Assessing the Effect of Functional Electrical Stimulation Training with the Xcite on Hand and Arm Function in Persons with Multiple Sclerosis

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Abstract

The purpose of this study was to assess the effects functional electrical stimulation (FES) training of the hand and arm in persons with multiple sclerosis (MS). This is a case series of four individuals with MS with varying hand and arm dysfunction, and Expanded Disability Status Scale (EDSS) scores ranging from 3.0-7.0. Two participants completed 1-hour FES sessions, 3 times per week for 8 weeks and two participants completed 10 weeks. Every session the following four hand and arm exercises were performed on the non-dominant limb: feeding, forward reach and grasp, opposition and lumbrical pinch on the Xcite iFES Clinical Station (Restorative Therapies, Baltimore, MD). Pre and post-testing was divided into two days. The first day included the Sollerman's hand function test, the Functional Independence Measure (FIM; self-care only), the Capabilities of Upper Extremity (CUE) instrument and the Grasp and Release Test (GRT). The second testing day participants performed grip strength testing (palmar and tip pinch) and two tasks on a haptic wrist device; a tracking task and a proprioception task to assess the effects of the FES training protocol. Pre-testing was completed within 24-72 hours prior to the first FES session and post-testing was within 72 hours of the final FES session. Three of the four participants showed marked improvements in palmar and tip pinch grip strength. Participants did not show meaningful improvement in the Sollerman's hand function test. The grasp and release test provided mixed results, two participants improved, two were inconsistent across the 6 items. When assessing the functional questionnaires, virtually no change was seen on the FIM and the CUE. Regarding the haptic wrist device testing, some improvement was seen in the tracking and proprioception task but most was not meaningful improvement in the trained limb. Anecdotally, most of the participants reported experiencing improved function in day to day life. The results of this study suggest that thrice-weekly FES of the hand and arm with the

Xcite clinical station for 8-10 weeks may elicit functional improvements in individuals with MS. However, more research is required to better understand optimal training parameters and limitations of this therapy.

Table of Contents

Abstract ……………………………………………………………………………ii

List of Tables …………………………………………………………………...vi

List of Figures..…………………………………………………………… vii

List of Abbreviations ..………………………………………………………..viii

Introduction ………………………………………………………………..1

Literature Review ……………………………………………………….....3

Background and Epidemiology of Multiple Sclerosis……………………....3

Types of MS……………………………………………………….4

Etiology and Pathophysiology of MS…………………………………......6

Etiology ……………………………......................................6

Pathophysiology…………………………...................................6

Physiological Consequences of MS………………………………………8

Sensorimotor Deficits ………………………………………………..8

Functional Impact……………………………………………...13

Autonomic Deficits……………………………………………….15

Cognitive and Psychological Deficits ………………………………17

Treatments Aimed at Improving Strength and Function After MS………..19

Pharmacological Treatments……………………………………..19

Exercise Rehabilitation After MS…………………………………..20

Functional Electrical Stimulation (FES) After MS………………… 26

Mechanisms Underlying Improvements with FES Training ……… 29

Purpose and Hypothesis…………………………………………………...30

Statement of Purpose …………………………………………………30

Hypothesis …………………………………………………………30

Overview of Study Design………………………………………………..31

Study Design and Participants ……………………………...……..31

Testing Session 1……………………………………………………..32

Testing Session 2……………………………………………………..34

Training Sessions……………………………………………………..36

Results 38
Participant 1.. 38
Participant 2 42
Participant 3 46
Participant 4 50

Results Summary...54

Testimonials...54

Discussion 56
Main Findings.. 56
Clinical Significance..60
Limitations 63
Future Directions 64

Conclusion..65

Appendix A: Types of MS.. 74

Appendix B: Carpenella Study Figures..................................... 75

Appendix C: Types of Grips used in GRT................................... 76

Appendix D: Haptic Wrist Device Hand Position.......................... 77

Appendix E
Depiction of Sollerman Hand Function Test Kit.......................... 78
Sollerman Hand Function Test Order of Subtests........................ 79
Sollerman Hand Function Test Scoring Guidelines...................... 79

Appendix F
Electrode placement for feeding task.. 80
Electrode placement for feeding task.. 81
Electrode placement for feeding task...82
Electrode placement for feeding task.. 83

Appendix G
Xcite iFES Clinical Station.. 84
Electrodes used during Xcite exercises.......................................84

List of Tables

Methods

Table 1. Participants Characteristics ...……………………………………… 32

Results

Table 2.0a Grasp and Release Data (Participant 1) ……………………………39
Table 2.0b Grasp and Release Data as a Percent (Participant 1)……………... 40
Table 2.1 Tracking Task Error Values (Participant 1)………………………... 41
Table 2.2 Proprioception task error values (Participant 1)……………………42
Table 3.0a Grasp and Release Data (Participant 2)…………………………... 43
Table 3.0b Grasp and Release Data as a Percent (Participant 2)……………... 44
Table 3.1 Tracking Task Error Values (Participant 2)………………………... 45
Table 3.2 Proprioception task error values (Participant 2)…………………… 46
Table 4.0a Grasp and Release Data (Participant 3)…………………………... 48
Table 4.0b Grasp and Release Data as a Percent (Participant 3)……………... 48
Table. 4.1 Tracking Task error values (Participant 3)…………………………49
Table 4.2 Proprioception task error values (Participant 3)…………………… 50
Table 5.0a Grasp and Release Data (Participant 4)…………………………… 51
Table 5.0b Grasp and Release Data as a Percent (Participant 4)……………... 51
Table 5.1 Tracking task error values (Participant 4)………………………….. 52
Table 5.2 Proprioception task error values (Participant 4)……………………..53
Table 6.0 Absolute Changes Pre-Post in trained limb ……………………….**..**54

List of Figures

Figure 1. Types of MS……………………………………………………… 74

Figure 2. Carpenella Study Figures……………………………...…………. 75

Figure 3. Types of Grips used in GRT……………………......................... 76

Figure 4. Haptic Wrist Device Hand Position.……………………………... 77

Figure 5. Depiction of Sollerman Hand Function Test Kit…………………… 78

Figure 6. Sollerman Hand Function Test Order of Subtests………………….. 79

Figure 7. Electrode placement for feeding task……………………………….. 80

Figure 8. Electrode placement for feeding task…………………...………….. 81

Figure 9. Electrode placement for feeding task………….……………..…….82

Figure 10. Electrode placement for feeding task…....…………………………. 83

Figure 11. Xcite iFES Clinical Station…………….…………………..…. 84

Figure 12. Electrodes used during Xcite exercises……..……………….……84

List of Abbreviations

ADL- Activities of Daily Living

ARAT- Action Research Arm Test

BBB- Blood Brain Barrier

CIS- Clinically Isolated Syndrome

CUE- Capabilities of Upper Extremity

CNS- Central Nervous System

EDSS- Expanded Disability Status Score

FES- Functional Electrical Stimulation

GRT- Grasp and Release Test

ROM- Range of Motion

FIM- Functional Independence Measure

MRI- Magnetic Resonance Imaging

MS- Multiple Sclerosis

MSWS-12- 12 Item MS Walking Scale

NSC- Neural Stem Cell

PPMS- Primary Progressive Multiple Sclerosis

PRMS- Primary Relapsing Multiple Sclerosis

PwMS- People with Multiple Sclerosis

RRMS- Relapse Remitting Multiple Sclerosis

SCI- Spinal Cord Injury

TUG- Timed Up and Go

T25FW- Timed 25 Foot Walk

QOL- Quality of Life

2MW- 2 Minute Walk

Introduction

The process of being diagnosed with multiple sclerosis (MS) can be long and frustrating due to its complexity and varying symptoms present in the early stages [MS Society, 2019]. Multiple Sclerosis (MS) is an autoimmune disease of the central nervous system (CNS), affecting the brain and the spinal cord such that the insulating myelin lining that ensheaths the nerves is attacked and damaged, causing chronic inflammation and a disruption of nerve impulses and transmission [MS Society, 2019]. This disruption in the system results in a number of motor, sensory, autonomic and cognitive symptoms and each symptom can range in severity in each individual and impact various components of the person's life [MS Society, 2019; National MS Society, 2016]. Worldwide, there are 2.3 million people living with MS. Canada has one of the highest rates of MS worldwide, with, approximately 77,000 cases, which translates to 1 in every 385 Canadians. Even with so many people affected by this disease the cause is still unknown. However, current research suggests that a combination of lifestyle, environmental, genetic and biological factors may all contribute [MS Society, 2019, National MS Society, 2016].

