013).

Dosage and frequency of resistance training with a robotic device is lacking in literature and in need of further investigation. Therapy dosage recommendations for these studies are based upon that of stroke patients. A recent systematic review shows that researchers have

concluded positive results with studies from as low as 6 weeks in duration with a frequency of 2 to 3 times per week compared to studies as long as 20 weeks with a frequency of 2 to 3 times per week (Lamers et al, 2016). Therefore, significant positive changes can be elicited within only 6 weeks of training. However, none of these studies reported on intensity of training sessions. Moreover, none of the studies included any background or reasoning behind the choice of therapy dosage. This is a large research gap that should be investigated further in the future.

2.5.2 Evidence – Motor Learning

Motor learning can be defined as "A set of processes associated with practice or experience leading to a relatively permanent change in the capability for skilled behaviour" (Schmidt & Lee, 2011). For individuals in rehabilitation, it is a constant battle to relearn daily skills such as dressing, brushing teeth or feeding. Those with neurological disorders such as MS experience difficulties in both cognition and physical limitations, adding extra challenges to the motor learning process (Kleynen, Beurskens, Olijve, Kamphius & Braun, 2018). Engagement from the participant is an essential part of learning. Robotics demand engagement from the participant that are quantifiable. Reward of positive feedback has also been shown to promote motor learning and behaviour (Mazzoleni, Duret, Grosmaire & Battini, 2017). Zeller and colleagues concluded that PwMS have similar cortical excitability and training induced motor learning changes as healthy populations. This expresses that plasticity remains intact despite demyelination and axonal damage as a cause of the disease (Zeller et al., 2010). To support this evidence, Tomassini also found that both short and long-term motor skills are still preserved in various levels and progressions of MS. After one week of motor skill training, PwMS improved the same performance levels as healthy populations (Tomassini et al., 2011). Nociti used a 9-HPT over the course of 12-weeks to monitor motor learning skills in 25 participants with

multiple severities of MS. Results showed positive effects that persisted for 3 months after the designated training period (Nociti et al., 2016).

Chapter 3 – Study Design

3.1 Sample size

15 community-dwelling individuals with MS were recruited from the community and Brock University's Power Cord facility (see recruitment poster – Appendix – C) to participate in this study. In total, 7 individuals with MS participated (see Table 1 subject demographics) and completed the 4-week training program. 7 individuals were forced to terminate the training due to COVID-19. Subject 5 lives with muscular dystrophy, not MS and was also eliminated from the study because symptoms were not comparable to the rest of the population. Due to the difficulty obtaining participants from this population, subject numbers are often low in the published literature (Vergaro et al 2010, Carpinella et al 2012). Inclusion criteria consisted of individuals with any phenotype and severity of MS whom experience upper limb motor impairments. No subjects were undergoing any additional therapy interventions such as physical or occupational therapy at the time of the study. Subjects were not taking any disease modifying drugs that would limit or enhance motor control of the upper limb. All subjects were encouraged to keep their daily routines as consistent and normal as possible over the 4-week intervention and training days were optimally scheduled on the same time of day each week. All experimental procedures were approved by the Brock Biosciences Research Ethics Board (REB# 19-119) and written consent (Appendix D) was obtained from all participants prior to participating.

Table 1: Subject Demographics

SUBJECT ID	AGE	MS PHENOTYPE	DOMINANT LIMB	AFFECTED/ TRAINED LIMB	YEARS SINCE DIAGNOSIS	EDSS	SEX	COMPLETED SESSIONS
S01	36	SPMS	R	L	14	7	Female	15*
S02	60	PPMS	R	L	20	7	Female	12
S03	71	SPMS	R	L	20	3	Male	15*
S04	43	RRMS	R	R	6	6.5	Female	12
S06	61	SPMS	L	R	34	6	Female	12
S07	27	RRMS	R	R	1 ½	4	Male	11
S12	30	RRMS	R	L	7	2	Female	11
MEAN	46.9 ± 15.9		6 – R 1 – L	3 – R 4 – L	14.6 ± 10.3	4.7 ± 1.8	5 – F 2 – M	12.6 ± 1.6

SPMS = secondary progressive MS, PPMS = primary progressive, RRMS = relapsing remittent. R = right hand, L = left hand

* denotes subjects beginning their 5th week of training when sessions needed to be terminated due to COVID-19

3.2 Experimental Set-up

Participants were asked to visit Brock University's Research and Innovation Centre (130 Lockhart Drive, St. Catharines, ON) to use a robotic apparatus (figure 7). Participants were seated in an upright neutral position in front of a monitor and a robotic device known as the WristBot (figure 7, Genoa, Italy, Iandolo et al, 2019). WristBot is a custom-built manipulandum developed at the Italian Institute of Technology (IIT). WristBot has a range of motion (ROM) that replicates typical human wrist motion in the three degrees of freedom (DoF): flexion/extension ±62°, radial/ulnar +45°/-40°, pronation/supination ±60°. WristBot was designed to provide force feedback to participants during motor training programs or therapy sessions. WristBot has been intended for rehabilitation use in clinical and research settings amongst patients with neurological impairments to induce neuroplastic changes in the brain. Motors allow the addition of real-time force feedback in any DoF. For each DoF, angular rotation of the handle is measured by a high-resolution incremental encoder and the corresponding torques are actuated by brushless motors that provide a maximum continuous torque of 1.53 Nm for flexion/extension, 3.81 Nm for radial/ulnar deviation and 2.87 Nm for pronation/supination. WristBot uses real-time visual feedback which allows participants to track a cursor on a monitor in various movement patterns. All kinematic data on tracking performance is sampled at 100Hz and stored for further analysis. Subjects rested their forearm (with a consistent elbow flexion of 135° ± 3.67°) in the robot, grasping the handle with their hand (figure 8). Additionally, the WristBot is adjustable in height so a chair or wheelchair could be used when necessary.

Initially, this work was designed to be an 8-week training program with training sessions 3x per week. 8-weeks in duration was chosen based off of previous literature that has

demonstrated positive neurophysiological changes in an MS population (Bonzano et al., 2014; Carpinella et al., 2009; Vergaro et al., 2010). However, due to COVID-19, the study was scaled back and participants were asked to come to the laboratory 3 times a week for 4 consecutive weeks for the "training sessions" with an additional 2 visits: One for baseline (T0, before the first training session) and one post-intervention (T2, after 4 weeks of training) "assessment sessions" (figure 9). Training days were optimally on the same days each week and the same time of day. Training sessions took approximately 1 hour and assessment sessions 1.5 hours. Training sessions were based on a high dose, high frequency and task-oriented bases (see section 3.4). Assessment sessions (see section 3.3) provided assessments of various measures, including functional movements, strength, endurance and proprioception.

Figure 7. WristBot (Iandolo et al, 2019).

Figure 8. Experimental set-up at Brock University's Research and Innovation Centre.

Figure 9. Timeline of study design.

3.3 Assessment Sessions

Outcome measures (described below – Table 2) were recorded at 2 time points: T0 (baseline) and T2 (post-intervention). All outcome measures took approximately 1.5 hours to complete and were performed on separate days aside from typical training sessions to avoid fatigue. Participants underwent 10 quantitative and qualitative outcome measures to track performance of both upper extremities (firstly the dominant arm, followed by non-dominant) in the order of (see table 2):

1) Expanded Disability Status Scale (EDSS) – to classify the severity to the subject's disease (See Appendix – A).
2) Modified Ashworth's Scale – as previously described above, was used to assess disabling spasticity and were analysed with rating scales provided by the National MS Society (refer to Figure 1 and 2).
3) PRWE questionnaire – patient rated wrist evaluation disabling score. The PRWE is a series of questions according to the patient's hand and wrist functionality in ADL's and were analysed with rating scales provided by the National MS Society (see Appendix – B) (MacDermid & Tottenham, 2004).
4) 9-Hole Peg Test – a measure of functionality and dexterity of the upper limb (refer to Figure 3 for image of the apparatus). Participants were seated in an upright position without elbows and forearms resting on the table. They were instructed to place 9 pegs from the table into the peg holes one by one then remove the pegs and place them back onto the table. 9-HPT was measured by time (seconds) to completion. 2 trials occur on each hand and the fastest time was recorded.

5) Maximum grip force – used to assess overall grip strength. Maximum grip force was performed with a Jamar grip dynamometer (Jamar Smart Digital Hand Dynamometer, Performance Health, Warrenville, USA) held with a straight arm, 45° abduction by the side and hand/wrist neutral. Subjects were instructed to squeeze the handle as hard as they could for 3 seconds. This test was performed twice on each limb and the highest force in kilograms (kg) was recorded for each limb.
6) Passive and Active wrist range of motion (ROM) – While in the robotic device, for the active ROM test, the subject moved their hand at 10º/second (tracking a dot on the computer screen in front of them) in flexion, extension, radial and ulnar planes until their voluntary maximum excursion had been achieved. For the passive ROM test, the robot moved the hand to end ROM and also calculated a wrist rigidity indicator by measuring the level of stiffness from the handle of the robot to the axis of rotation (wrist joint) as the wrist was moved through the action. Subjects performed 3 repetitions of both passive and active ROM and the maximum ROM in each DOF was recorded.
7) Joint Position Sense – to assess proprioception. Subjects wore noise cancelling headphones and were asked to close their eyes. The robot passively moved the subject's wrist in flexion or extension and would stop at a randomized joint angle (target). The robot then moved the subject's wrist back to the neutral position. The subject was then asked to match the position of the robot by actively moving the handle and pressing a manual button with their alternate hand when they believed that they had matched the previously presented wrist angle target. 12 trials total, flexion (N=6) and extension (N=6) were performed.

8) Unassisted tracking – to quantify level of motor control and ability to track a moving target. The subject was asked to follow a moving target over a Lissajous figure (8-shaped, see figure 11) with the handle of the robot for 6 complete laps without assistance from the device. The size of the figure was set to 80% of the subject's maximum active ROM previously recorded (the one recorded at T0 for the entire experiment, refer to Figure 11). Tracking errors were quantified as described below.

9) Maximal isometric wrist force – Isometric wrist force was performed using a load cell (Wagner Force One Pressure Gauge, Wagner Instruments, Greenwich, CT). Isolating the wrist joint with the arm fully extended and rested on the table, subjects 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 was rested on the metacarpophalangeal joints. Subjects were positioned in supination for maximal wrist flexion, pronated for maximal wrist extension and maintained a neural wrist position for radial and ulnar deviation. Two trials were taken in each direction and the highest force was recorded.

10) Grip force endurance test – to measure muscular fatigue. In the same anatomical position as the maximum grip force, subjects squeezed the grip dynamometer at 50% of their maximum grip force for as long as possible and time to fatigue was recorded in seconds. Due to the fatigability of this task, only 1 trial on each limb was performed. The task was terminated when the subject reached less than 50% of their maximum grip force (previously recorded) for 2 consecutive seconds. Verbal, positive encouragement and motivation was provided by the researcher.

Aside from the outcome measures listed above, data such as MS phenotype, handedness, age, most affected limb, number of years since diagnosis, medications, current physical activity status and typical medical history were verbalized by the subject and recorded by the researcher. Anthropometrics and hand length were measured and recorded by the researcher. As MS affects every individual differently, this was essential to analyze and categorize the data and results. Only at T0, before the start of the assessment, subjects completed a familiarization session where they became accustomed to the researcher, robotic apparatus, reviewed the informed consent and were able to ask any additional questions. Subjects performed as many practice trials of the tasks as needed until the tasks were fully understood before commencing the assessment.

Table 2: Outcome measures in protocol order.

1. Expanded Disability Status Scale	6. Passive and Active ROM
2. Modified Ashworth's Scale	7. Joint position sense
3. Patient Rated Wrist Evaluation	8. Unassisted Tracking
4. 9-hole peg test	9. Maximal isometric wrist force
5. Maximum grip force	10. Grip force endurance test

Note: Red = robot-based measures.

3.4 Training Sessions

The format of the training protocol was the same across all training sessions. In each training session, only the subject's self-reported most affected limb was trained, the opposing limb was used as a control. In each session, before beginning the protocol, subjects underwent a manual ROM test performed using the robot. Manual ROM was tested in 2 planes (flexion/extension, radial/ulnar deviation). Subjects were asked to follow a visual dot located on the monitor in front of them to their maximal wrist ROM. Once their maximum range was achieved, the position was stored, and the robotic device moved the subject's hand back to the neutral position. This procedure was implemented for the safety of the subject, to ensure that, for any unpredictable reason, the ROM was not decreased in respect to the one collected in T0 and that the tracking session parameters were specific to that individual on each individual day. The tracking parameters (the size of the figure) never exceeded 80% of the subject's passive ROM collected in T0.

Using WristBot, participants traced a Lissajous curve (8-shaped) on the monitor by tracking a moving target on the computer screen (see image – figure 11). Participants were asked to follow the target to the best of their abilities. The 8-shaped figure was chosen because it allows the wrist to move in a combination of directions: flexion, extension, radial and ulnar deviation. Additionally, tracing of the 8-shaped figure can be translated into ADL's, such as the curvature of the shape mimicking the turning of a doorknob. Motors locked the supination and pronation planes in the neutral position which can be defined as the mid-way point between pronation and supination. The target moved at 20 degrees per second with a lap duration of approximately 30 seconds (considering 80% of the ROM at T0). The velocity and time of the entire session and across all training sessions was maintained the same in order to ensure the

same displacement executed for all the subjects which averaged to 32 completed laps in a single training session.