Motor symptoms associated with MS often impact a person's physical function, and include muscle spasms, fatigue, weakness, contractures, and reduced ROM and coordination. These symptoms can be experienced throughout the entire body, involving both upper limb and lower limb function [MS Society, 2019]. Regarding rehabilitation after MS, the emphasis is often on improving function of the lower body, as gait is commonly affected in most neurological diseases. However, strategies to improve upper limb function for those who experience MS-related motor symptoms in the hands and arms is still necessary. The combination of wrist movement (flexion/extension, radial/ulnar deviation) and forearm rotation provides the distal upper extremity with immense movement capabilities and many degrees of freedom, allowing one to perform fine and gross motor tasks that require coordination and precision. Without optimal function of the upper extremity, activities of daily living (ADL) become increasingly more difficult to perform, and some tasks may not be possible to complete at all. With this loss of function comes a loss of independence which in turn, has a high correlation to decreased quality of life; often seen in those with MS [sadovnick et al, 1996; Mitchell et al., 2005].

Regular exercise in the form of resistance training, aerobic exercise, yoga, or high intensity interval training (HIIT) can improve overall fitness, cardiovascular health, muscle strength, balance and fatigue, which in turn can have a positive impact on quality of life [Petajan & White, 2000; Wonneberger & Schmidt, 2019; Guoy et al., 2012; Salgado et al., 2013]. However, these forms of exercise seldom target the upper limbs and hands in a way that may impact functional improvements in those with MS [Dalgas, 2011; Taylor et al., 2006].

Functional electrical stimulation (FES) may offer more promise than traditional exercise as a means to improve upper limb strength and function, and research in the last decade has demonstrated such improvements in the stroke and spinal cord injured populations [Popovic et al., 2006; Venugopalan et al., 2015] as well as those with MS [Kutlu et al., 2017; Patil et a., 2015; Sampson et al., 2015]. A study conducted in 2016 investigated the effects of a 10-week protocol consisting of 18, 1-hour sessions involving FES combined with passive robotic support during a reaching task in persons with MS [Sampson et al., 2015]. A range of 18-33 minutes of actual stimulation was involved which resulted in an average tracking improvement of 12.8% and 23.6% for the elbow and shoulder, respectively [Sampson et al., 2015]. Further, a reduction of 49.2% and 48.8% of maximal stimulation was required to effectively complete the tasks on the elbow and shoulder, respectively. Taken together, these findings suggest that the participants were gradually becoming more efficient in successfully completing the reaching tasks following the FES training. Although such research is positive and encouraging, more research involving newer technologies and functional impact is certainly warranted. In recent years, a company called Restorative Therapies has designed a FES device known as the Xcite, that can be used to mimic functional tasks and ADL. For example, with the electrodes applied to the upper limb and hands, movements such as forward reach and grasp (as if reaching and grabbing a cup), or lumbrical pinch (similar to holding onto a coin or picking up a pen) can be evoked and trained. The Xcite provides a simple but precise interface that holds over 40 pre-programmed functional movements that the user can customize to best meet their needs. This device is currently being used in rehabilitation centers as therapy for various neurological conditions including stroke, spinal cord injury (SCI), cerebral palsy (CP) and MS but there has yet to be a formal study conducted on its effectiveness.

The purpose of the present study is therefore, to investigate the effects of a ten-week, thrice weekly, FES training intervention on upper limb strength and function in individuals with MS.

Literature Review

Background and Epidemiology of Multiple Sclerosis

Multiple Sclerosis (MS) is an autoimmune disease of the central nervous system (affecting the brain and the spinal cord) where the insulating myelin lining ensheathing the nerves is attacked and damaged, causing chronic inflammation and a disruption of nerve impulses and transmission [MS Society, 2019]. Inflammation accumulates in the brain and spinal cord, eventually resulting in further neurodegeneration and demyelination of the efferent/afferent pathways thus, decreasing motor, sensory and autonomic capabilities [MS Society, 2019].

This neurodegenerative disease was first recognized by clinician, Jean Martin Charcot in 1868 [Frohman et al., 2011]. Then, the diagnostic criteria were referred to as the Charcot's triad which included speech impairments, intention tremor and nystagmus. Today, the process of diagnosing a person with MS is much more extensive and several tests are conducted. A medical history, a neurological exam and clinical symptoms are fundamental to the diagnosis process. Preliminary symptoms that may be experienced and help in the diagnosis include vison problems, tingling and numbness, pains and spasms, balance issues or dizziness and fatigue. Also, performing an MRI and evoked potentials are useful in confirming a suspected MS case [MS Society, 2019].

MS affects nearly 1 million individuals in North America and 2.3 million worldwide. Canada has one of the highest rates of MS worldwide, with, approximately 1 in 385 Canadians (more than 77,000) diagnosed with the disease as of 2019 [Canada, 2019].

In most cases, diagnosis is determined during young adulthood (20-49 years of age) [MS Society, 2019, National MS Society, 2016]. However, there are cases of younger children as well as older adults being diagnosed. Also, women are three times more likely to get MS and overall, this condition is more common in people of a Northern European background [National MS Society, 2016].

Types of MS

Often times MS begins with a clinically isolated syndrome (CIS), which is the first episode of neurological symptoms caused by inflammation and demyelination in the CNS. To be considered a CIS the episode must last at least 24 hours, however, experiencing this does not necessarily mean that the person has or will have MS [National MS Society, 2016]. After a CIS, if an MRI scan detects brain lesions similar to those seen in MS, the chances are high for the person to experience a second episode and develop relapsing-remitting MS [National MS Society, 2016]. Once diagnosed with MS the person will be classified into one of the four types of MS described below. See Appendix A for further description of each classification.

The most common type of MS is Relapsing-Remitting Multiple Sclerosis (RRMS), which is characterized by clearly defined attacks/episodes of new or increasing neurological symptoms followed by periods of partial or complete recovery, referred to as remission [National MS Society, 2016]. Remission provides a period of time in which all symptoms may disappear, or some symptoms may continue and even become permanent but there is no measurable progression of the disease at this time. The intensity of each relapse may increase, decrease or stay the same as the previous episode and each bout is unique in every case. Following a relapse, the new symptoms may disappear without causing any increase in level of disability, or the new symptoms may partially disappear, resulting in an increase in disability. Approximately 85% of people with MS are initially diagnosed with RRMS [National MS Society, 2016].

The second type of MS is Secondary Progressive MS (SPMS). Approximately 50% of people initially diagnosed with RRMS will develop SPMS within 10-20 years which involves the consistent worsening of neurological function over time, either with or without sporadic relapses [National MS Society, 2016].

The third type of MS is Primary Progressive (PPMS), which is characterized by a worsening of neurological function from the initial stages, without early relapses or remissions. At various times the disease can be characterized as active (with sporadic relapses) or not active, as well as with progression (worsening of the symptoms over time, with or without relapses) or without progression [National MS Society, 2016].

The final type is Progressive Relapsing MS (PRMS). This type involves steadily worsening neurological function with occasional relapses from the initial stages of the disease. Those who have been diagnosed with PRMS are now considered to have primary progressive; active or not active [National MS Society, 2016].

Etiology and Pathophysiology of MS

Etiology

The cause of MS is still unknown. Current research suggests that a combination of lifestyle, environmental, genetic and biological factors may all contribute [MS Society, 2019; National MS Society, 2016]. Some examples of lifestyle and environmental factors that may increase risk of MS include low vitamin D levels, childhood obesity, and smoking. Genetics are a key factor since an expression of a changed gene of the human leukocyte antigen (HLA) family, specifically, HLA-DRB1, can influence the immune system to be unable to discriminate between our own body's proteins and those made by foreign invaders [MS Society, 2019]. A more recent theory looks at gut health and how one's microbiome may be a contributor to the damaging of the blood-brain barrier (BBB) and in turn signal the immune response [Lee at al., 2011].

Pathophysiology

As mentioned previously, MS is an autoimmune disease which attacks the myelin sheath. The demyelination is accompanied by an inflammatory reaction with T-cells and macrophages as well as axon destruction via lesions. Myelin is the primary target of destruction but axons, nerve cells and astrocytes are also affected, to a lesser degree [Ontaneda et al., 2012]. There is an ongoing destruction of myelin referred to as active lesions, in which macrophages and activated microglial cells infiltrate the tissue. These cells are responsible for the uptake and removal of the myelin debris. It has been said that demyelination can be repaired to some degree through remyelination, from the neighbouring oligodendrocytes but, axonal destruction is irreversible [Ontaneda et al., 2012]. This differential degree of damage is illustrated in the relapsing-remitting functional impairment. Inflammation and demyelination cause many of the sporadic relapses, whereas the baseline or unremitting neurological impairments are due to the axonal destruction [Lassmann et al., 2001]. Research suggests that the inflammatory process is driven by a Th1-mediated autoimmune response. T-cells are believed to play a role in causing impairment in this disease due to the ability of Th-17 (a T-cell subtype) to open the blood-brain barrier and then cause axonal damage and neuronal death [Ontaneda et al., 2012]. Blood samples show that an elevated number of autoreactive T-cells with the cytokine spectrum of Th1 cells are present in those with MS, backing this theory [Ontaneda et al., 2012; Lassmann et al., 2001].

Another contributing factor to the pathology of MS are the white matter lesions, however, new research has discovered gray matter lesions are also present. These cortical lesions appear in the early stages of the disease, accumulate over time and may even exceed white matter lesion in progressive MS [Ontaneda et al., 2012]. Cortical lesions usually have fewer infiltrating leukocytes and more prominent neuronal degeneration compared to white matter lesions. Cortical atrophy occurs early in MS and worsens more rapidly than white matter atrophy. This progression correlates more strongly with physical and cognitive impairment [Ontaneda et al., 2012].

Complete neural repair and remyelination is unlikely to be achieved, however, remyelination does occur naturally to some extent. Once CNS tissue damage occurs, the oligodendrocyte progenitor cells migrate to the lesions where they differentiate into re-myelinating oligodendrocytes that spread processes to demyelinated axons [Ontaneda et al., 2012; Lassmann et al., 2001]. Even in the early stages of the disease and sheath destruction, remyelination is unable to compensate for the continuing demyelination in most people. It is thought that multiple mechanisms may contribute to the failure of remyelination [Lassmann et al., 2001]. The mechanisms involved in triggering this process are still uncertain and therefore, finding successful therapies has been difficult.

Physiological Consequences of MS

Inflammation and the immune system play a key role in initiating the damage to the CNS but it is the resulting lesions that determine what deficits the person will experience. The differences in symptoms between people with MS, both in type and severity depend on the location and size of the CNS lesions. Sensorimotor deficits and problems in physical functioning of the extremities result from cerebellar, brain stem and spinal cord lesions, whereas cognitive and psychological deficits are due to lesions in the frontal and parietal lobe [Bishop & Rumrill, 2015].

Sensorimotor Deficits

Fatigue. Persons with MS can experience two different types of fatigue, either cognitive or physical. Unlike able-bodied individuals fatigue occurs and presents somewhat differently. It can be due to a ‘short-circuiting’ when a limb is weakened from demyelination and repeatedly asked to perform, feeling similar to general muscle fatigue [Schapiro & Schapiro, 2003]. However, completely eliminating movement or exercise of effected limbs, resulting in muscle atrophy can also cause fatigue. Another type of fatigue that is commonly experienced among the

MS population is called lassitude, where an overwhelming sleepiness comes about abruptly and severely at any time of the day [Schapiro & Schapiro, 2003; Crayton & Rossman, 2006]. Approximately 80% of people with MS experience fatigue and half of these cases report it as being their most debilitating symptom [MS Society, 2019, Giovannoni, 2006; Crayton & Rossman, 2006].

In 2007, Greim and colleagues completed qualitative and quantitative assessments of fatigue in 79 people with MS and 51 control subjects using the vigilance test and a vigorimeter test [2007]. The vigilance test assesses mental fatigue in terms of mistakes and reaction time, it requires the participant to listen to a series of high and low tones with the goal of detecting any irregular tones in the sequence. To test physical fatigue, grip strength was assessed using the vigorimeter test, requiring the participant to squeeze a rubber ball 10 times, alternating hands, at 3 second intervals at maximal effort [Greim et al., 2007]. Compared to the healthy controls, the MS group demonstrated significantly lower levels of concentration shown as omission mistakes and slower reaction time during the vigilance test (MS: 34.4 mistakes and 43.1 RT; C: 45.7 mistakes and 50.6 RT converted to the T-standard scores). When assessing physical fatigue there was a significant decrease in strength over the 10 trials in the MS group decreasing from 0.88kp to 0.80kp opposed to the control group who only decreased from 1.10kp to 1.06kp [Greim et al., 2007].

A study by Petajan and White used transcranial magnetic stimulation (TMS) to observe central conduction impairments in persons with MS before and after a fatiguing task (3-minute maximal grip test) [2000]. At rest, motor-evoked potentials (MEPs) were reduced, more dispersed, and varied greater in MS participants and after a fatiguing task, MEP was reduced to a greater extent, varied more and recovery of the MEP was prolonged [Petajan & White, 2007]. An interesting aspect of this study was its ability to assess and interpret cortical excitability. Before the fatiguing exercise, all groups demonstrated an increased MEP amplitude and shorter central motor conduction time (CMCT) during the contralateral hand grip, showing that facilitatory mechanisms were normal/present at rest. However, following the exercise, MS subjects were unable to facilitate the MEP with contralateral hand grip [Petajan & White, 2007]. This confirms that there is a loss of muscle strength associated with prolonged physical activity that cannot be increased by effort. Assessing what goes on before and after exhausting tasks allows us to better understand the fundamentals of fatigue in MS.

Muscle Weakness. A common symptom seen in those with MS is muscle weakness. In able-bodied people when muscle weakness or atrophy is seen it is usually from a lack of exercise. In the case of MS, muscle weakness can be attributed to both inactivity as well as a problem in transmission of electrical impulses to the muscle from within the CNS [Schapiro & Schapiro, 2003]. In MS, other common symptoms can cause or worsen muscle weakness such as spasticity and fatigue. When muscle tone increases due to repetitive spasms it can limit ROM but also restrict the strength of its antagonist muscle as it may cause it to lengthen over time. This interconnection between symptoms makes it nearly impossible to separate them when creating management and treatment plans, therefore, they are usually treated in combination. If spasticity and/or fatigue can be reduced it provides the person a better chance to improve muscle strength [Schapiro & Schapiro, 2003]. Muscle strength can also decrease as the disease progresses and depending on the stage of the disease and lesion severity, individual strength deficits can differ. Muscle weakness can also be a catalyst for a number of other functional problems as it becomes more severe. Older persons with MS, with more severe symptoms tend to have loss of coordination and motor control due to muscle weakness. Research conducted by Krishnan in

2008 found that there was impairment of strength across dynamic and static tasks [Krishnan et al., 2008].

Grip strength was assessed in a study examining central and peripheral effects of fatiguing exercise in 10 healthy controls, 16 MS subjects with hand weakness (MS-W) and 16 MS subjects with normal motor function (MS-NM) [Petajan & White, 2000]. A custom-built hydraulic force transducer was used to compare average peak force (mmHg) between the 3 groups. Controls achieved an average of 622mmHg, the MS group with normal function averaged 516mmHg and the MS group with weakness averaged 406mmHg. The time for the participants grip strength to decline to 50% max took longer in the control group (29sec) compared to MS-NM (18sec) and MS-W (15sec) further demonstrating the muscle weakness and fatigue that is present in MS [Petajan & White, 2000].

Contractures. Prolonged muscle tone and constant short joint angles lead to contractures, which are characterized as hardening of muscles, tendons or other tissues which lead to joint rigidity and reduced flexibility. In most cases, contractures are present in the hip flexors and hamstrings due to prolonged sitting from wheelchair use. This limits the person's ability to stand upright without assistance or walk, with or without assistive devices.

A study examining the prevalence of joint contractures, stiffness and muscle weakness in those with MS was done in Australia in 2014 [Hoang et al., 2014]. Out of the 330 participants with MS, 56% of them reported having contractures in at least one major joint. Although contractures are more prevalent in the lower body, this study estimated upper body prevalence (averaged across right and left sides) as follows: shoulder 8.3%, elbow/forearm 3.5%, wrist/hand 2.5% [Hoang et al., 2014]. Another study assessed spasticity of those with MS and 84% reported at least minimal spasticity (31% minimal, 19% mild, 17% moderate, 13% severe and

4% total/prevents daily tasks) [Rizzo, 2004]. It was revealed that one-third of those with MS modify or eliminate daily activities due to spasticity. It was also concluded that there is a strong correlation between muscle weakness and contractures at large joints of both the upper and lower limbs and an inverse relationship between quality of life (QoL) and spasticity severity [Hoang et al., 2014].

Spasticity. Due to spasticity and muscle atrophy persons with MS may also experience decreased range of motion (ROM) in affected joints. Spasticity can occur simultaneously or sequentially as increased muscle tone during active movements or during passive stretching. It can also be unprovoked and persistent, transient and sometimes painful [Patejdl & Zettl, 2017]. Upwards of 80% of people with MS experience spams in some capacity [Crayton & Rossman, 2006].

Aside from limiting their efficiency in completing reaching tasks, decreased ROM in the upper limbs can also affect gait patterns. A study conducted on 52 adults with low severity RRMS and 25 healthy age-matched controls measured upper extremity function during gait [Bonnefoy-Mazure et al., 2017]. Those with MS walked slower, with increased mean elbow flexion and decreased overall amplitude of elbow flexion during the gait cycle. There was also a significantly higher average movement of the arm angle in the sagittal plane compared to control group [Bonnefoy-Mazure et al., 2017]. This study as well as other studies have described a relationship between arm swing and gait speed, explaining that it reduces energetic cost, may play a role in stability as well as facilitate leg movements. A decreased ROM in arm swing may be disruptive to one's gait due to a lesser angular momentum [Bonnefoy-Mazure et al., 2017.