The robot provided assistance in an adaptive, individually tailored way. In particular, every 3 laps there was an evaluation of the average figural error (an index of kinematic performance) and the result of this error was used to modify the assistance according to its deviation from the ideal value and from the previous performance. The figural error was measured to characterize performance as the trajectory of the subject from the ideal 8-shaped figure, regardless of the subject's speed. Figural error was measured with the equations below.

$$dist_{AB}(i) = \min_{j} \left|\left|A_i - B_j\right|\right| \quad i = 1, 2, \dots n$$

$$dist_{BA}(j) = \min_{i} \left|\left|A_i - B_j\right|\right| \quad j = 1, 2, \dots m$$

$$FE_{AB} = \frac{\sum_{i=1}^{n} dist_{AB}(i) + \sum_{j=1}^{m} dist_{BA}(j)}{n + m}$$

Figure 10. Algorithm used to compute degree of figural error.

Where "A" and "m" are the time series and total samples of the target trajectory and "B" and "n" are the time series and total samples of the handle trajectory. The first equation calculates the distance between a single data point of the target and every point of the handle. The minimum distance of all the comparisons is taken. The second equation compares every data point of the target against a single data point of the handle (reverse order to the first equation). The third equation adds the sum of all the minimum distances and divides it by the sum of the two samples (Forman et al., 2019).

Assistance was implemented as a virtual spring that pulled the handle of the robot towards the moving target. If the subject was performing the task with a high degree of error, the robot increased assistance in real time by pulling the subject's hand towards to target and opposingly, if there was very little error, the virtual spring would push the subject away from the target, effectively adding resistance or a challenge to task completion. Subjects performed 20 minutes (as many repetitions as possible within the allotted time) of the tracking task, followed by 5 minutes of rest and then an additional 20-minute dosage. Within the 20 minutes of training there was a rest of 1 minute every 4 minutes. One complete session lasted approximately 1 hour, taking into account 40 minutes of effective training (see timeline of the training session – figure 12).

At the end of each training session, subjects were asked to rate their level of satisfaction with the robot and the training on a scale of 1-10 (1 - indicating low satisfaction and 10 – highest satisfaction) as part of a visual analog scale to help determine amount of personal motivation and provide feedback to the researcher.

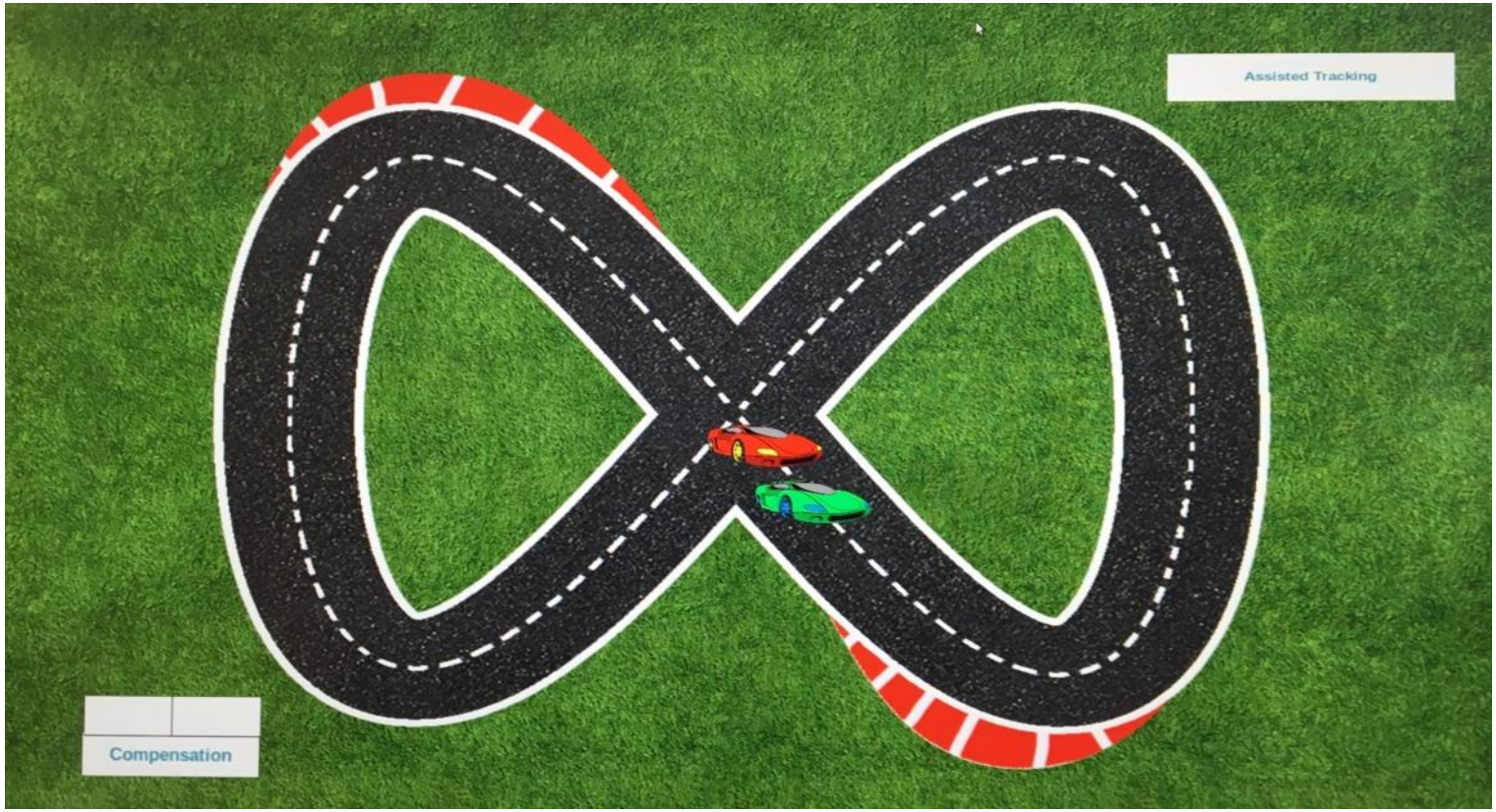


Figure 11. 8-shaped figure of the tracking task. Red image is the target, green image is the subject following the target with assistance or resistance provided by the robot.

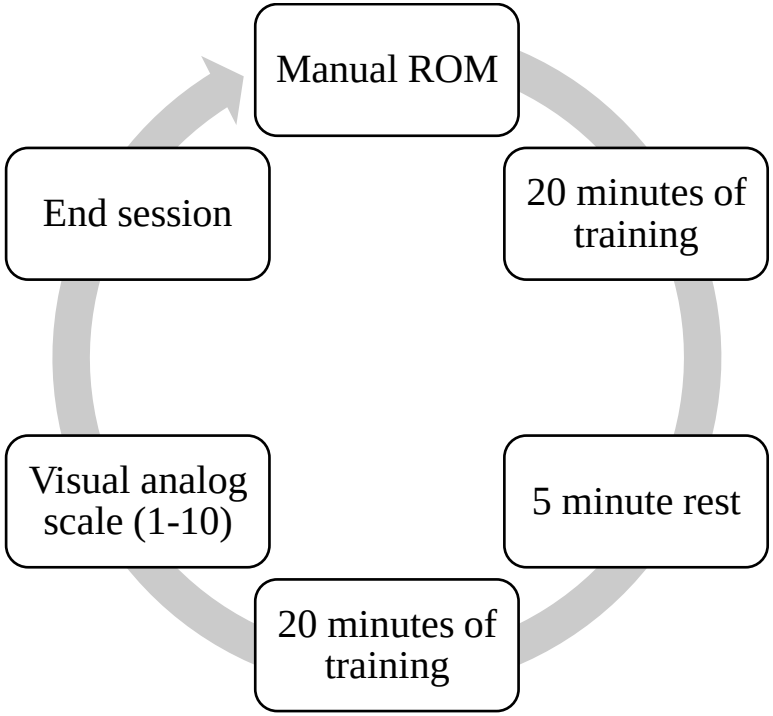


Figure 12. Timeline of training session in appropriate protocol order. Within each 20 minutes of training, there was 1 minute of rest every 4 minutes.

3.5 Data Analysis

Kinematic data of the end-effector (subject's hand position) and the target icon was sampled at 100Hz and analyzed off-line (MatLab 2019a, Mathworks Inc., Natick, MS, USA).

Figure Parameters: For each individual subject the parameters of the 8-shaped figure were 80% of the subject's maximum active ROM in all directions (lowest value recorded of the 3 trials) that were previously recorded and stored at T0 assessment and was given by the formula:

$$\text{Lissajous: } \begin{cases} x = x_0 + A * sin(a * t) \\ y = y_0 + B * sin(b * t) \end{cases}$$

Where, A = 80% ROM value among flexion, extension, radial, ulnar; B is computed based on A.

Assistance Component: During each tracking trial (a complete lap on the figure), the haptic device collected the subject's kinematic data. Every 3 laps this was calculated to adjust the amount of assistance provided during the training (see above 3.4 - Figure 10). The first level of assistance was solely based on the amount of figural error. Assistance was adjusted as a computation of the mean figural error and the assistance of the past 3 laps and was computed with the equation below:

$$\text{Assistance}_{new} = \text{assistance}_{old} + a * (\text{figError}_{last3} - \text{figError}_{old}) + b$$

Whereas, "assistance$_{new}$" is the level of assistance to be adjusted to for the next 3 laps and "assistance$_{old}$" is the level of assistance from the previous 3 laps. "figural error $_{last\ 3}$" represents the subject's figural error from the prior 3 laps with the old assistance and "figural error $_{old}$" is

the degree of error from the previous 3 laps without assistance. “a” and “b” are experimental parameters (b = 0.1).

Exerted Forces: Once the assistance value turned from positive to negative, the exerted forces moved from pulling the subject towards the target to pushing the subject away from the target (resistance). At each instant, the exerted forces depended on the distance between the target and end-effector which acted as a spring on the target. The assistance value was computed with a multiplication factor (below) to be able to change the initial rigidity of the spring (denoted by k):

$$F = \text{assistance} * k * \Delta x$$

Where, F = the exerted force, k = stiffness, modelled as a spring and Δx represents instantaneous distance between target and end-effector.

Tracking Error: Figural error was calculated as described in figure 10 above. Tracking error (distance of the hand position from the ideal target) was measured to track performance including the differences in velocity of the end-effector and the target (subject faster or slower than the target). Tracking error was defined as the mean instantaneous distance of the handle (participants target) to the actual target. The error at each data point was summed over the total tracking trial and was divided by the total number of samples. Tracking error was separated into 4 directions: left, right, up and down which is representative of flexion, extension, radial deviation and ulnar deviation. The measure is 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 = target position at an instantaneous position and H,i = hand position at the instantaneous position.

Joint Position Matching: From the joint position matching (JPM) test, overall performance, actual (active) and desired (passive) positions were compared. Matching error (ME), variability (V), 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=12) and is computed by the absolute mean distance between the proprioceptive target and the subject's matched point:

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

Where, θ_i = final position of the wrist, θ_T is the target position and N = number of trials (N=12).

Error bias (EB) was used to measure the average directional distance and deviation of error from the target angle. Undershooting the target is represented with a negative EB and overshooting is represented with a positive EB:

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

Variability Error (VE) demonstrates how similarly and consistently the subject matched the target, representing precision and is evaluated as the standard deviation across all trials:

$$V = StD(\theta_{i=1:N})$$

Active and Passive ROM: From active and passive ROM exercises the corresponding active and passive maximum excursion for each joint angle were derived and stored by the robot (degrees).

3.6 Statistical Analysis

All outcome measures (robotic and clinical) were measured at baseline (T0) and post intervention (T2). Due to our small sample size and assuming the data does not have a normal distribution, non-parametric tests were performed. A Wilcoxon Matched Pairs Test was conducted to compare all outcome measures in the trained limb at baseline and post training (T0 vs T2), as well to compare all outcome measures for the control limb T0 vs T2. Mann-Whitney U Tests were conducted to compare the differences in the outcome measures at T2 between the two independent groups (trained and control limb). Significance was set to $p<0.05$. Correlations were performed with a linear regression model to fit the data and the goodness of each fit can be evaluated by r_2 (how much variance of the dependent variable). Pearson product moment correlation was used to measure the linear correlation. “y” can be predicted knowing the independent variable and “x” is determined by the p-value for the F-test on the model. This approach tests whether the model fits significantly better than a model consisting of a constant term and was performed to evaluate relationships between robotic measures and

functional/traditional measures. Text data is presented as mean ± standard deviation and figures are presented as standard error bars.

Chapter 4 – Results

4.1. Wrist Strength

All wrist strength data can be found in table 3 for trained limbs and table 4 for control limbs. As hypothesized, for the trained limb, mean isometric wrist force significantly increased from pre (T0) to post-intervention (T2) for flexion ($p = 0.043$), radial ($p = 0.028$) and ulnar deviation ($p = 0.028$). Isometric wrist force significantly increased by 2.77kg, 3.71kg and 2.51kg for flexion, radial and ulnar deviation, respectively. There was a significant improvement in the control limb from T0 – T2 for radial deviation, increasing by 3.84kg (T0: 9.14 ± 3.69 kg, T2: 12.73 ± 2.95 kg, $p = 0.028$). Although not statistically significant the control limb showed improvements in wrist force for all other directions increasing by 2.15kg, 1.89kg and 3.04kg for flexion, extension and ulnar deviation, respectively. No significant differences were found between the trained and control limbs at T2 as both limbs showed almost equal improvements (see table 3 & 4).

There were no significant differences for maximum grip force in the trained limb from T0 – T2 (T0: 29.81 ± 10.23 kg, T2: 29.46 ± 9.58 kg, $p = 0.933$). There were also no significant differences in the control limb from T0 – T2 (T0: 31.67 ± 10.33 kg, T2: 32.49 ± 10.28 kg, $p = 0.249$), indicative that both limbs did not significantly increase grip force post-intervention. No significant differences were found between the trained and control limbs at T2 ($p = 0.798$).