Nerve Pain. Persons with MS may experience many different forms of pain but one that is more closely link to MS is neurological pain. This form of pain is usually reported as being significantly more severe than non-neurological pain [Crayton & Rossman 2006]. Nerve pain occurs due to the damage of demyelination of the CNS, such that interference of transmissions to the brain result in misunderstood signals presented as numbness, shooting or stabbing pain, crawling or burning sensations anywhere in the body without cause [MS Society, 2019]. It can come about anytime during the day or night and last seconds to hours, not only disrupting daily activities but possibly sleep as well. The main treatment for neurological pain is an anti-convulsant pharmaceutical although it, and other drugs for neuropathic pain do not completely resolve it [MS Society, 2019, Crayton & Rossman, 2006].

A study conducted in 2017, determined the relative association between daily changes in pain, fatigue, depressed mood, and cognitive function against 4 outcomes: well-being, participation in social roles/activities, upper extremity (UE) functioning and lower extremity (LE) functioning [Kratz et al., 2017]. Daily pain was associated with decreased social participation (B= -1.00; P= 0.002), UE functioning (B=-1.04; P=0.01) and LE functioning (B= -0.71; P= 0.04). Although nerve pain is not physically visible the impact it can have on a person's ability to complete simple tasks physically and mentally can be devastating [Kratz et al., 2017].

Functional Impact

Although no case of MS is the same, many symptoms such as chronic pain, spasticity, diminished strength and coordination, muscle fatigue, bladder dysfunction and sensory impairments are commonly present [MS Society, 2019; National MS Society, 2016]. These symptoms can cause debilitating effects on wrist and upper limb function, making it difficult to complete daily activities. For example, if there is a high degree of spasticity in the wrist extensors, over time muscle tone increases, stretching and weakening the flexor muscles. In severe cases even a maximal muscle contraction of the wrist flexors cannot overcome the force of the extensors, leaving the wrist in an extended position until passively stretched.

Reilmann and colleagues conducted a study in 2013 assessing quantitative motor assessment on persons with MS as well as a matched control group. Grip strength of a pincher grip was tested with a force transducer device allowing grip force variability during an isometric grip to be tested. Those with MS had significantly higher variability during the 30 second grip force (5.2) trials compared to the control group (3.6) [Reilmann et al., 2013]. These findings illustrate how daily activities can be more challenging for those with MS, by having irregular grip forces, affecting their coordination needed for lifting or carrying objects [Reilmann et al., 2013].

Another study assessed upper limb motor function in people with MS with an instrumented action research arm test (ARAT), evaluating the ability to hold and carry various objects as well as the nine-hole peg test for precision grasping [Carpinella et al., 2014]. The 12 healthy participants and 21 participants with MS wore single inertial sensors on their wrist, accelerometers and gyroscopes signals were also used to determine the duration of each task as well as a jerk index for smoothness of movement. ARAT tasks completed by the group with MS were significantly slower and less smooth compared to the control group by 70% and 16% respectively [Carpinella et al., 2014]. This study showed that completing everyday tasks with upper limbs can be difficult for people with MS but it was also insightful as to the specific challenges. They directly compared a healthy control and a participant with MS completing a sub-task of ARAT by measuring angular velocity across time and break down the task into 5 sections: reaching, manipulation, transport, release, and return. The time required for the participant with MS subject to manipulate and release the object accounted for much of the time difference, showing that grasping and releasing are the greatest deficits [Carpinella et al., 2014]. See appendix B for graph depicting the comparison.

Further, a study by Squillace and colleagues in 2015 assessed fine and gross motor function in 36 adolescents with MS against 36 control adolescents, and these researchers found that one may be more affected than the other [Squillace et al., 2015]. Using a hand dynamometer, a nine-hole peg board (NHPB) and a purdue peg board (PPB) the researchers found significantly lower scores in left, right and both hands for fine motor tasks in the group with MS compared to the age-matched control group. When comparing the NHPB tests, the time scores in the group with MS averaged 25.1s and 26.6s compared to the control group who averaged 19.7s and 19.8s right and left hand, respectively. A similar superior performance by the control group was seen in the PPB; with the average peg scores of 15.4, 14.0 and 12.6 compared to the MS group who scored an average of 12.6, 11.0, and 9.6 for the right, left and both hands, respectively [Squillace et al., 2015]. However, gross motor function did not show a significant difference between the two groups [Squillace et al., 2015].

Autonomic deficits

The autonomic nervous system (ANS) controls many important aspects of the body, including efferent neurons, smooth muscle, cardiac muscle and gland cells in an involuntary or automatic fashion. As a result of demyelination, disruption to the central centers of the autonomic system is frequently seen in MS, impacting what signals, if any, are sent from body to brain and vice versa. Since lesions rarely affect one concentrated area, a complex network of symptoms from both the sympathetic and parasympathetic systems are seen [Merklebach et al., 2006; Lensch & Jost, 2011]. As a result of this complexity much is yet to be understood regarding ANS deficits in MS, such as cardiovascular issues, pupillomotor, or sweat gland changes [Merkelbach et al., 2006]. Two areas that are commonly impacted and better understood are bladder/bowel function and temperature regulation.

Bladder/Bowel dysfunction. Yet another uncomfortable symptom of MS is bladder and bowel dysfunction. This can present in a number of different ways, constipation, urgency due to detrusor hyperreflexia, incomplete emptying of the bladder, and/or incontinence. Dysfunction can worsen in association with impaired muscle control, spasticity and cognitive impairment [Crayton & Rossman, 2006]. Similar to other symptoms of MS, there can be a cascading effect, such that bladder dysfunction can cause other serious health conditions, UTIs are much more common due to the dysfunction making treatment more difficult as antibiotics have limitations. Untreated and reoccurring UTIs can put a healthy individual in the hospital let alone someone with a compromised immune system. Aside from the negative health implications it also changes a person's washroom routine; perhaps daily laxatives are needed, catheterization, manual assistance from a caregiver and with that, something that should take a few minutes may now take an hour. To help mitigate the physical discomfort and the emotional strain, surgery can be a solution to some individuals [Crayton & Rossman, 2006].

Temperature dysregulation. For many people with MS temperature regulation is affected and can be quite distressing. Due to the research interest in heat-sensitivity in MS because of its nature of triggering symptoms, it can be forgotten that temperature dysregulation/dysfunction also means cold-sensitivity. While an overwhelming feeling of heat or having a lower threshold in tolerating warmer temperatures is common, it is equally as common for people with MS to be sensitive to the cold [MS Society, 2019; Bobryk, 2016]. As mentioned, most research is focused on heat-sensitivity as it can inhibit one's ability to perform physical activity and exercise by bringing on symptoms.

A study put temperature to the test, exploring pre-cooling to see if it could improve symptoms of heat-sensitivity in persons with MS [Reynolds et al., 2011]. Cooling the head and neck for 60-minutes effectively decreased core temperature by 0.37°C which resulted in improved performance during a 6-minute walk task and timed up-and-go test. Although no significant changes occurred for grip strength, this could still be a safe and effective addition to an exercise regimen for somebody who has MS and is heat-sensitive [Reynolds et al., 2011].

Cognitive and psychological deficits

Aside from the many physical deficits that a person with MS may experience, they may also encounter cognitive and psychological impairments. There is a high prevalence of depression in the MS population, compared to the general population with a lifetime prevalence of approximately 50% and an annual prevalence of 20% [Siegert & Abernethy, 2005]. There are a number of reasons as to why the rate of depression is so high in the MS population including other symptoms such as fatigue or spasms that cause sleep problems, other symptoms altering or inhibiting the completion of daily activities, the location of lesions or from pre-existing cognitive impairments [Siegert & Abernethy, 2005]. Most cases of depression in MS appear to be in the early stages, as the person adjusts to the diagnosis. It also seems to worsen with the accumulation of greater disability, impairment of ambulation, reduced self-care, and clinical relapses [Turner et al., 2016]. The literature around depression in MS is quite extensive but more recently research has shift to explore anxiety in MS. Presently, research suggests that higher levels of anxiety may be associated with longer disease duration and may be more common in SPMS and/or in women with RRMS [Turner et al., 2016; Jones et al., 2012]. With these high rates of mental health problems, a better assessment and management should be investigated to provide greater help to people with MS.

Cognitive deficits involving short-term memory/working memory, new learning, information processing and executive functioning occur in roughly 40% of MS cases but the literature is not clear that it progresses linearly over long-term prognoses [Crayton & Rossman, 2006; Siegert & Abernethy, 2005]. In a study conducted on 200 people with MS, 46% reported cognitive impairment with 34% being memory and 33% being executive functioning problems [Siegert & Abernethy, 2005]. Any degree of cognitive deficits can make daily tasks more challenging and frustrating for the person with MS and possibly their caregiver or spouse. Even simple tasks such as creating a grocery list, using smart phone efficiently, remembering appointments and making decisions may become taxing.

QoL. The motor, sensory, autonomic and cognitive impairments described above may greatly reduce one's independence and in turn, their quality of life [Sadovnick et al., 1996; Mitchell et al., 2005]. Whether the physical/musculoskeletal symptoms are appearing separately or in combination, function can be greatly impacted not only causing inconveniences but, in some cases, a part or full-time caregiver may be needed. Even if little assistance is required, the loss of independence and the stress of letting somebody into your home and training them can take its toll on their mental health. Another aspect that should be noted is with this condition's nature of varying highs and lows and overall progression over time, the impact on health and function changes day to day and year to year. This inconsistency also decreases quality of life. Booking events and appointments ahead of time can be troublesome since it is impossible to predict how severe one's symptoms will be on any given day and time. Many people who have

MS even experience shifts in limitations and capabilities throughout the day. They may feel strong and alert in the morning, become fatigued, weak and incapable of completing usual tasks by mid-afternoon and then regain strength and energy again later in the evening [Ontaneda et al., 2012].

Persons with this neurological disease have shown a strong susceptibility to depression as previously mentioned [Sadovnick et al., 1996, Zwibel, 2009]. The physical impairment that comes with MS and the lack of independence is a key factor in developing depression. In a study conducted in 2009, pain and/or physical impairment which impacts daily activities and quality of life is present in 86% of persons with MS [Zwibel, 2009]. If these symptoms could be mitigated through physical therapy and exercise this may greatly reduce depression and improve overall quality of life [Mitchell et al., 2005; Zwibel, 2009]. For some of the other symptoms such as bladder/bowel dysfunction, cognitive impairment and anxiety other forms of therapy such as cognitive behavioural therapy, and pharmaceuticals may be required to provide relief. Peer support is also key in aiding those with MS and improve their QoL.

Treatments Aimed at Improving Strength and Function After MS

Pharmacological Treatments

The majority of treatments for persons with MS involve disease modifying drug(s) which slow the progression of the disease, lessening the severity of relapses and lengthen remission duration [n.d, 2008]. These immunosuppressant drugs such as corticosteroids and B-Interferons work to stop the T-Cell from crossing the blood brain barrier (BBB) or lessen the degree of which the T-Cells react to the neurons within the brain, limiting the amount of immune response it signals to the system [Naqvi., 2008]. By reducing the immune response this lessens the amount of inflammation and demyelination that occurs thus, reducing the severity of the symptoms. Research is continuingly trying to improve the drug plans for people with MS, to find medicine to help everybody, and better limit the progression of the disease. Still, medications for MS have unwanted side-effects and can be prohibitively expensive and other strategies to improve health and symptoms in the MS-population are needed.

Exercise Rehabilitation After MS

In the early stages of MS, the functional deficits may be relatively simple to manage with the use of specific rehabilitation strategies and some medications [Feinstein, 2015]. Over time the disease changes, and with that overall function does as well. Therefore, the interventions in place should adjust to match the demand. As explained previously, the symptoms can become quite complex as they worsen, or new deficits can arise and impact one another. The treatment should reflect this and take a multi-disciplinary approach with different physicians and therapists who have a long-term perspective opposed to 'quick-fixes' [Feinstein, 2015]. For the purpose of improving strength and function it may be most effective to use physical therapy as the primary strategy. Physical rehabilitation includes many specialized facets including, massage, physiotherapy, chiropractic treatments, osteopathy and exercise. The rehabilitation and treatment prescription for MS has changed greatly over the last several decades. One of the biggest changes concerning recommendations for physical therapy is the attitude towards exercise and rehabilitation, and some controversy as to how to prescribe exercise to people with MS still exists today. Although exercise is beneficial in creating a healthy lifestyle, those with MS were traditionally discouraged from participating in exercise for fear of aggravating their symptoms [Dalgas, 2011]. As mentioned in the previous section, heat impacts those with MS to a greater extent than able-bodied persons, and traditional dogma stated that exercise-induced increases in body temperature may trigger relapses in individuals with MS. Exercise was not recommended as a treatment tool until after 1937 because many physicians thought that visual impairment and paresis would likely occur during exercise due to a dysautonomia, resulting from temperature dysregulation [Doring et al., 2012]. Exercise was also thought to be a 'waste' of energy and may increase fatigue, nerve pain or cognitive impairments, thus further reducing the ability to complete ADL. This theory is known as Uhthoff's phenomenon and 60-80% of the MS population do experience temporary worsening of neurological symptoms when body temperature is elevated [Davis et al., 2010; Doring et al., 2012]. However, this does not mean that all physical activity should be completely eliminated from the lives of persons with MS.

Presently, exercise is commonly suggested as a form of treatment for those with MS, albeit a few modifications and safety consideration may be needed. As mentioned previously, muscle weakness after MS is due, in part, to poor transmission of nerve impulses, and thus, resistance movements completed to exhaustion may fatigue the nerve further and not provoke muscle growth [Schapiro & Schapiro, 2003]. Luckily, there are many forms of exercise and modifications that can be made for each individual. Exercising through the style of yoga, aerobic training, HITT or resistance training may be effective exercise for persons with MS [Oken et al., 2004; Sampson et al., 2015; Filipi et al., 2011].

In a six-month study, participating in either a yoga or aerobic cycling class significantly improved measures of energy and fatigue on the multidimensional fatigue inventory (MFI) and profile of mood states (POMS) compared to an inactive control group [Oken et al., 2004]. The yoga classes were 90-minutes long, 19 poses were performed once a week, and the aerobic cycling classes followed a similar format. The initial and final 5-minutes consisted of stretching, and participants were instructed to exercise at a 2-3 on the 10-point Borg scale of ratings of perceived exertion (RPE) and continue cycling until they were fatigued, felt onset of symptoms or reached their personal goal (1hr for most subjects). Occasionally, the cycling group were required to add some arm, trunk and balance work during the session. Significant improvements were seen in the yoga and the cycling groups in general fatigue (14.7 to 13.0 for yoga and 13.2 to 12.1 for cycling) and energy (43.1 to 51.2 for yoga and 45.7 to 52.8 for cycling). The yoga only group also experienced improvements in health transition reducing their score from a 42.9 to 35.7. Mental health also improved in the cycling only group as their score increased from a 79.2 to 83.7. Many studies have examined the effectiveness of using yoga as a management strategy for MS symptoms including pain, mental health, fatigue, spasticity and balance [Frank & Elarimore, 2015]. From interventions ranging from 8-weeks to 6-months in duration most have found improvement in either energy or reduced fatigue, improved mood/mental health, quality of life and some improved balance or gait [Guner & Inanici, 2015; Frank & Elarimore, 2015, Grossman et al., 2010]. However, several studies have found that there is cognitive benefit, there is not strong evidence that yoga can improve physical or functional deficits [Salgado et al., 2013; Garrett et al., 2012]. As a rehabilitation strategy, yoga may work most effectively when partnered with another form of exercise that elicits physical adaptations that work to minimize functional deficits.

Resistance training has been a staple exercise regimen for decades in the general population and in more recent years, it has been effectively implemented in rehabilitation plans for those with MS. Filipi and colleagues found that people with MS of varying disabilities benefitted from a 6-month standardized whole body resistance training program [Filipi et al., 2011]. Participants exercised for 50 minutes twice per week focusing on strength development in lower body, upper body, trunk and balance, and unilateral exercises were also presented in the later stages of the training. Improvement was seen in all exercises based on resistance/weight used during sessions except for the participants with the most severe disability (EDSS 7.5-9) in the abdominal crunches due to unknown reasons. The majority of resistance training studies ranging from 3 weeks to 5 months show muscular strength improvements as measured by MVC, EMG, 1RMs, or rate of fatigue in men and women with varying severities of MS [Kjolhede et al., 2012; Taylor et al., 2006; Dodd et al., 2011; Dalgas, 2011]. Depending on the length and intensity of the program, changes of 7%-21% knee extensor MVCs, 14% 1RM arm press or 10%-22% peak knee flexor torque can be seen [Taylor et al., 2006; Dodd et al., 2011; Dalgas, 2011]. Self reported fatigue has improved in progressive resistance training studies as well as depression assessments but there are conflicting results in mood or quality of life [Dalgas, 2011; Sabapathy et al., 2010, Dodd et al., 2011]. Lastly, gait performance shows mixed findings following strength training. Improvement has been seen in the timed up and go test (TUG) ranging from 8%-13%, as well as the stair climb test (SCT), and chair stand test (CST) with 12% and 28% increases respectively [Taylor et al., 2006; Dalgas, 2011 DeBolt & McCubbin, 2004; Sabapathy et al., 2010]. However, these tests rely more on strength during short duration compared to longer and more gait-focused tests such as 2- or 6-minute walk tests, timed 25-foot walk test, and 10-minute walk test which show conflicting results from a number of different progressive resistance training studies [Dodd et al., 2011, Filipi, 2011; Taylor et al., 2006; Broekmans et al., 2011]. Progressive resistance training is an effective form of exercise and has a place in MS rehabilitation to improve muscle strength, but, more research is needed to clarify the other functional benefits it may consistently provide.