There were no significant differences for the submaximal grip force endurance test for the trained limbs from T0 – T2 ($p = 0.128$). However, group averages showed a 20.61 sec or 60.12% increase from baseline after the 4-week intervention (Mean values T0: 34.28 ± 43.86

sec, T2: 54.89 ± 40.08 sec). Similar results were found in the control limb, as no significant differences were found T0 – T2, but group average increased by 25.64 sec or 78.0% (Mean values T0: 32.86 ± 11.16 sec, T2: 58.50 ± 45.79 sec, $p = 0.063$). No significant differences were found when comparing the trained limb to the control limb at T2 ($p = 0.180$), both limbs showed almost equal improvements in time to fatigue (seconds) (refer to tables 3 & 4).

Table 3: Wrist strength results showing baseline (T0) and post intervention (T2) scores for the trained limb of each subject.

Subject-ID		***S01***	***S02***	***S03***	***S04***	***S05***	***S07***	***S12***	***Mean (SD)***	***p-value***
Grip Force (kg)	Baseline	27.50	20.20	39.10	32.90	19.50	48.10	20.30	29.81(10.23)	0.933
	Post	26.10	21.50	41.20	26.70	19.80	46.80	24.10	29.46(9.58)	
Endurance Hold (s)	Baseline	26.28	16.25	133.00	21.83	14.43	18.35	9.63	34.28(43.86)	0.398
	Post	86.00	27.36	94.00	18.53	28.13	26.65	12.06	54.89(40.08)	
Isometric Wrist Force (kg)										
Flexion	Baseline	6.33	6.86	16.50	9.89	6.78	14.3	7.56	9.75(3.78)	0.043*
	Post	12.35	8.84	14.79	13.61	10.62	14.79	12.67	12.52(2.02)	
Extension	Baseline	5.87	5.64	19.30	9.42	6.59	17.6	6.01	10.05(5.46)	0.499
	Post	7.79	9.08	14.79	11.80	8.39	14.88	11.19	11.13(2.69)	
Radial Deviation	Baseline	5.23	5.92	12.20	8.03	5.74	15.10	7.35	8.51(3.46)	0.028*
	Post	10.69	8.17	15.33	13.88	10.54	15.06	11.84	12.22(2.46)	
Ulnar Deviation	Baseline	4.78	4.20	9.40	5.89	2.72	12.16	3.51	5.76(2.59)	0.028*
	Post	4.43	5.23	14.88	7.44	7.07	13.00	6.71	8.27(3.53)	

Note: * denotes significant difference, $p<0.05$.

Table 4: Wrist strength results showing baseline (T0) and post intervention (T2) scores for the control limb of each subject.

Subject-ID		***S01***	***S02***	***S03***	***S04***	***S05***	***S07***	***S12***	***Mean (SD)***	***p-value***
Grip Force (kg)	Baseline	33.9	19.3	54.4	33.1	28.1	25.1	27.8	31.7(10.33)	0.499
	Post	25.1	21.1	48.3	32.3	25.6	47.7	27.3	32.5(10.28)	
Endurance Hold (s)	Baseline	16.98	9.25	73.00	59.42	29.26	24.26	17.86	32.86(11.16)	0.063
	Post	45.44	22.53	111.00	52.50	133.00	32.62	13.41	58.5(45.79)	
Isometric Wrist Force (kg)										
Flexion	Baseline	6.67	8.05	17.10	9.37	6.54	13.73	8.33	9.96(3.67)	0.128
	Post	10.69	9.56	13.24	13.12	10.20	15.62	12.33	12.12(1.95)	
Extension	Baseline	5.22	7.86	16.82	9.72	8.63	14.54	7.23	9.99(3.84)	0.128
	Post	9.66	9.51	13.24	13.43	10.02	16.66	10.71	11.88(2.45)	
Radial Deviation	Baseline	5.71	7.32	16.22	8.91	5.78	12.92	7.13	9.14(3.67)	0.028*
	Post	11.69	8.69	15.06	15.47	11.18	17.06	11.73	12.98(2.73)	
Ulnar Deviation	Baseline	2.45	3.65	5.88	7.33	3.24	13.23	2.42	5.41(3.52)	0.063
	Post	3.76	3.59	15.64	8.98	8.28	11.97	6.97	8.45(3.99)	

Note: * denotes significant difference, $p<0.05$.

4.2 Range of Motion

All wrist joint ROM data can be found in table 5. There were no significant improvements between mean active ROM from T0 – T2 across all directions in the trained limb (flexion: $p = 0.611$, extension: $p = 0.735$, radial: $p = 0.091$, ulnar: $p = 0.735$). No significant improvements were found between mean active ROM from T0 – T2 in the control limb (flexion: $p = 0.866$, extension: $p = 0.600$, radial: 0.310, ulnar: 0.735). No significant differences were found between the trained and control limbs at T2 for all directions (flexion: $p = 1.000$, extension: $p = 1.000$, radial: $p = 0.074$, ulnar: $p = 1.000$).

There were no significant improvements for passive ROM for the trained limb at T0 compared to T2 in all directions (flexion: $p = 0.715$, extension: $p = 0.735$, radial: $p = 0.463$, ulnar: $p = 0.345$). No significant improvements were found between T0 – T2 for the control limb (flexion: $p = 0.500$, extension: $p = 1.000$, radial: $p = 0.273$, ulnar: $p = 0.180$). No significant differences were found when comparing the trained limb vs control limb (flexion: $p = 0.896$, extension: $p = 0.898$, radial: $p = 0.272$, ulnar: $p = 0.682$).

Table 5: Wrist joint range of motion (degrees) in each plane for comparison of trained limb vs. control.

Direction	Active ROM			Passive ROM		
	Trained mean (SD)	**Control mean (SD)**	**p-value**	**Trained mean (SD)**	**Control mean (SD)**	**p-value**
Flexion	54.39(3.42)	53.76(2.47)	1.000	53.91(2.34)	54.47(0.62)	0.896
Extension	50.16(8.36)	53.36(4.92)	1.000	52.54(29.57)	52.51(3.62)	0.898
Radial Deviation	32.69(3.87)	32.88(4.54)	0.074	33.81(1.14)	33.05(2.44)	0.272
Ulnar Deviation	30.48(1.7)	31.26(2.44)	1.000	29.57(0.83)	29.72(0.75)	0.682

Note: Significance was set to $p < 0.05$.

4.3 Joint Position Matching (JPM)

Matching Error (ME)

There were no significant differences in ME between the trained and control limb at T2 for either direction (flexion: $p = 0.307$, extension: $p = 0.898$) (Figure 13 & 14). No significant differences were found in flexion for the trained limb from T0 – T2 (Mean T0: 7.62 ± 2.74°, T2: 7.54 ± 4.67°, $p = 0.866$). No significant differences were found in extension from T0 – T2 for the trained limb (Mean T0: 6.22 ± 3.24°, T2: 6.15 ± 2.61°, $p = 0.866$). However, when compared individually, subject 7 had significantly less ME from T0 – T2 in the extension direction ($p = 0.028$). No significant differences were found for the control limb at T0 – T2 for either direction (flexion T0: 5.61 ± 1.83°, T2: 8.44 ± 4.75°, $p = 0.176$) (extension T0: 7.36 ± 5.64°, T2: 5.69 ± 2.09°, $p = 1.000$).

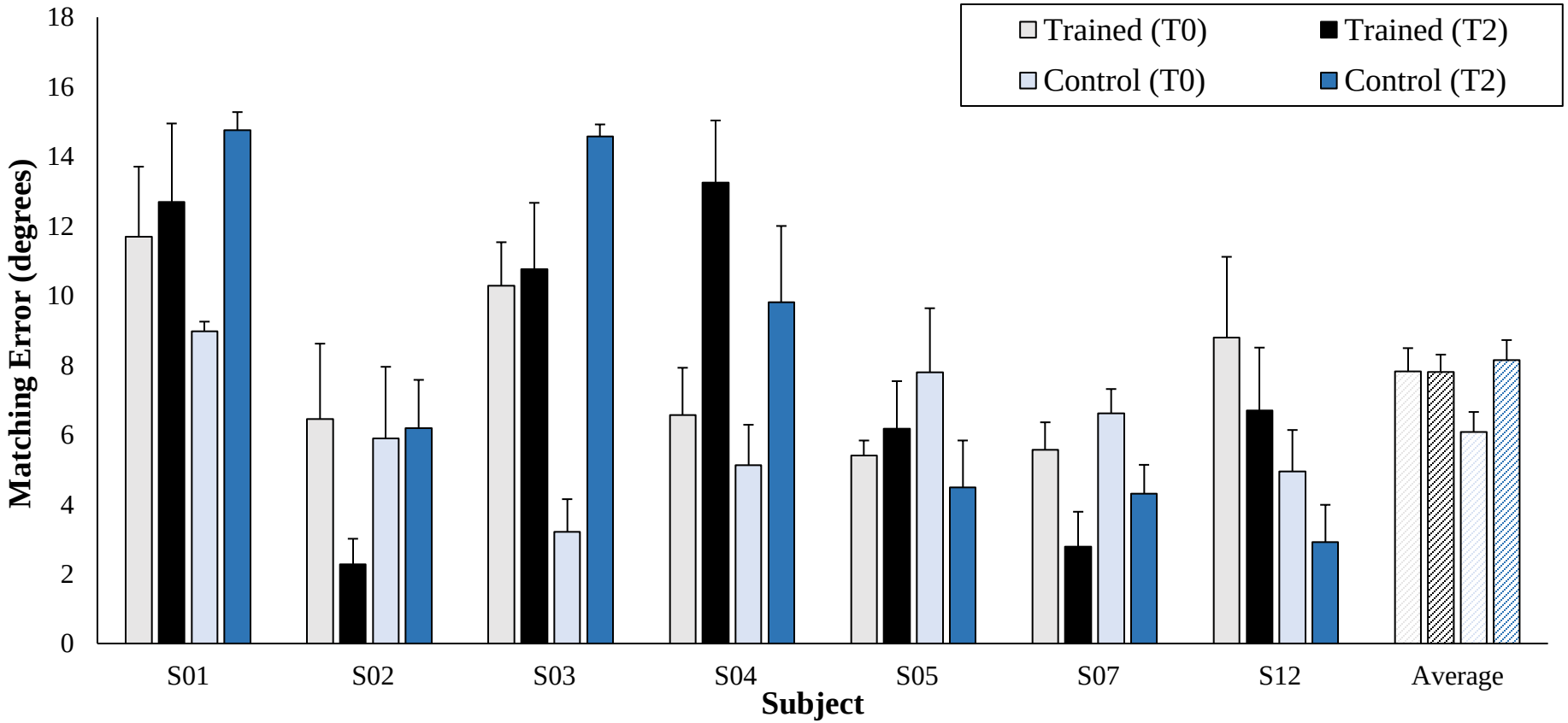


Figure 13. Average ME (degrees) in flexion. Comparing trained limb (grey) to the control limbs (blue). Note: standard bars are presented as standard error bars.

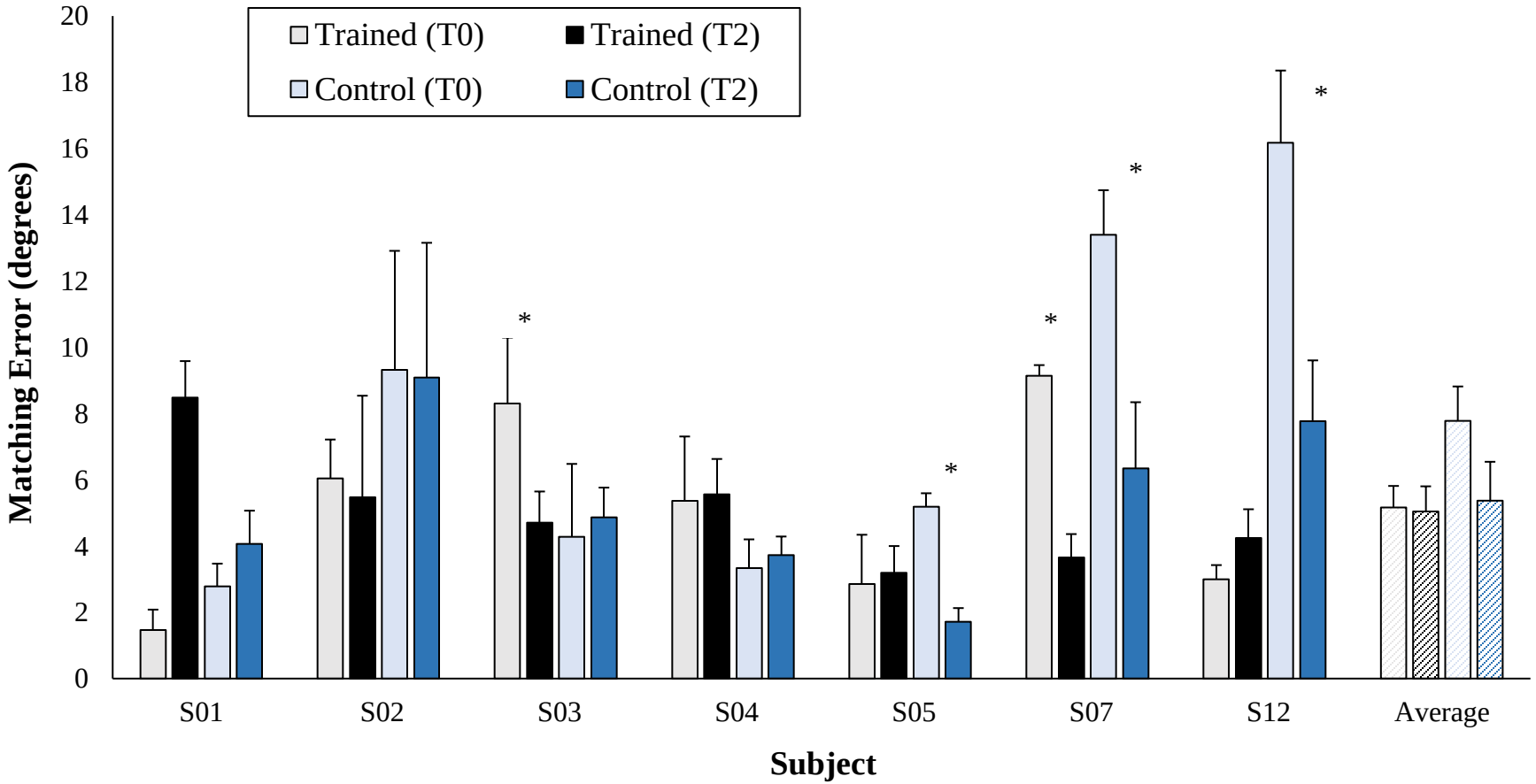


Figure 14. Average ME (degrees) in extension. *denotes significance, $p<0.05$. Note: standard bars are presented as standard error bars.

Error Bias (EB)

No significant differences were found between trained and control limbs in either direction (flexion: $p = 0.307$, extension: $p = 0.701$). There were no significant differences found in the trained limb from T0 – T2 (Mean flexion T0: 3.38 ± 5.86°, T2: 5.59 ± 5.77°, $p = 0.398$), (Mean extension T0: -3.40 ± 5.52°, 0.27 ± 5.77°, $p = 0.237$). However, subject 7 showed significant decreases in EB at T0 vs T2 (flexion: $p = 0.028$, extension: $p = 0.028$). No significant differences were found in the control limb from T0 – T2 for either direction (flexion T0: 0.285 ± 4.92°, T2: 8.44 ± 4.75°, $p = 0.063$) (extension T0: 7.38 ± 5.64°, 5.69 ± 2.09°, $p = 0.735$).

Variability Error (VE)

No significant differences were found between trained and control limbs at T2 for either direction (flexion: $p = 1.000$, extension: $p = 0.609$). Additionally, no significant differences were found in mean error for the trained limb T0 – T2 for both directions (flexion T0: 5.83 ± 3.13°, T2: 5.09 ± 2.49°, $p = 0.735$), (extension T0: 4.54 ± 2.55°, T2: 4.96 ± 2.19°, $p = 0.735$). No significant differences were found in the control limb from T0 – T2 for either direction (flexion T0: 4.48 ± 2.68°, T2: 3.53 ± 1.94°, $p = 0.499$), (extension T0: 6.00 ± 4.02°, T2: 5.54 ± 3.21°, $p = 0.398$).

4.4 Wrist Kinematics

4.4.1 Tracking Error

Subjects tracked a target icon around the 8-shaped figure with no assistance ($N = 6$). As hypothesized, tracking error in the trained limb improved significantly for each individual subject from T0 to T2. There was a significant group reduction in tracking error, with an average

of 0.97 ± 1.09º less error at T2 (mean T0: 3.77 ± 2.12 º, T2: 2.79 ± 1.99 º, p = 0.028). No significant improvements were found in the control limb from T0 – T2 (mean T0: 2.91 ± 2.12º, T2: 3.45 ± 2.51º, p = 0.866). No significant differences were found when comparing group averages of the trained vs control limb (p = 0.250), indicative that the trained limb improved closer to values of the control limb (Figure 15).

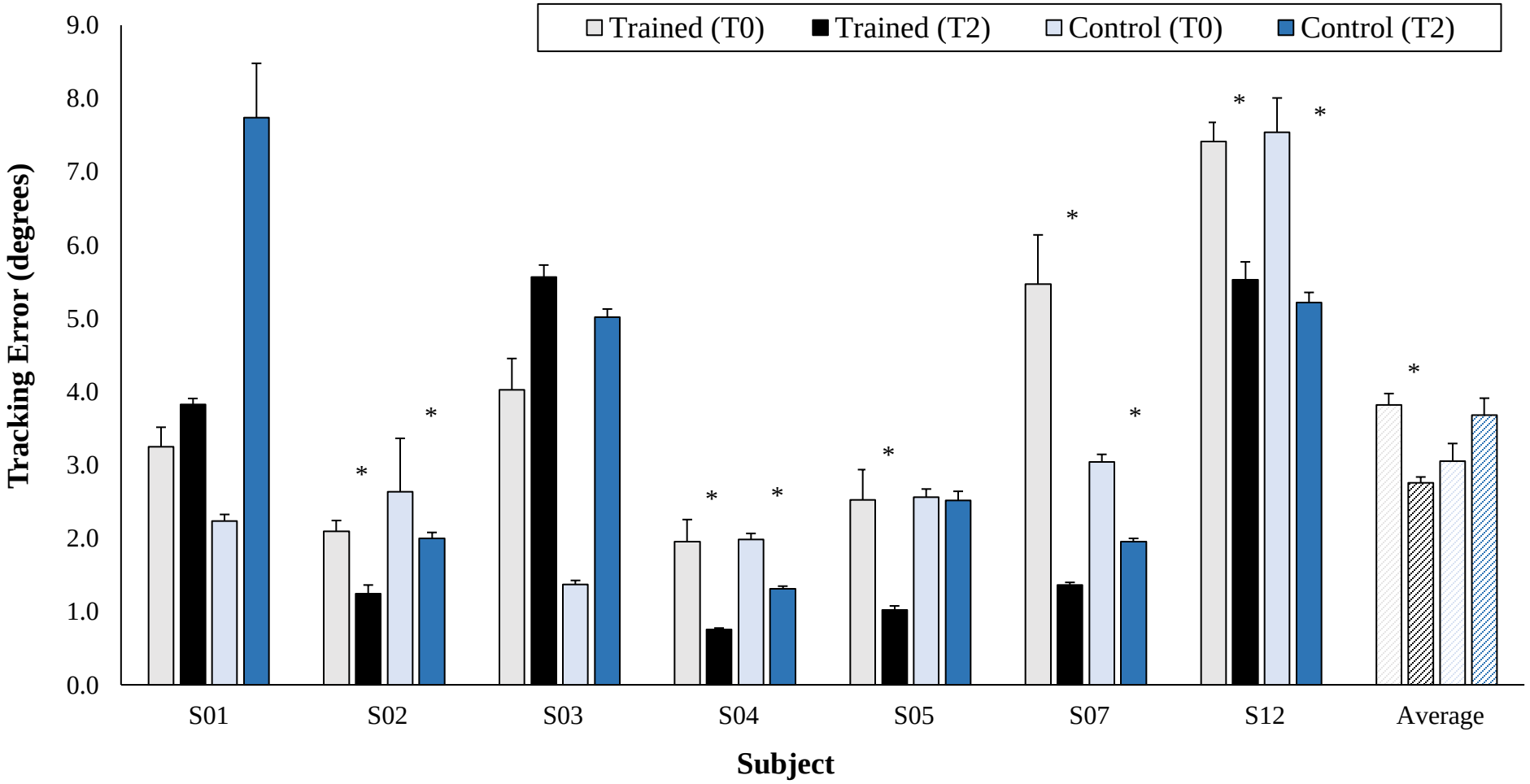


Figure 15. Mean tracking error (degrees) comparing the trained and control limbs at T0 and T2. The x axis represents each subject and the y axis is the error. Subjects significantly decreased the amount of tracking error from T0 to T2 ($p = 0.028$). * denotes significant differences, $p<0.05$.
Note: standard bars are presented as standard error bars.

There was a significant correlation between tracking error and maximum isometric wrist force from T0 – T2. When wrist force increased (kg), there was a decrease in tracking error (°) for the trained limb. This correlation occurred in flexion/extension and radial deviation (see table 6 and figure 16a-d) where r^2 represents how much variation of the dependent variable (wrist force) is explained by the independent variable (tracking error).

Table 6: Linear regression correlation between isometric wrist force and tracking error of the trained limb at T2 (mean values).

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

*denotes significance, $p<0.05$.

Figure 16. a. Correlation between maximum wrist force in flexion (kg) and tracking errors (º).

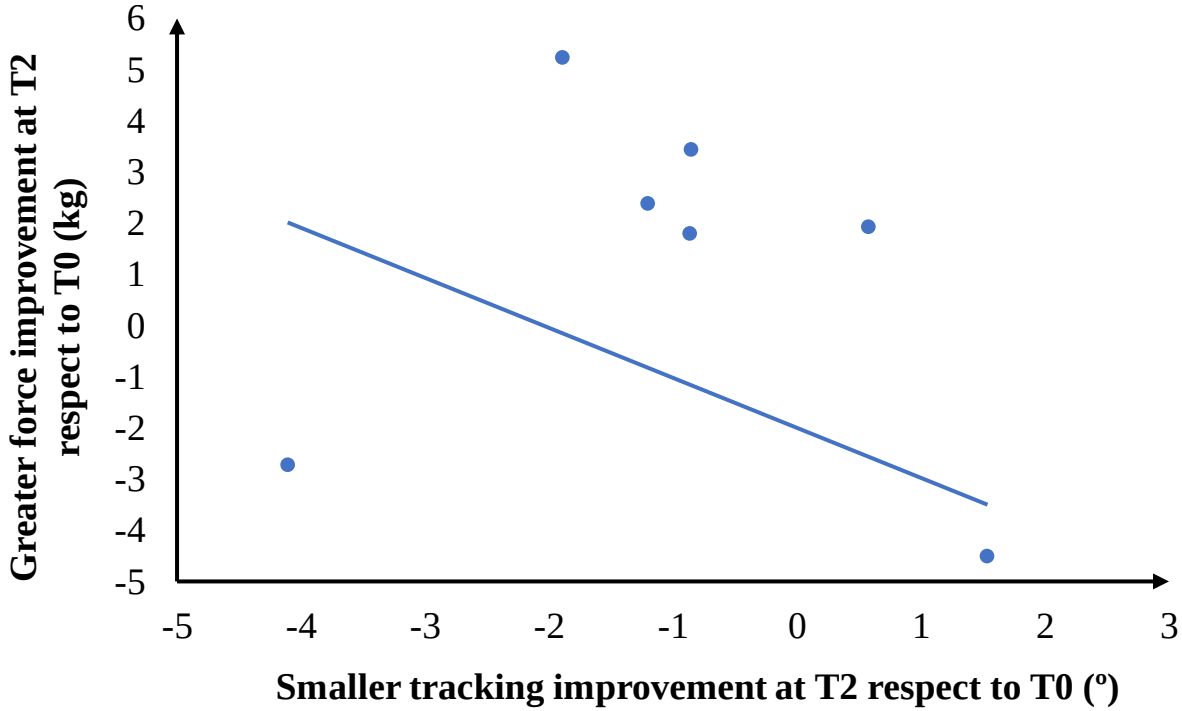


Figure 16. b. Correlation between maximum wrist force in extension (kg) and tracking errors (º).

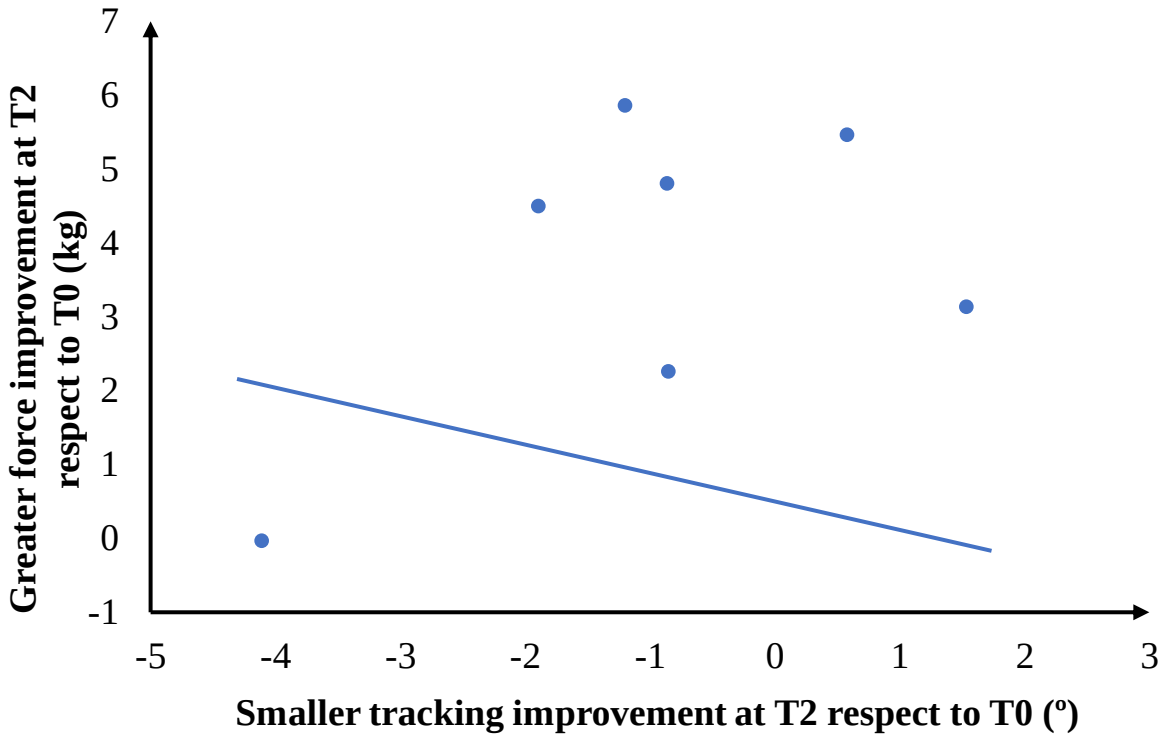


Figure 16. c. Correlation between maximum wrist force in radial deviation (kg) and tracking errors (º).