Another traditional form of exercise commonly used is aerobic training. This form as also been seen to be beneficial to the MS population. In a 15-week intervention conducted by Gappmaier and colleagues (year), 17 participants with MS performed arm/leg ergometry 3 times/week for 40 minutes. VO_{2PEAK}, HR_{PEAK}, peak work rate, as well as functional measures including the Timed get-up and go (TUG), 6-min-walk test (6MWT), Stair climbing test (ST) and tests of balance [Functional reach (FR) and Berg balance test (BBT)] were measured before and after the exercise training program. Increases in VO_{2PEAK} (18%), peak work rate (25%), as well as an improvement in TUG (-18%), and ST (-20%) were seen [Gappmaier et al., 2005]. However, FR and BBT scores and 6MWT distance remained unchanged following the exercise training. Skjerkbaek and colleagues took a slightly different approach and had 6 individuals with MS perform 10 upper-body endurance interval training sessions across 4-weeks while 5 individuals with MS performed more traditional rehabilitation that was individualized with a specialized multidisciplinary team [Skjerbaek et al., 2014]. The upper body exercises included arm-ergometry and arm/leg ergometry that consisted of a hybrid interval workout; 6 3-minute intervals (65-75% VO_{2peak}) were performed with maximal sprints (30-60sec) performed at the end of each 3-minute intervals. The exercise group showed improvement in VO_{2peak} (pre: 645, post: 950ml O_2/min), a reduction of 13.2 and 6.2 points on the MS impact scale and major depression inventory respectively, and no changes were seen in the rehab group [Skjerbaek et al., 2014]. Aside from physical adaptation, some studies have used aerobic training in the form of walking, recreational sports, or arm/leg cycles to help mitigate cognitive impairment and fatigue in those with MS with varying degrees of disability [Guyot et al., 2012, Chenet et al., 2016]. As shown, aerobic training improves many cardiovascular and fitness measures, but this form of exercise does little to no good for upper limb function.

Research involving high intensity interval training (HIIT) as exercise has shown promise in being a suitable alternative as it avoids triggering thermosensitivity [Campbell et al., 2018; Dalgas, 2011]. Due to the nature of high intensity training, both aerobic and strength capacity can be challenged. In a study by Zaenker and colleagues (2016), participants completed an 8-week program with the initial 4 weeks involving one aerobic-interval cycling session and one session of muscular strengthening, and in the remaining 4 weeks participants added one other session of their choice [Zaenker et al., 2016]. Results showed muscle strength increases in quadriceps and hamstrings by 10% at varying speeds. Other improvements included increases in VO_{2peak} and maximal tolerated power by 13.5% and 9.4%, and the SEP-59 self-questionnaire showed an improvement in vitality, emotional and general well-being [Zaenker et al., 2016]. An 8-week program with 40 people with MS compared HITT to moderate continuous endurance training in the form of cycling 3 times/week for 30 minutes [Wonneberger & Schmidt, 2019]. A few different assessments were completed, including, VO_{2peak}, ambulation as measured by the 25-foot walk test (T25-FWT) and fatigue based on the fatigue severity scale (FSS). Only the HIIT group showed significant improvements in VO_{2peak} (pre: 26.7, post: 29.7ml/min/kg), and no change was seen in T25-FWT or FSS from either group [Wonneberger & Schmidt, 2019]. More research needs to be done to further investigate the amount of improvement that can be achieved through HITT although improvements in upper limb function are unlikely with this form of exercise.

Although these various forms of exercise can elicit cardiovascular, muscle strength, overall health and fitness improvements, in some cases improvement in cognitive symptoms or even gait, they do little for function of the arms and hands required for ADL, even in the few training programs that incorporated upper-body exercise.

Functional Electrical Stimulation (FES) After MS

Functional Electrical Stimulation (FES) was first used as a rehabilitative treatment in the 1960's to correct drop foot [Melo et al., 2014]. This technique involves placing adhesive electrodes over top of the muscles, which are in turn, connected by a set of leads/cables to the FES machine. Small amounts of electrical current (approximately 5-140mA) are then sent to the electrodes, which go on to stimulate peripheral nerves, resulting in involuntary muscle contractions.

The primary purpose of FES is to help minimize muscle atrophy and promote muscle hypertrophy. Other benefits include improved circulation and decreased spasticity [MS Trust, 2018; Daly et al., 1996]. This technique stimulates the muscle using surface electrodes, enabling a bypass of the central nervous system. By stimulating the muscle fibers through the peripheral nerves, persons with a damaged CNS can achieve muscle contractions and movement [MS Trust, 2018; Daly et al., 1996].

FES has been used as a rehabilitation technique for several decades; initially in those who have had a stroke and those with a spinal cord injury. Over time this technique has been adapted to training and rehabilitation for those with MS [MS Trust, 2018]. There have been several studies showing the benefits of FES cycling in those with MS [Edwards et al., 2018; Chang et al., 2011; Street et al., 2015]. In a study conducted by Edwards et al 2018, eleven participants with MS were randomly allocated to FES cycling exercise or passive leg cycling three times per week for 24 weeks [Edwards et al., 2018]. A number of tests were performed pre and post intervention including, Timed-25-Foot Walk (T25FW), Timed up and Go (TUG), 2-Minute Walk test (2MW) and the 12-Item MS Walking Scale (MSWS-12). Walking speed, endurance, as well as peak knee flexion and extension forces were also measured before and after the intervention [Edwards et al., 2018]. Results showed that the FES training elicited clinically significant improvements in walking speed during the T25FW (0.15m/s or 22.9% increase after FES compared to no change in the control group) as well walking endurance during the 2-minute walk test (27m or 11.7% increase compared to the control group). Improvements were also seen in VO_{2peak} (13.8%) and WR_{peak} (15.3%) as well as knee extensor strength (21Nm a 22.7% increase) [Edwards et al., 2018].

Central fatigue is a primary limitation in daily life for those with MS. An eight-week FES training regimen of the quadriceps resulted in a reduction of general, central fatigue as well as a slight increase in knee extensor maximal contraction strength [Chang et al., 2011]. Initially maximal and supramaximal quadricep contraction was tested. Then the participants completed an at-home training protocol for eight weeks, three days per week, 30 minutes each session. The stimulation steadily increased for the first two weeks until it elicited 40% of MVC and then this intensity was used for the remainder of the intervention.

Another study by Street and colleagues in 2015 used FES over the peroneal nerve, at the fibular head or the popliteal fossa, and over the motor point of the tibialis anterior on 187 (falling to 166 after 20wks) individuals with MS [Street et al., 2015]. Participants used FES during walking for 20 weeks to mitigate foot drop. The result of the study demonstrated significant improvement in walking speed during a 10m walking test from 0.07m/s to 0.11m/s, a 27% improvement. This improvement exceeds the threshold required for clinical relevance of 0.05m/s. The intervention also reduced the physiological cost of walking [Street et al., 2015; Krause et al., 2007]. Improving walking function to a clinically relevant degree allows individuals to experience daily life with more independence. If clinical significance can be achieved via FES for gait, a similar FES protocol targeting one's hands and arms may also yield clinical significance in completing activities of daily living. This hypothesis has been demonstrated several times with persons who have suffered a stroke or SCI [Venugopalan et al., 2015; Kutlu et al., 2017; Patil et al., 2015].

A small study using FES on the upper limb had two participant groups, a SCI group and a Stroke group. Persons with SCI received 5 consecutive sessions (1 hour long) of FES treatment on the hand and forearm during a reach and grasp task [Hodkin et al., 2018]. Persons who suffered a stroke received FES treatment, 1-hour long on the triceps for 9-10 days. Both groups benefited from the stimulation and improved their Action Research Arm Test (ARAT) score to an average of 22 (+8 points) and 30.85 (+3.4 points) out of 57, for the stroke and SCI, groups respectively [Hodkin et al., 2018]. This demonstrates that even after a short period of time, functional improvements can be seen when using FES in these populations.