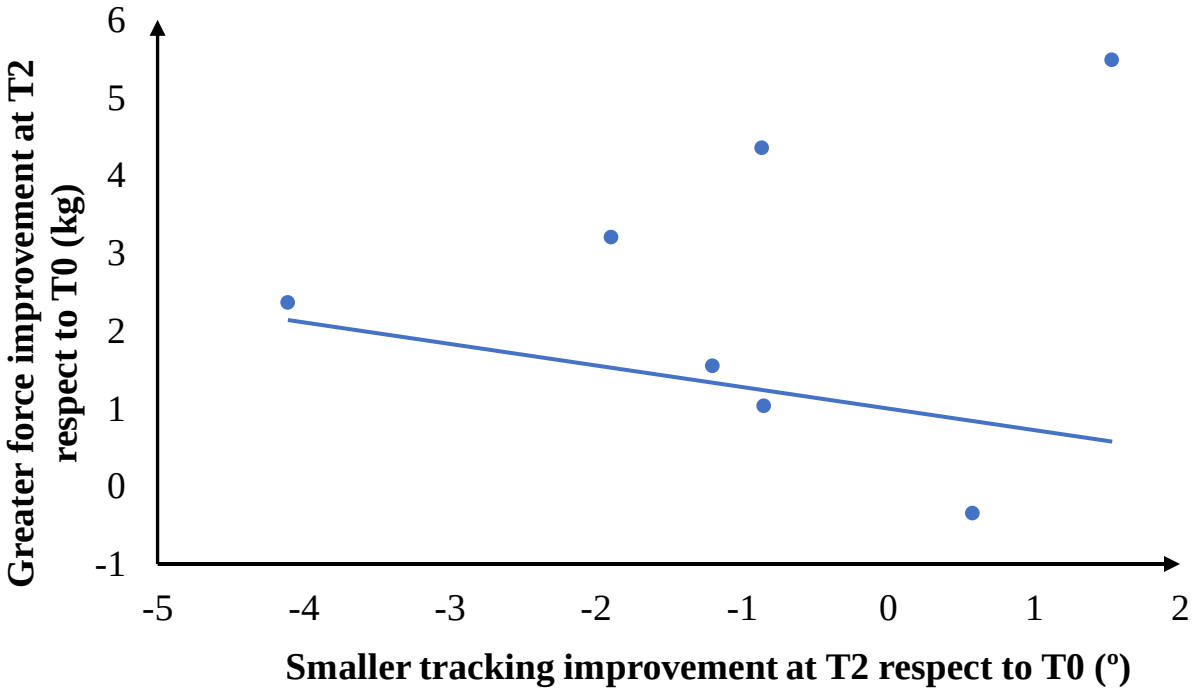


Figure 16. d. Correlation between maximum wrist force in ulnar deviation (kg) and tracking errors (º).

There was no significant correlation between tracking error and EDSS score ($p = 0.09$, $r^2 = 0.47$). Subjects with a higher EDSS score (greater severity of disease) did not have a higher degree of tracking error (worse performance) than subjects with a lower EDSS score for the trained limbs at T2 (Figure 17).

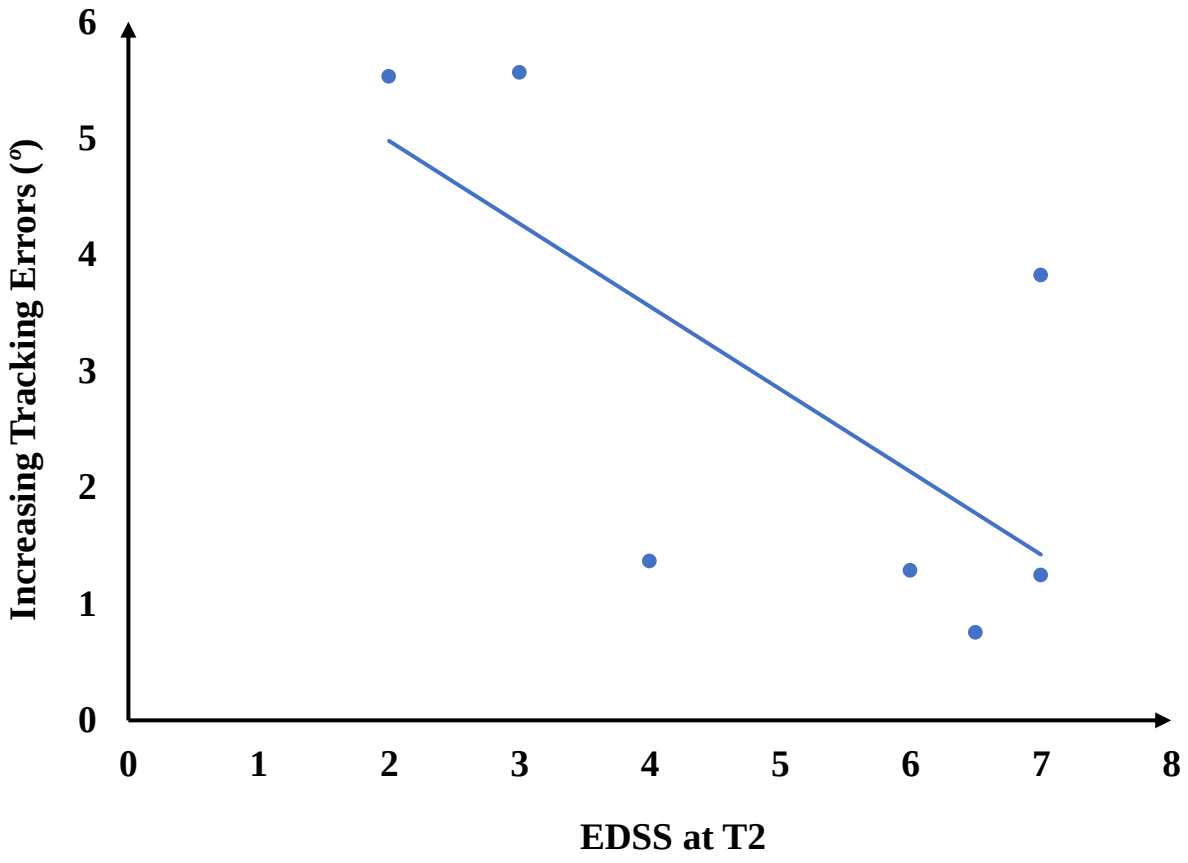


Figure 17. Correlation between EDSS score and tracking errors for trained limb at T2.

4.4.2 Figural Error

Figural error was calculated from each of the unassisted laps (N = 6) performed of the tracking task. As hypothesized, all subjects significantly improved (less figural error) from T0 to T2 (mean T0: 1.06 ± 0.07º, T2: 0.57 ± 0.03º, All $p<0.028$) with the exception of subject 1 ($p = 0.176$). There were significant differences were found in the control limb from T0 – T2 (mean T0: 0.83 ± 0.18º, T2: 0.66 ± 0.22º, $p = 0.018$). Although both limbs significantly improved, there were significant differences found between trained and control limbs ($p = 0.002$), as trained limbs had less figural error (Figure 18). Figure 19 demonstrates an individual participants data and tracking accuracy from T0 to T2 (Figure 19).

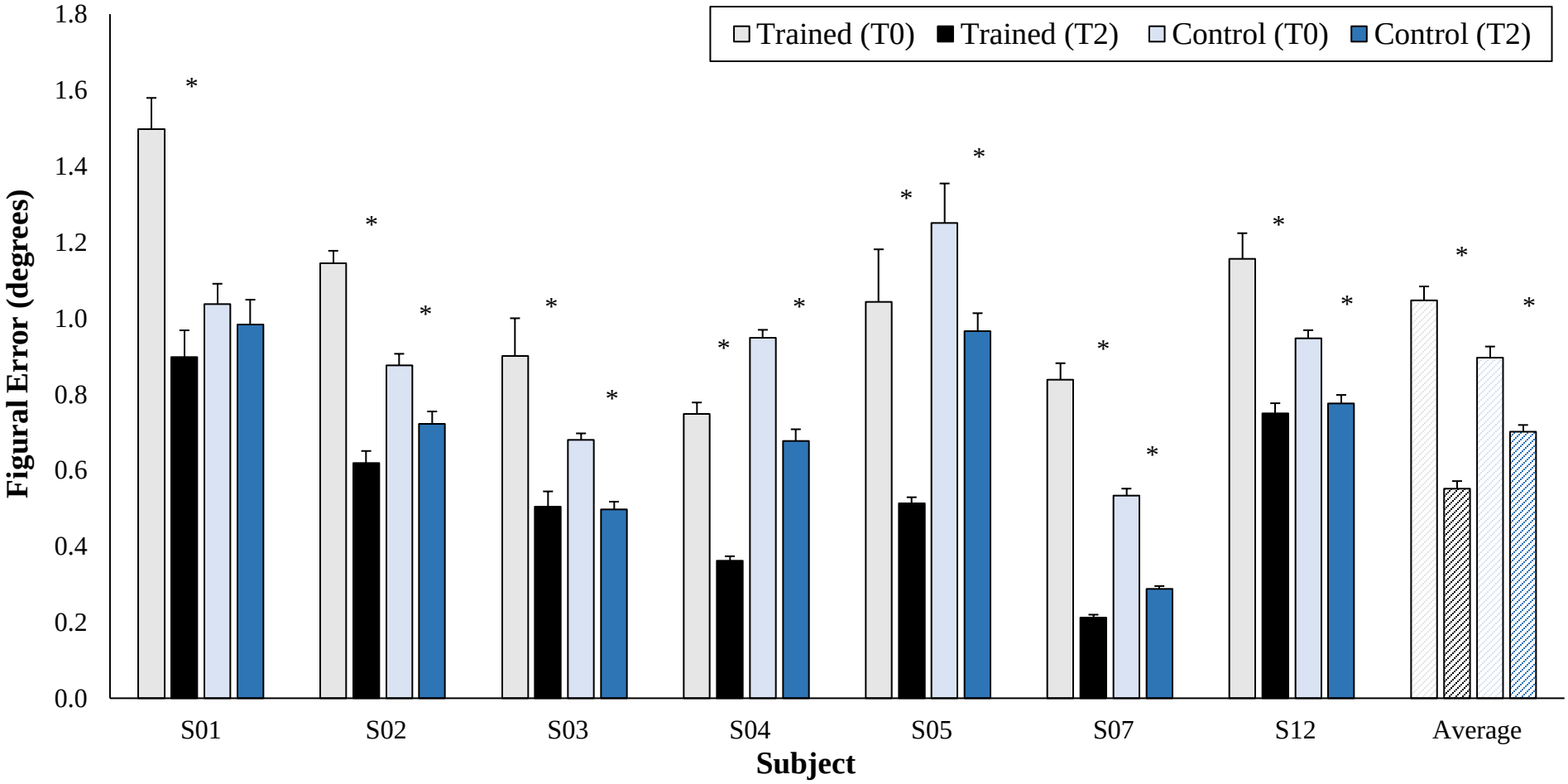


Figure 18. Mean figural error is displayed for trained and control limbs at T0 and T2 for each individual subject. The x axis represents the subject number and the y axis is the error. * denotes significant difference, $p<0.05$. Note: standard bars are presented as standard error bars.

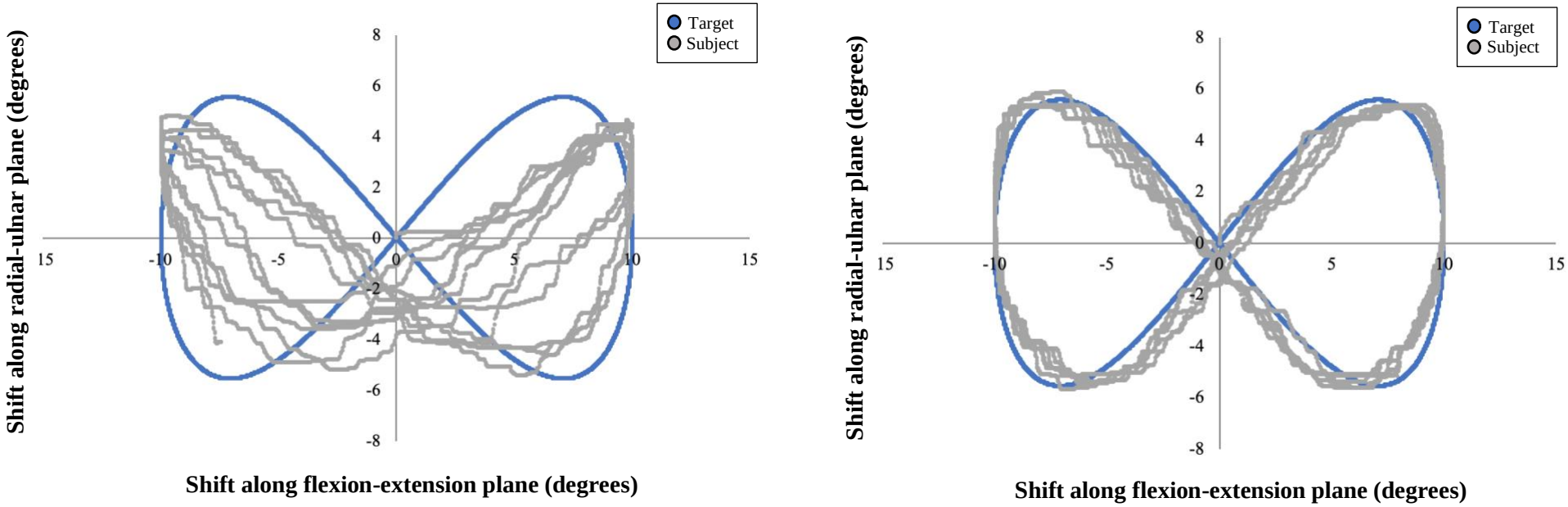


Figure 19. Figural error displayed for S07 at T0 (left) compared to T2 (right) for the trained limb. Significant reduction in figural error from pre – post intervention ($p = 0.028$). Blue line represents the template "perfect" trace of the curve and the grey line represents the subject's trace attempt for each of the 6 laps.

4.5 Clinical Outcome Measures

4.5.1 9-Hole Peg Test

The 9-HPT was performed twice on each limb and the fastest time to competition (in seconds) was reported. No significant differences were found between trained vs control limbs ($p = 0.836$). No significant improvements were found for the trained limb at T0 – T2 (T0: 30.48 ± 5.34 sec, T2: 27.64 ± 4.18 sec, $p = 0.116$). Subject 1, was physically unable to complete the test with the most affected hand (trained limb) at baseline (T0) due to a disabling intention tremor and was eliminated from the mean values (refer to figure 20). No significant differences were found in the control limb from T0 – T2 (T0: 28.99 ± 2.79 sec, T2: 25.47 ± 2.66 sec, $p = 0.249$).

4.5.2 Patient Rated Wrist Evaluation

Subjects responded to 15 questions that pertained to pain in the affected limb, ADL's in the affected limb and ADL's that require the use of both limbs. No significant differences ($p = 0.836$) were found between the responses of any of the 3 categories for T0 and T2 (refer to figure 21).

4.5.3 Modified Ashworth Scale

The MAS was recorded but removed from statistical and further analysis due to the subjectivity of the assessment to avoid any researcher bias.

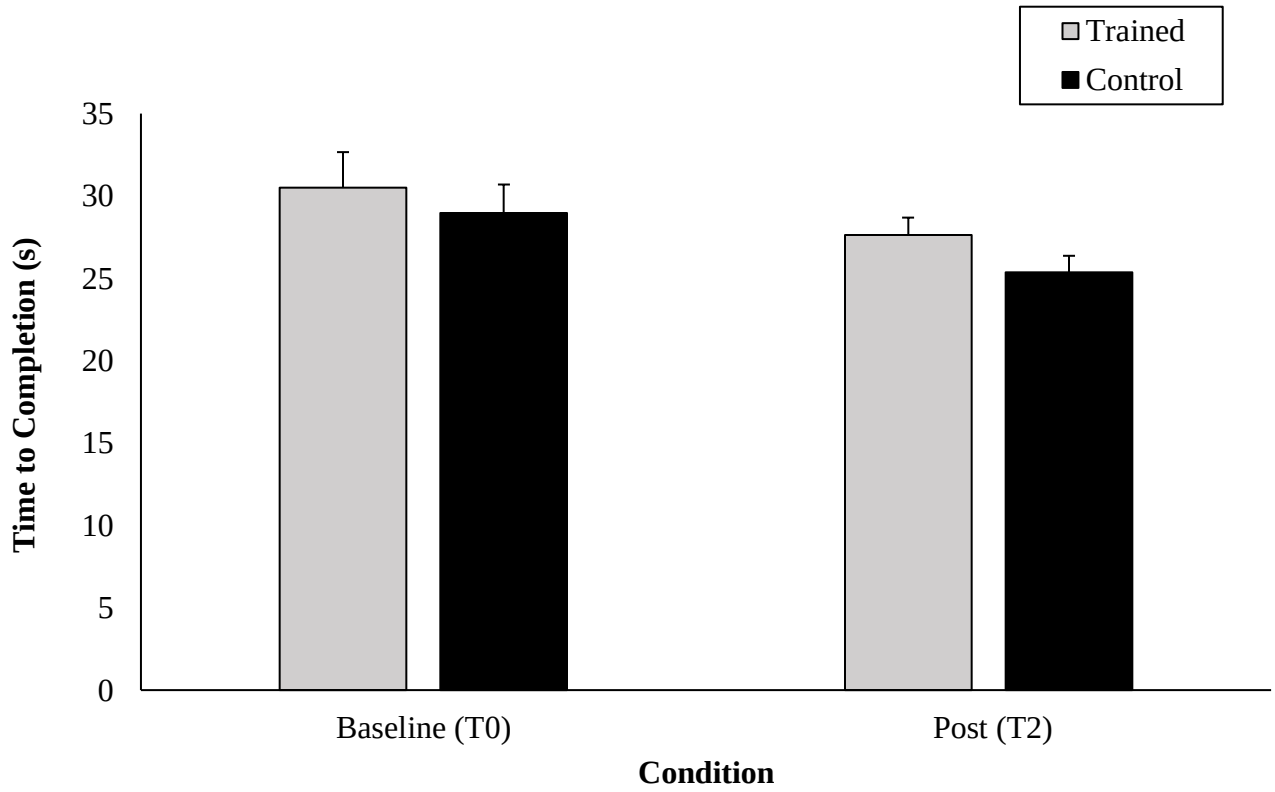


Figure 20. 9-HPT. Represents time to completion (seconds) of the 9-HPT from the trained limb (grey) compared to the control limb (black) at baseline and post-intervention (n = 6). No significant differences were found. Note: standard bars are presented as standard error bars.

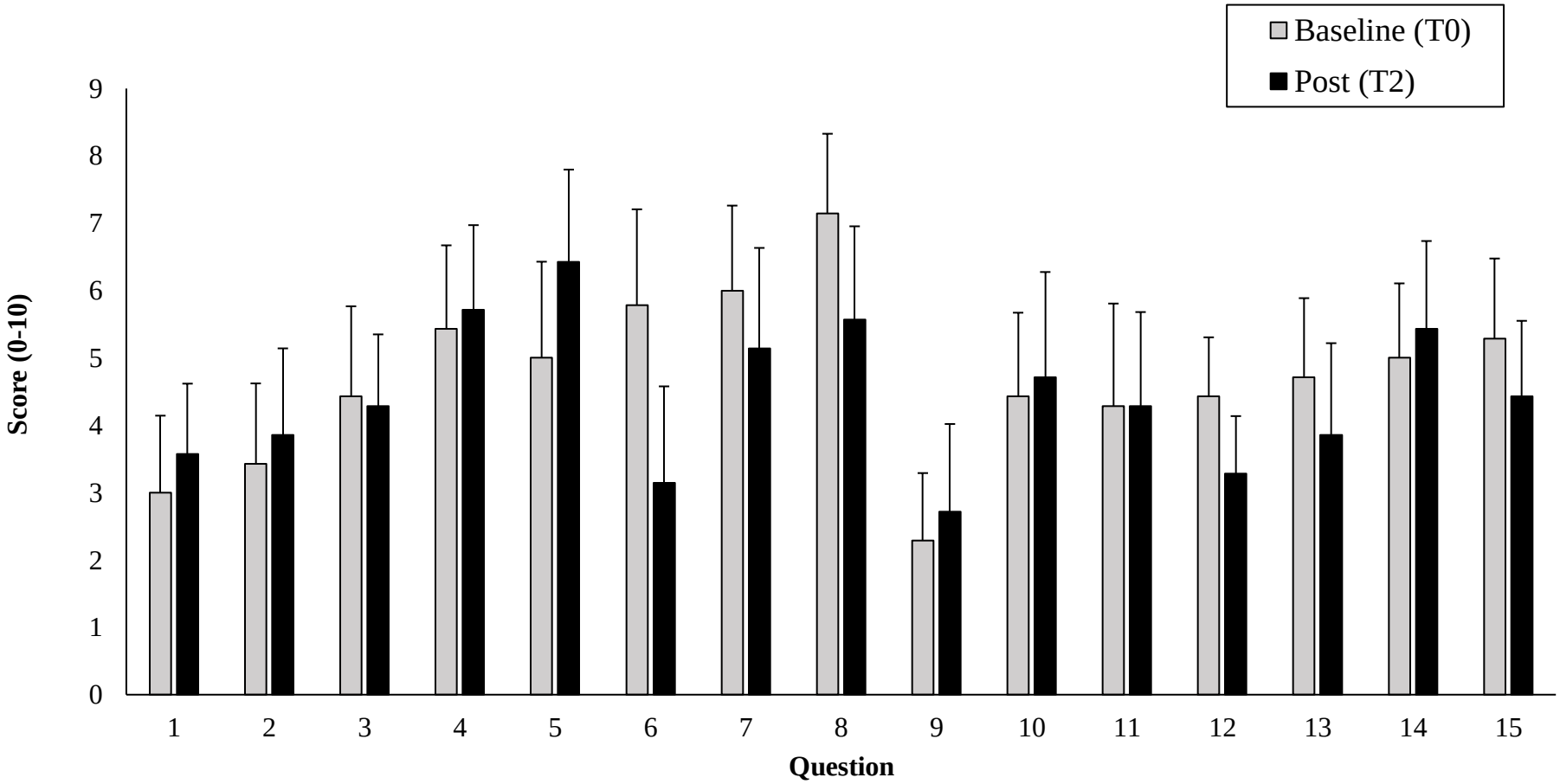


Figure 21. PRWE. Mean PWRE results compared from T0 to T2. No significant changes to the answers in the questionnaire were found pre to post intervention (p = 0.836). Note: standard bars are presented as standard error bars.

Chapter 5 – Discussion

In this work we showed that a robotic rehabilitation program for the hand and wrist demonstrated improvements in tracking accuracy, wrist strength and grip endurance for PwMS. This work implemented a 4 week (3 visits/week) adaptive training program that used figural error as a means of quantifying tracking accuracy. This error was used to implement an algorithm which adapted in real time to the individualized user's performance. Figural error was selected as our objective function for the designed algorithm for several reasons: 1) it is a measure of how well a subject matches a desired trajectory and recreates the target path/shape; (Conditt et al., 1997) and 2) the measure is insensitive to speed, so it removes individual bias about being ahead of or behind the target. Therefore, we developed a training program that focused on tracking error and we found that tracking and figural errors were significantly reduced from baseline to post intervention across all subjects. Despite a small sample size, this work suggests that, a 4-week adaptive robotic training program of the hand and wrist, improved hand control. This work also demonstrated that, in addition to control improvements, the high dosage training also elicited muscular strength gains with significantly greater maximum isometric wrist forces generated post-intervention and improved grip endurance (measured via a grip force hold test). This work provides evidence that robotic rehabilitation has statistical and clinical significance for neuromuscular adaptations of the upper limb for PwMS. This adaptive and individually tailored approach has proved beneficial for each participant in the intervention which included various types of MS, severity of disease and years since diagnosis. These improvements can potentially improve functionality in activities of daily living and thus, increasing quality of life.

Hypothesis 1 was supported by this work as significant decreases in tracking and figural error occurred from pre to post intervention for group means of the trained limb. Our adaptive and repetitive protocol was designed to promote, not just learning, but improvements in hand control of the tracking task. The significant decreases in error are an indication of this, with improved hand control by accuracy and control of the trajectory without assistance. Figural error reduced by 46% (mean T0: 1.06 ± 0.07º, T2: 0.57 ± 0.03º, All $p < 0.046$). Tracking error, including the analysis of speed of the trajectory from the target also reduced from pre – post intervention, with a 26% decrease (mean T0: 3.77 ± 2.12º, T2: 2.79 ± 1.99º, $p = 0.028$). There were no significant differences in tracking error between the trained and control limb. Indicative that the trained limb (most affected) improved closer to values of the control (less affected) limb post intervention. Significant reductions in both figural and tracking error demonstrate improvements in task performance, significant reduction in error between the target and the end-effector, and an increase in motor control of the distal upper limb to correctly perform the task without the assistance of the robot. These results are similar to existing work on robotic rehabilitation of the upper limb for stroke and MS populations. Hu et al., 2009, reported a significant decrease in error between the target and the actual wrist angle during a tracking activity within the first 7 training sessions. Additionally, studies report improvements or demonstrated a reduction in errors from pre – post intervention of reaching and tracing tasks (Carpinella et al., 2009; Colombo et al., 2005; Nordin et al., 2014; Vergaro et al., 2010). The accuracy of movements is generally reported significantly smoother or the curvature and measure of end-point trajectory is significantly decreased post-intervention, as also demonstrated in our results. It should be noted that our previous work with healthy populations tracing a similar shape using Wristbot, suggests that learning of this task plateaus after 12 traces (Forman

et al. 2020). Given that participants in this work performed greater than 12 traces in every session (3x/week), it is reasonable to suggest that this was not just a learning effect, but a result of improvements in neuromechanical control of the hand. However, further work is needed to explore retention of the task/learning skill in this population. Therefore, these findings suggest that the repetitive and high-dose tracking task improved overall performance of the skill and the combination of wrist movements necessary to complete the 8-shaped figure tracking task can be a fundamental component in many ADL's.