Recently, studies are beginning to examine the effects of FES after MS [Kutlu et al., 2017; Sampson et al., 2015]. A study conducted in 2016, analyzed the effects FES combined with passive robotic support during a reaching task [Sampson et al., 2015]. Persons with MS took part in a 10-week intervention that consisted of 18, 1-hour sessions with 18-33minutes of actual stimulation. Tracking accuracy and percent of maximal stimulation were measured throughout each session. There was an average tracking improvement of 12.8% and 23.6% for the elbow and shoulder, respectively [Sampson et al., 2015]. A reduction of 49.2% and 48.8% of maximal stimulation required to effectively complete the task on the elbow and shoulder, respectively, were seen. Both of these measures suggest that the participants were gradually becoming more efficient in successfully completing the reach tasks. The result of the many studies with persons with a SCI, paraplegia or tetraplegia, or suffering from a stroke, suggest that using FES on the upper limbs of persons with MS may elicit similar functional benefits.

Mechanisms underlying improvements with FES therapy

There are both peripheral and central mechanisms responsible for the positive effects of FES. The peripheral mechanisms include improvements in muscle mass, increased blood flow and reduced spasticity [Sujith, 2008]. Research has also shown an improvement in energy exchange allowing for improved oxygen transport within the stimulated tissues through FES [Daly et al., 1996]. The primary central changes that provide benefit include cortical reorganization and neuronal plasticity [Sujith, 2008]. Since FES utilizes surface electrodes the stimuli activate both motor and sensory nerve fibers, attributing to the change or modification of cortical connectivity [Daly et al., 1996]. Possible nerve regeneration, neuroplasticity, enhanced delivery and secretion of tropic factors have also been proposed mechanisms of FES-induced central changes. Nerve regeneration using FES has been successful in animal studies [Daly et al., 1996]. In a study using rabbits, further insight in nerve regeneration by stimulation was collected and the recovery may be due to nerve regrowth or functional connections being established [Nix & Hopf, 1983]. Electrical stimulation has been shown to promote remyelination of nerve fibres, and thus, the repeated muscle contractions associated with FES exercise may enhance peripheral nerve transmission and muscle strength [Nix & Hopf, 1983]. The mechanism behind FES-induced remyelination is not fully understood and requires more research however, electrical stimulation has shown to increase protein metabolism of nerve cells which is assumed to aid in the maintenance of myelin and improved motor activity [Nix & Hopf, 1983]. A more recent article published in 2019, has concluded that electrical stimulation promotes neural stem cell (NSC) development and growth [Zhu et al., 2019]. Since biophysical changes can be triggered at the cell surface, membrane proteins such as enzymes, membrane receptor complexes and ion-transporting channels are affected through altering charge distribution with FES. Electrical stimulation has been shown to play a role in each stage of a neural stem cell's life, including migration, proliferation, alignment and differentiation; the most significant effect being during migration and differentiation [Zhu et al., 2019]. Electrical stimulation encourages NSCs to migrate to the injured site and induce neurogenesis as well as neurite outgrowth and orientation [Zhu et al., 2019].

The mechanisms outlined above have been shown to account for the FES-induced functional improvements in animals [Daly et al., 1996] and individuals who have suffered a stroke, SCI or traumatic brain injury [Edwards et al., 2018]. The peripheral adaptations mentioned above have also been seen in persons with MS, however, more research is required to confirm whether or not the central mechanisms are also experienced.

Purpose and Hypothesis

Statement of Purpose

The purpose of this study is to investigate the effects of a ten-week unilateral FES training intervention on upper limb strength and function, in the exercised limb compared to the control limb, in individuals with MS.

Hypotheses

I predicted that there would be functional improvement in the exercise trained limb only due to enhancement of muscle strength and neural adaptation, as demonstrated by improved scores of the Sollermans test, the Grasp and Release Test (GRT), the Capabilities of Upper Extremity Instrument (CUE) and the haptic wrist device tasks.

Overview of Study Design

Study Design and Participants

Participant recruitment occurred between November 2019 and January 2020. The study included three exercise sessions per week for ten weeks. Testing sessions were conducted prior to beginning the 10-week protocol and at least 24-72 hours after each participant's final exercise session, and each phase of testing (pre, post) required two visits 24-48 hours apart. Participants with a chronic MS of varying severity were recruited from the Brock-Niagara Centre for Health and Well-Being, Power Cord exercise program. Inclusion criteria included (1) relapsing-remitting or secondary progressive MS with an EDSS between 3-9 (Kurtzke Expanded Disability Status Score), (2) at least 1-year post diagnosis. Exclusion criteria included (1) unstable medical condition within 2 weeks prior to testing, (2) had been performing upper body exercises on the Xcite <8wks prior to pre-testing.

Five individuals, (4 females, 1 male) age 58.4 ±7.9 years with chronic MS (12-41) years post-diagnosis, EDSS (3.0-7.0) were recruited for participation in the study. Participant 5 was not able to complete two of the three post-testing sections (functional tests and haptic wrist device tasks) due to COVID-19, questionnaires were completed via phone call. The study received ethical approval from the Brock University Research Ethics Board (File No. 19-103 – DITOR/HOLMES). All data was collected on-site at Brock University and the Brock-Niagara Center for Health and Well-Being.

Prior to the first session, each participant was briefed on the workings of the Xcite machine and the testing and training requirements of the study by reading and signing informed consent and verbal explanation.

Table 1: Participant Characteristics

Type of MS	EDSS	SEX	AGE (YEARS)	TIME POST-DIAGNOSIS (YEARS)	TRAINED HAND/ARM
RRMS	3.0	F	45	12	L
RRMS	7.0	F	66	32	L
SPMS	6.5	F	60	29	L
SPMS	6.0	M	59	37	R*
RRMS	6.5	F	62	41	R
AVG ± SD	**5.8 ±1.6**		**58.4 ±7.9**	**30.2 ±11.17**	

*Participant 4 is right-handed, but has greater impairment in his right hand due to MS

Testing Session 1

The first testing session included two measures of grip strength using a hand dynamometer (*Jamar® Smart*) and two tasks completed on the haptic wrist device. All tests were performed on both hands and took approximately 35 minutes in duration. Once the participant was familiar with the tests the session began. First, palmar grip strength was measured. Participants held the dynamometer's handles with their whole hand, fingers around one handle and thumb around the other, then they squeezed their hand into a fist as hard as possible. Two trials were completed on both hands with 1.5 minutes of rest between each trial. Second, tip pinch grip strength was measured. In this test participants held the dynamometer using the tips of their fingers on one handle and the tip of their thumb on the other then squeezed as hard as possible, imagining pinching a piece of paper. Two trials were completed on both hands with 1.5 minutes of rest between each trial and the average of the two attempts (for each hand) was recorded as the maximum grip strength. Both forms of grip strength were conducted in a seated position with arm down at their side since not all participants were able to confidently complete the task standing. Note that for each participant the hand dynamometer handle was set according to the size of their hand, the lower handle should lay across their proximal interphalangeal joints while the upper handle lay across their palm.

Next, participants were seated in front of the haptic wrist device (WristBot, Genoa, Italy) with their forearm placed on the arm plate, so their hand was grasping the handle in a neutral position, see appendix D for images of testing setup. The first task on the haptic wrist device was *active tracking*, in which the participant traced a figure 8 shape on the monitor by tracking a dot as it moved around the shape. Participants were asked to follow the dot to the best of their abilities using their hand/wrist strength. The figure 8 shape allows the wrist to move in flexion, extension, radial and ulnar directions. The target dot moved at +/-25 degrees per second in flexion/extension and +/- 45 degrees in radial/ulnar. The target moved at a mean speed of 8.6 degrees per second and took 20 seconds to complete one repetition. Participants were asked to perform 2 repetitions of the completed shape for 3 separate rounds with 1.5 minutes of rest in between. The first round of 2 laps were used as familiarization and therefore omitted from the results. The haptic device recorded the 2D position of the participant's target, in relation to the desired target. The accuracy of each trial was determined by calculating the magnitude of error in degrees between the participants target location and the desired/optimal location (+/-
). Performance was measured in two ways, tracking error and figural error. Tracking error measures the displacement between the target and the participant over the course of the trial, whereas figural error assesses accuracy, measuring the participant's ability to recreate the target path/shape during the trial.

Lastly, a proprioception test on the haptic wrist device was conducted. The device moved the participants' hands to a predetermined wrist joint angle, held it for 3 seconds and then returned the participant to the starting (neutral) position. The participant was then asked to move the device (exerting muscle activity and effort) to the position that the device previously completed. Participants had their eyes closed during the trials and were in a quiet room. This proprioception task includes moving the hand into wrist flexion and extension only. Participants performed 12 repetitions of each target at an angle of 25° +/- 1°, with the robot positioning the hand at a speed of 15° per second during the passive trials. All wrist joint angles were randomized. Two measures of performance were calculated; matching error and error bias. Matching error can be thought of as absolute error, as it is the angular deviation from the target, measuring accuracy during the activity, whereas error bias also considered the direction of the error, over or under shooting the target (leftward being negative and rightward being positive).

Both haptic wrist device tasks were performed on both hands. It should also be noted that the following joint angles were measured on both sides to allow for a similar body position during post testing, elbow flexion, shoulder abduction, shoulder flexion and shoulder lateral rotation.