Interestingly, significant differences were found pre – post intervention for both the trained limb and control limb for figural error, maximum isometric wrist strength and submaximal grip force endurance. These results indicate that both limbs, although only the most affected limb underwent the physical training protocol, showed improvements. This was likely the result of a neurophysiological concept known as cross-education, when one limb is trained, and the control or untrained limb also shows improvements in strength measures following unilateral resistance training (Carroll et al., 2006). This finding is certainly interesting and was not one of our original hypotheses. Considering that our adaptive program focused on reducing tracking error, rather than muscular strength increases, we failed to consider a cross-education effect. Cross-education was first documented in the literature in 1984 (Scripture EW, Smith TL, Brown EM, 1984) and has been highly researched for healthy populations for over 100 years. Current literature reports an approximate 7.6% increase in strength on the untrained limb after unilateral maximal resistance training. The effects of cross-education are amplified in patient populations as compared to healthy adults and have shown a 17% gain in the untrained limb and 30% gain in the trained limb (Green & Gabriel, 2018). After a 5 week maximal wrist extension intervention, Sun et al, 2018, found an increase of 42% for strength gains in the trained arm and

a 35% increase in the control arm for 20 stroke patients (Sun et al., 2018). Although literature is lacking the investigation of cross-education in an MS population, it is known that MS affects the CNS, causing damage to structure and function. The CNS relays information via afferent and efferent pathways and rehabilitation of one limb helps with overall CNS conduction (Olek, 2005). Because neuroplasticity underpins recovery of motor function (Vergaro et al., 2010), positive changes in neuroplasticity helps countermeasure the decline in CNS conductivity by relaying this information to both upper limbs respectively. Carroll et al, 2016, propose two additional hypotheses as to how cross-education occurs. The first being that unilateral training can cause a "spill over" of neural drive to the untrained side to induce changes in the control system. The second being that unilateral strength training allows these changes to the control system to be accessed by the opposite limb (Carroll et al., 2006). Further research is necessary to fully understand the neurophysiology behind cross-education for this subject population. Regardless, the high repetitions of the training task, support the theory by (Bogue, 2018) suggesting that if an individual is suffering from CNS damage, repetitive and resistance exercises with the affected limb causes the brain to develop new neural pathways controlling motor functions. The development of new neural pathways leads to functional restoration in overall motor functions (i.e. both limbs) and is the backbone to robotic rehabilitation.

There was a significant increase in isometric wrist joint strength in both the trained and control limbs. The 8-shaped figure required the wrist to move along 4 planes: flexion/extension and radial/ulnar deviation to complete a lap. As the protocol was adaptive, once assistive values transitioned from positive to negative, the exerted forces moved from pulling the subject towards the target to resistive by pushing the subject away (all subjects received added resistance by the end of the 4-weeks). These progressions could have acted as a strength training model towards

the end of the training, requiring the muscles of the forearm to increase in activation to complete the lap. Over the 4-week duration of the training, there was an increase in isometric wrist strength in each of the 4 planes, with an average increase in the trained limb of 28% flexion, 11% extension, 44% for radial and ulnar deviation. For the control limb, only radial deviation showed statistically significant improvements, however the other directions show a likely clinically significant improvement by an average increase of 22% flexion, 19% extension, 42% radial and 56% ulnar deviation. While our protocol was not necessarily meant to be a strength training procedure, it is evident that as training progressed and the tracking was made more challenging, this likely increased muscular effort and forearm muscle activation. These results are expected as resistance training for PwMS have been shown to increase fMRI activation and changes in white matter architecture (that form the brain communication network) (Bonzano et al., 2014). Furthermore, Bonzano et al., (2014), found that 2-months of upper limb rehabilitation positively influenced motor behaviour. The control group's MRI results (no rehabilitation) showed white matter damage progression whereas the trained group showed no significant white matter changes indicating preservation of the white matter fiber bundles. The improvements in muscular strength seen here in our work combine both of these theories. Although no MRI's were conducted, it can be assumed based off of previous literature that the resistance-like training increased muscular strength, whereas the motor training induced preservation of white matter bundles, improving overall CNS conductivity and improvements in both upper limbs. Increases in muscular strength are typically observed after near maximum training and the resistance provided in the tracking task was a very low percentage of the participant's maximum wrist force. However, low loads at a high dosage can still elicit strength gains. This has been validated in work by Schoenfeld, 2013 & 2017, that low loads can promote increases in muscle growth

especially for untrained subjects (Schoenfeld et al., 2017). Burd et al., 2010, found that low load (as low as 30% maximum) and high-volume exercise programs were more effective at increasing muscle protein synthesis than high loads and low volume. Thus, these gains may be both functionally and metabolically meaningful. In the low load strength and hypertrophy literature, one common theme required for strength gains is exercise to fatigue/failure. It is likely that our low intensity resistance still leads to muscular fatigue in our population and could help support the strength gains observed. It has been shown that resistance training in PwMS is often attributed to neural adaptations rather than an increase in muscle mass (Carlos et al., 2014). Muscular strength is a novel outcome measure for robotic training studies of the upper limb. In 2 systematic reviews of 41 studies and 20 studies of robotic rehabilitation of the upper limb for stroke patients, none of the literature included a grip force, or muscular strength assessment (Eraifej et al., 2017; Nordin et al., 2014). This also agrees with literature on robotic rehabilitation for PwMS as a systematic review of 51 articles confirmed the lack of muscular endurance, motor strength and active ROM were rarely evaluated despite their importance on the ability to perform ADL's (Lamers et al., 2016). Future studies should focus on this area of research, particularly with the use of quantitative assessment tools such as electromyography (EMG).

There were no significant differences for the submaximal grip force endurance test for the trained limbs from T0 to T2 ($p = 0.128$). However, group averages showed a 60% increase from baseline to post intervention in the trained limb (Mean values T0: 34.28 ± 43.86 sec, T2: 54.89 ± 40.08 sec). An increase in time to fatigue for this test is indicative of an augmented muscular endurance post-intervention. No significant differences were found in the control limb from T0 – T2 ($p = 0.063$). However, the control limb also showed a 78% increase from pre to post intervention (Mean values T0: 32.86 ± 11.16 sec, T2: 58.50 ± 45.79 sec). Increased fatigue

(81%), impaired hand function (60%) and impaired sensory function (85%) are the most reported symptoms of the upper limb within the first year of MS diagnosis (Kister et al., 2013). Accordingly, improving overall muscular fatigue can positively impact one's quality of life. Our repetitive and high dosage intervention improved grip force endurance and thus, reduced hand/forearm fatiguability. Although not statistically significant, grip force endurance improved with a 60% increase in the trained limb and a 78% increase in the control limb for the submaximal endurance hold for both limbs (a 20.61 and 25.64 second increase, respectively). While not statistically significant, a 60% increase is likely functionally/clinically significant and is most certainly a meaningful improvement that would likely translate to improved functional outcomes for activities of daily living. Such as muscular strength, muscular endurance is an under used assessment in literature to date. In an intervention study with the use of a shoulder and elbow robot, subjects with MS were able to increase the amount of exercise in a session before fatiguing by the end of a 6-week therapy program. Although muscular endurance was not overtly measured, these results indicate possible improvements in muscle fatigue following repetitive reaching movement tasks (Sampson et al., 2016). Again, future studies should investigate muscular endurance in an MS population further to form any firm conclusions.

Significant correlations were found between wrist strength and tracking errors. This finding suggests that as isometric wrist strength increased, tracking errors decreased. Due to the small sample size, this finding should be interpreted with caution, but it may suggest a linear correlation between wrist strength and hand motor control and should be investigated further in this population. Interestingly, there was no correlation found between EDSS score and tracking error. A higher score on the EDSS is representative of an increase in severity/disability of disease. It could be expected that those with a greater level of disease would have increasingly

poorer tracking performance. In particular, tracking error could be linked to functional performance or ability to perform activities of daily living. This finding could suggest that EDSS is not an appropriate indicator of upper limb disability and additional quantitative measures should be taken by the clinician or the researcher when investigating the upper limb in PwMS. This is in agreeance with Lamers et al., 2016, who suggested that because the EDSS scale is primarily dedicated to ambulatory disability, the International Classification of Functioning, Disability and Health (ICF) framework is a better indicator of upper limb dysfunction for MS. This poor correlation in our population suggests that further work is needed in this area. There is a great need to develop robotic assessment tools that are objective and validated such that clinicians no longer need to rely on subjective questionnaire assessments.

Despite improvements in tracking error and wrist strength, this work also demonstrates that our progressive robotic rehabilitation program for this specific population may not promote the transfer of learned skills. In our work, it appears that this population benefits from task-specific or goal directed exercises, rejecting our original hypothesis (4). This is shown in grip force, ROM, 9-HPT and proprioception measures. No significant improvements for grip force were found when comparing T0 to T2. This is to be expected as the intervention protocol did not directly include a specific grip force component. Furthermore, when comparing the maximal grip force of healthy, normative age matched individuals to the maximal grip force of our MS subjects, there was no differences. The normative values for maximal grip force for healthy males' average 40.15kg and our MS male population had an average of 44kg for the most affected limb. Normative grip force for healthy females is 27.34kg and our MS female population recorded an average maximal grip force of 23.64kg for the most affected limb (Peters et al., 2011). This suggests that, for our population, grip force was not compromised or affected

by the disease. It was not surprising that pre-post intervention grip force did not change in our population, considering the intervention did not include an intense or directed grip force component. These results are similar for our active and passive ROM tests. Most subjects did not present rigidity issues or reduced ROM at baseline therefore, additional improvements were not expected. This is further validated when examining the results for the active ROM radial deviation values. Although there was no significant change, ROM for this direction was the most reduced value at T0 compared to the other directions and resulted in a largest ROM change at T2. These results are similar to the findings of Mazzoleni et al., 2017, after repetitive robotic movement therapy at the wrist, ROM did not significantly improve for flexion, extension, radial or ulnar deviation for PwMS.

Proprioception is a test of somatosensory function and body spatial awareness (Proske & Morgan, 2001). Signals are received from peripheral mechanoreceptors, involving the CNS and are essential for motor control (Marini et al., 2016). Proprioception is one of the most common distortions of sensation and is most common in MS than any other neurological disease (Olek, 2005). The demyelination causes damage to the white matter pathways, resulting in a decrease in sensory signal conduction (Iandolo et al., 2020) which as previously discussed, is a frequently reported symptom. When the visual system is impaired (or in this case, absent), the subject is forced to recreate the joint angle position using only the somatosensory system. Due to the deficit in sensory signal conduction, motor performance is impaired and is most likely the result from the inability to organize a movement with lack of sensation (Olek, 2005). In our ipsilateral JPM test, subjects did not improve from baseline to post, suggesting that the tracking task involved in the intervention cannot be transferred into improvements in somatosensory feedback or spatial awareness. In order to show improvements in the transmission of sensory feedback,

directed proprioceptive rehabilitation is required. This is similar to the findings of stroke subjects, where robotic therapy displays little transfer to movements that have not been explicitly trained (Vergaro et al., 2010). These results have clinical importance. If the goal of the rehabilitation is to improve spatial body awareness, the clinician will need to develop a specific mode of therapy that challenges this system directly either with the robot or in addition to treatment with the robot.

Performing the task of the 9-HPT relies heavily on cerebellar functioning and fine finger manipulation, which is often damaged due to demyelination (Wilkins, 2017). Our results demonstrated no significant improvements in the time to completion (seconds) of this test from T0 to T2. Our hand/wrist intervention targeted muscles of the wrist, specifically in flexion, extension, radial and ulnar deviation and did not explicitly train the finger extensors and digits. Therefore, it is not surprising that the dexterity or fine manipulation training of the fingers did not improve. This concludes that training the muscles of the forearm do not transfer to improvements in coordination or dexterity of the distal upper limb. Different from the grip force which presented a ceiling effect, values generated at T2 for the 9-HPT were still significantly less than healthy aged matched controls. Normative male values (dominant limb: 22.2sec, non-dominant limb: 23.4sec) as compared to the MS group male averages (dominant: 25.43sec, non-dominant: 28.66sec). Similarly, for females: normative values (dominant: 19.18sec, non-dominant: 20.8sec) compared to the MS group averages post training (dominant: 30.44sec, non-dominant: 52.39sec) (Wang et al., 2015). 53% of the discrepancy in 9-HPT scores is explained by muscle strength, tactile sensitivity of the thumb, and the presence of intention tremor (Feys et al., 2017). Our subject scores were not significantly reduced post intervention because, if our training protocol targeted strength at all, if would have only directly trained forearm muscular

strength and the variance may be due to tactile sensitivity and intention tremor that was not directly trained.

The PRWE was a questionnaire pertaining to how the subject was feeling based upon pain and daily functioning at home on a 0-10 scale. No significant group differences were observed. There are limitations that arise with self-reported and qualitative assessments. Response bias is a commonly known issue with self-reported questionnaires. In this case, a response-shift bias may have altered the participant's responses at two time points (Rosenman et al., 2011). The goal of the intervention may have influenced the participants to respond differently pre and post intervention. An additional limitation to this questionnaire could have been the large rating scale. Perhaps because the participants were to respond to the difficulty of performing a task on a scale of 1-10, it was too broad and insensitive to capture these anecdotal responses. Self-reported diaries to better capture changes in ADL's could be a more accurate or appropriate tool. Such that in this work, although there were no significant improvements in the PRWE, participants verbally reported on their mental or physical progress throughout the training. Subject 2 reported "I am able to squeeze lemons while I bake now", in which the subject was unable to do before the training. Subject 3 reported "better use of wrist and coordination while performing daily at-home tasks". Subject 4 reported "feeling 25% better when cutting vegetables for dinner". Subject 12 reported "less fatigue in most affected wrist when typing at work" which would usually be unusable towards the end of a workday. The reports suggest that rehabilitation of any kind can reverse the effects/symptoms caused by inactivity due to the MS. Subjects in this study were not undergoing any additional therapy for training programs and were mostly inactive. Thus, for a population such as this it is important to

engage in any active rehabilitation programs to promote improvements in mental and physical well-being.

Limitations

This study is not without its limitations. Results from the study act as a proof of concept for robotic rehabilitation for MS. Further research with a larger sample size is needed to form firm conclusions. Firstly, subject numbers were low and non-parametric statistics were used. For stronger statistical significance, a future study should include a larger subject pool. Rehabilitation programs for MS populations have been successful with anywhere between 15 (Kesser et al, 2015; Cuypers et al, 2010; Bonzano et al, 2014 & Bayraktar et al, 2013) and 36 subjects (Jones et al., 1996). In addition, subjects should undergo an equal number of training sessions. More so, the training sessions should be prolonged to an ideal 6-8 weeks training program. Lastly, the training protocol can be more intensified. This can be done by increasing the frequency of the training from 3 to 5 days per week or longer than 40-minute sessions. In order for positive changes in neuroplasticity to occur, the training program must be greater than the effects of everyday activities. Perhaps 3 days per week for 40 minutes was not a high enough dosage of training and a higher dosage could elicit addition findings from our outcome measures. Nonetheless, 4-weeks (3x/week) of the tracking task in this intervention, evoked motor learning effects leading to improved neuromechanical control of the hand and an overall positive performance for our given task. Our work provides insight that robotics for rehabilitation of the upper limb for an MS population can yield beneficial results and combined with conventional therapy might promote increased motor control and motor function.

Future Directions

Current literature is lacking evidence of cross-education effects in patient populations. Given our interesting results in the untrained limb, future research should investigate the neurophysiology of cross-education for a MS population. Future directions include further exploration of progressions in robotic rehabilitation. This work provides evidence that adaptability of the program is efficient for neuromuscular adaptations, but future research should dedicate to quantifying progressions according to severity of upper limb disability. Lastly, this work was novel in that it was adaptive in real-time in an individually tailored way and was the first robotic rehabilitation study to implement two opposing forces (assistance and resistance). This methodology will be further explored and implemented into a longer duration of training with increased levels of forces to further examine this theory. Along with the longer duration of training, a retention test should be conducted where subjects are asked to come back to the laboratory several weeks after the program to distinguish if there has been a relatively permanent change in overall motor control and a long-lasting change in learning of the skill.

Chapter 6: Conclusion

In conclusion, to our knowledge, this study was the first adaptive and individualized robotic rehabilitation program providing both assistance and resistance to the hand/wrist for PwMS. Despite only being a 4-week training intervention, results of this work provide a proof-of-concept that motor control and muscular strength can be improved by this type of rehabilitation modality. Moreover, this approach has provided an effective way to properly individualize the therapy process with correct assistance levels and progressions for various types of MS, severity of disease and age levels. This work suggests that rehabilitation should be provided for both limbs to maximize progressions and fast forward the recovery as both limbs showed improvements despite only one limb being physically trained. It has also been demonstrated that this population benefits from task-specific exercises. Thus, the clinician should individualize rehabilitation programs to each personalized goal. Subject numbers were low in this preliminary investigation, and results should be taken with caution, however, this work acts as a stepping-stone into future investigations of robotic rehabilitation for an MS population.

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Appendices

Appendix A – Expanded Disability Status Scale Form

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.

*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.

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Appendix B – Patient Rated Wrist Evaluation Questionnaire

Optimal Performance Physical Therapy

Patient-Rated Wrist Evaluation

Name: _____ Signature: _____ Date: _____

The questions below will help us understand how much difficulty you have had with your wrist in the past week. You will be describing your average wrist symptoms over the past week on a scale of 0 to 10. Please provide an answer for ALL questions. If you did not perform an activity, please ESTIMATE the pain or difficulty you would expect. If you never performed an activity, you may leave it blank.

PAIN - Rate the average amount of pain in your wrist over the past week by circling the number that best describes your pain on a scale of 0 to 10. A zero (0) means that you did not have any pain and a ten (10) means that you had the worst pain you have ever experienced or that you could not do the activity because of pain

Rate Your Pain:	Never										Always
At Rest	0	1	2	3	4	5	6	7	8	9	10
When doing a task with a repeated wrist movement	0	1	2	3	4	5	6	7	8	9	10
When lifting a heavy object	0	1	2	3	4	5	6	7	8	9	10
When it is at its worst	0	1	2	3	4	5	6	7	8	9	10
How often do you have pain	0	1	2	3	4	5	6	7	8	9	10

Function

A. SPECIFIC ACTIVITIES - Rate the amount of difficulty you experienced performing each of the items listed below, over the past week, by circling the number that best describes your difficulty on a scale of 0 to 10. A zero (0) means you did not experience any difficulty and a ten (10) means it was so difficult you were unable to do it at all.

	No Difficulty										Unable To Do
Turn a door knob using my affected hand	0	1	2	3	4	5	6	7	8	9	10
Cut meat using a knife with my affected hand	0	1	2	3	4	5	6	7	8	9	10
Fasten buttons on my shirt	0	1	2	3	4	5	6	7	8	9	10
Use my affected hand to push up from chair	0	1	2	3	4	5	6	7	8	9	10
Carry a 10 pound object in my affected hand	0	1	2	3	4	5	6	7	8	9	10
Use bathroom tissue with my affected hand	0	1	2	3	4	5	6	7	8	9	10

B. USUAL ACTIVITIES - Rate the amount of difficulty you experienced performing your usual activities in each of the areas listed below, over the past week, by circling the number that best describes your difficulty on a scale of 0 to 10. By "usual activities," we mean the activities you performed before you started having a problem with your wrist. A zero (0) means that you did not experience any difficulty and a ten (10) means it was so difficult you were unable to do any of your usual activities.

	No Difficulty										Unable To Do
Personal care activities (dressing, washing, etc.)	0	1	2	3	4	5	6	7	8	9	10
Household work (cleaning, maintenance, etc.)	0	1	2	3	4	5	6	7	8	9	10
Work (your job or usual everyday work)	0	1	2	3	4	5	6	7	8	9	10
Recreational activities	0	1	2	3	4	5	6	7	8	9	10

(MacDermid & Tottenham, 2004)

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Appendix C – Recruitment Poster

HolmesLAB Neuromechanics Ergonomics

Brock University

Robotic Rehab Training Study for Multiple Sclerosis

Looking For:

- Persons with **Multiple Sclerosis** (all levels of disease)

Purpose of Study:

- Implement a progressive training program of the forearm and wrist for people with multiple sclerosis using a robotic device
- Assess wrist and grip strength, muscle activation, coordination and spasticity of muscles with the goal of changing overall hand functionality

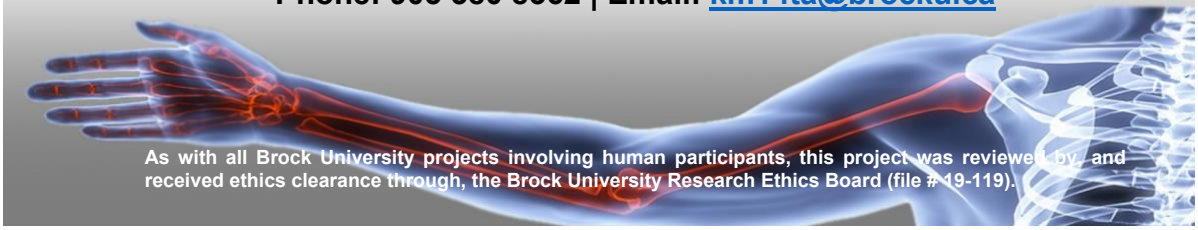
Time Commitment:

- 3 sessions per week (35-minutes each) for 6 weeks
- Sessions start January 2020
- You will be compensated for your travel and parking @ Brock

As a participant, you will be asked to trace an image with your hand (virtual reality) using a robotic device (picture above). We will evaluate the biomechanical and functional changes throughout the weeks of training.

For more information about this study, or to volunteer, please contact:

Kailynn Mannella, Msc Candidate
Brock University | Department of Kinesiology
Phone: 905 380 8362 | Email: km14ta@brocku.ca



As with all Brock University projects involving human participants, this project was reviewed by, and received ethics clearance through, the Brock University Research Ethics Board (file # 19-119).

Appendix D – Consent Form

Informed Consent

Michael W.R. Holmes, PhD
Canada Research Chair in Neuromuscular Mechanics and Ergonomics
Assistant Professor
Brock University | Department of Kinesiology
Niagara Region | 1812 Sir Isaac Brock Way | St. Catharines, ON L2S 3A1
brocku.ca | Phone: 905 688 5550 x4398 | Fax: 905 984 4851
Email: michael.holmes2@brocku.ca

Date: _____

Project Title: **Investigating the effects of a 6-week robotic training program for persons with multiple sclerosis**

Principal Investigator (PI):
Michael Holmes, Associate Professor
Department of Kinesiology
Brock University
905 688 5550 x4398**;** michael.holmes@brocku.ca

Dave Ditor, Professor
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Brock University
905 688 5550**;** dditor@brocku.ca

Principal Student Investigator:

Kailynn Mannella, MSc. Graduate Student
Department of Kinesiology
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905 380 8362; km14ta@brocku.ca

INVITATION
You are invited to participate in a research study. The human hand and forearm have great complexity and the neuromuscular processes required to perform fine motor tasks is vast. It is important to understand how the central nervous system outputs a task to the muscles, and to understand the physical consequences if this system is interrupted by neurological diseases such as multiple sclerosis (MS).

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.

Therefore, the purpose of this study is to use a robotic apparatus to implement an adaptive, patient tailored 6-week training program for the forearm and wrist in persons with MS. The aim of this work is to increase wrist and grip strength, increase muscle activation, reduce spasticity and increase coordination of muscles and joints to ultimately improve overall hand functionality.

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 6 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. You will also complete a questionnaire about your functional capability in everyday life. 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, 3, 6), 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 three degrees-of-freedom (DoF) haptic wrist manipulandum (Figure 1). It is a mechanical system that can deliver torque (forces) to the human hand that is interacting with the device and is integrated with a virtual reality environment and computer display. The device allows for movements along the three DoFs of the human joint: flexion/extension (F/E), radial/ulnar deviation (R/UD) and pronation/supination (P/S). The device is controlled by custom programs and taking the haptic device to its full range of motion, wouldn't result in stress or strain on the human hand as our human ranges are typically greater than the end range of the device. In each experiment, you will sit in front of the haptic wrist device 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 haptic wrist exoskeleton 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 (Modified Ashworth's Scale)
A researcher will demonstrate and ask you to perform flexion/extension movements of your elbow, wrist and finger. The researcher will rate the amount of spasticity that occurred during the movement on a scale of 0-4. Zero indicating no increase in tone and 4 indicating affected areas are rigid in flexion and extension.

Task 2 (Patient Rated Wrist Questionnaire)
The PRWE is a 15 patient-reported questionnaire used to assess pain in the wrist joint and functional difficulties in activities of daily living. Together, we will carefully read through the 15 questions and the you will rate your pain on a scale of 0 (no pain) to 10 (worst pain).

For the following tasks below, both your dominant and non-dominant upper limb will be tested separately:

Task 3 (9-Hole Peg Test)
You will be asked to complete a 9-hole peg task testing hand and arm function of both the dominant and non-dominant upper limb. A 9-hole peg apparatus will be secured to the table horizontally in front of your arm that is being tested. You are to perform the task as quickly as possible by taking 9 pegs and placing them in empty holes on the other side of the apparatus, then removing the pegs and placing them into a container. Trials occur twice on each arm and are recorded based off of time to completion from when the first peg is touched to when the last peg is placed into the container. Any circumstances in which could affect your daily performance (i.e. forgot glasses and cannot see the pegs clearly) will be indicated on the appropriate recording sheets provided by the National MS Society.

Task 4 (Passive and Active Range of Motion)
The robotic device will slowly move your wrist in flexion, extension, radial deviation, ulnar deviation and pronation, supination planes. 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 terminated 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 5 (Grip Force and Isometric Strength):
You will be asked to place your forearm in the haptic wrist device, gripping a custom-built handle with a transducer 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 and measure the force that is applied. 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. 1) flexion, 2) extension, 3) radial deviation, 4) ulnar deviation (up, down, left and right). Lastly, you will be asked to grip the force handle maximally for as long as you can, this will be a timed task.

Task 6 (Proprioception):
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 flexion, 2) moving in just wrist extension. 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 (65-70 degrees in flexion and extension) 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 7 (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 6 weeks, you will perform task 7 for 35 minutes.

ELIGIBILITY

We aim to recruit 12 participants with MS for this study. 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.

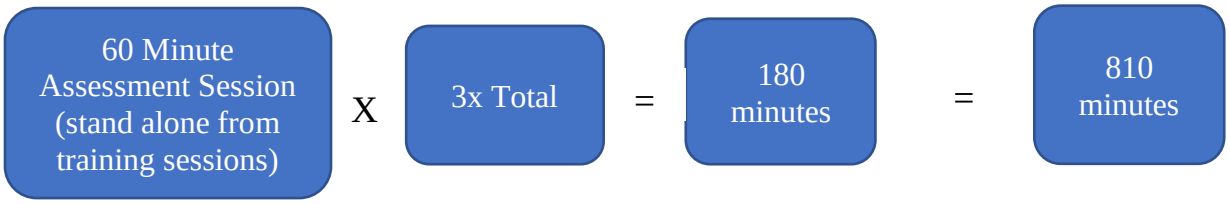
TIMELINE

Including instrumentation and experimental setup, it is expected that you will be in the laboratory for 18 “training” sessions” (35 minutes for each session) separated by at least 48 hours. This will occur 3x/week for 6 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. All tasks will be performed in the same order: Modified Ashworth’s Scale, PRWE questionnaire, 9-hole peg test, passive and assistive range of motion, maximum grip force, isometric force in flexion/extension and radial/ulnar deviation, proprioception and grip force endurance hold.

Time Commitment:

35 Minute Training Sessions X 3x week for 6 weeks = 630 minutes



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 haptic device 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. You may also withdraw from the study at any time without penalty at either facility (if you are affiliated with PowerCord or Hotel Dieu Shaver).

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 data cannot be considered confidential, as the researchers (and only the researchers) can match your results to you. However, your information will otherwise 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, Dr. Ditor 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, de-identified 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 or Hotel Dieu Shaver 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. You will also obtain a Lab T-Shirt.

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 # 19-119). 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 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