Testing Session 2

Between 24 and 48-hours after the completion of Session 1, participants attended a second testing session to perform a set of functional tests and questionnaires. First, participants performed the Sollerman Hand Function Test which involved both hands. This test involved completing 20 tasks testing functional grip that is commonly used in daily living. The tasks required the participant to use a number of different hand grips such as, palmar, pulp pinch, lateral pinch, tripod, five-finger pinch, diagonal volar, transverse volar grip and extension grip. Many of the tasks have been mounted to a wooden box (Appendix E, Fig. 5) for ease of test administration. The subtests include using a Yale lock, picking up coins off a flat surface, zipping a coin purse, lifting small wooden blocks, lifting an iron, using a screwdriver, picking up nuts, unscrewing a jar lid, doing up buttons, cutting Play-Doh with a knife and fork, writing with a pen, folding a piece of paper and placing in an envelope, using a paperclip, lifting telephone to ear, turning a door handle 30°, pouring water from a jug and from a cup. These tasks were performed in a seated position with the test box on a table directly in front of them. The tasks were completed consecutively, in a specific order with minimal rest in between. The participants received a brief description of the task before attempting it. Seventeen of the twenty subtests are done with a single hand, and the remaining three were completed with both hands. Each task had a time limit of one minute to complete and the participant was scored on a scale of 0-4, based on their ability to complete the tasks. The guidelines/order of subtests, scoring and depiction of the test kit can be found in appendix D. After completing the Sollerman test with either hand they completed the Capabilities of Upper Extremity Instrument (CUE) questionnaire.

The CUE is a questionnaire that focuses on the individuals' ability to reach or lift, pull and push with their arms, move their wrists and use their hands and fingers. There are 32 questions, most regarding unilateral function and some regarding bilateral function. Each question was answered using a 7-point scale representing self-perceived ability to perform the action (1-unable to perform, 7-can perform without difficulty). The responses were summed into a total score and a percent of normal function score was calculated, using the equation (total score – 32)/192 X 100%. Left and right hands/arm function were analyzed separately.

Next, the Functional Independence Measure (FIM) was completed. The FIM is a questionnaire which assesses various activities of daily living (ADL) in a person's life including self-care, bowel management, locomotion, transfers and cognition on a 7-point scale. For the purpose of the current study, only the self-care section of the questionnaire was assessed. This section assesses the independence of the person when doing the following: eating, grooming, bathing, dressing-upper body, dressing-lower body and toileting. The responses were summed into a total score and assessed.

Lastly, a final functional test was performed. The Grasp and Release Test (GRT) is another functional assessment to measure hand capabilities. There are six objects that the participant was asked to pick up (using a palmar or lateral grasp), move and release with each hand, one at a time. The objects included, a peg, paper weight, fork, block, can and videotape. These objects were chosen to represent one or more objects commonly used for ADL. The participant was scored based on how many times they were able to pick up, move and release the object within 30 seconds, (mean number of successful completions and mean number of failures performed in 30 seconds, for each object over 3 trials). If a subject fails to move an item, they score zero for that particular item.

Training Sessions

The Xcite iFES Clinical Station by Restorative Therapies or the 'Xcite' utilizes FES as a method of active therapy that coordinates electrical stimulation of peripheral nerves resulting in FES induced functional tasks of the upper limbs, lower limbs and full body. The Xcite comes preloaded with a therapy program library stored on the stimulator. All tasks are preprogramed with default values, coordinated patterns and the ideal muscles to be used to complete that task. However, all tasks can be personalized to fit the user's needs and goals. One can adjust stimulation strength, add/remove stimulated muscles, add pauses during a task and slow down or speed up the entire movement of any task. The order in which muscles contract or the specific grade and rate of stimulation being sent cannot be changed. These parameters are permanently set by software to ensure smooth and fluid movements are made for every functional task. This device uses the same principles as traditional FES machines, using surface electrodes that connect to leads of the stimulator control panel.

Participants completed a 10-week training program with the Xcite machine. There were 3 sessions per week, with every session involving four upper limb exercises that were performed by the non-dominant (affected) hand/arm, allowing the dominant hand/arm to serve as a control. The exercises were performed in the same sequence each session as follows: feeding, forward reach and grasp, opposition and lumbrical grasp. Electrode placement for the four Xcite exercises can be found in Appendix F. The participants completed two sets of 20-30 reps of each task every session, depending on stimulation levels and stage of the participant's progression, taking approximately 50 minutes including set-up and rest. A profile was then set up on the Xcite where their exercises were stored. Prior to the first training session each participant went through the four exercises and had each muscle/muscle group involved in the task tested to determine the appropriate stimulation intensity required to perform the task or as tolerated (ranging from 8 to 80mA, depending on stimulation tolerance). The pulse width for every task for every participant was 250μs and the pulse frequency was 40Hz. Other alterations such as the overall speed of each task and audio cues were made as needed with each participant. If the participant required manual assistance to complete full range of motion of the exercise it was provided each session as needed. After all the stimulation levels were set and saved to the participant's program, they began their training, completing the previously specified repetitions and sets for all four exercises.

Individualized programs and alterations were allowed, to yield the most benefit for each participant. As the participant advanced through the ten weeks, training was progressed by increasing the stimulation intensity, as individually tolerated, every other session (as needed to achieve full muscle contraction and joint excursion). For example, the intensity may have been increased by 2 mA over the extensor digitorum muscle, in order to achieve greater range in wrist and finger extension to open the hand. In addition, training was progressed by increasing repetitions (by 2) every 2-3 sessions, adjusting the speed of the task to make it comfortable and functional for the participant as was well as decreasing any manual assistance that was provided. Each participant had their own set of electrodes for their exercises, and program adherence was tracked and reported by the student investigator.

Results

Participant 1

Participant 1 completed 8 weeks of training with the Xcite, 23 sessions in total.

Strength Tests:

Grip Strength

Palmer grasp and tip pinch were measured pre and post training for both the trained (non-dominant) and control (dominant) hands. Participant 1 showed a small reduction in grip strength for the palmer grasp in both hands. The trained hand showed a reduction from 22.2kg at pre-testing to 18.2kg after the 8 weeks of training, while the control hand showed a reduction from 23.8kg at pre-testing to 19.5kg at post-testing. In contrast, tip pinch strength increased in the trained hand from 8.8kg at pre-testing to 9.1kg after the 8-week FES program, while tip pinch strength in the control hand decreased from 10.3kg at pre-testing to 8.8kg at post-testing.

Functional Tests:

Sollermans Hand Function Test (SHFT)

Participant 1 showed a one-point improvement on the SHFT (from 75/80 to 76/80) following the 8-week training program in the trained limb, with no change in the control limb (78/80 at pre and post-testing).

Grasp and Release Test

The following table shows the number of successes and the number of failures for each of the six tasks at pre and post-testing for both the trained (non-dominant) and control (dominant) hands. The number of successes increased, but number of fails also increased for some of the tasks, likely due to the overall increased number of grasps. Improvement in number of successes were seen in all six objects, and a mix of improvement and decline in number of fails was also seen across the six objects, likely due to the great increase number of grasps. When successes and failures are expressed as a percent of the total number of grasps, the only increase is in the fork in the trained hand. A similar pattern was seen in the control hand, increases were present in the weight and the fork. When trials were averaged across the six items it appears there was improvement in successes in both hands but the opposite is present when the data is taken as a percent.

Table 2.0a *Grasp and Release Data*

	Trained				**Control**			
	Pre-testing		**Post-testing**		**Pre-testing**		**Post-testing**	
	Successes	**Failures**	**Successes**	**Failures**	**Successes**	**Failures**	**Successes**	**Failures**
Peg	28.5	0	61	4	34	1	60	2.5
Weight	48.5	1	50.5	6	50.5	0	55.5	0.5
Fork	34.5	1.5	44	0.5	33	1	43.5	0
Block	46.5	2.5	96	2.5	51	1	88.5	2
Can	47.5	2	76.5	6.5	53	1.5	86.5	5.5
Tape	55.5	0	86	5.5	56	0.5	84	5.5
AVG	43.5	1.2	69	4.2	46.3	0.8	69.7	2.7

Table 2.0b *Grasp and Release Data as a percent*

	Trained				Control			
	Pre-testing		Post-testing		Pre-testing		Post-testing	
	Successes	Failures	Successes	Failures	Successes	Failures	Successes	Failures
Peg	98.9%	1.1%	95.3%	4.7%	97.1%	2.9%	96.6%	5.4%
Weight	95.9%	4.1%	90.9%	9.9%	98.1%	1.9%	99.5%	0.5%
Fork	94.6%	5.4%	99.3%	0.7%	96.7%	3.3%	100%	0%
Block	98.6%	1.4%	97.5%	2.5%	100%	0%	98.4%	1.6%
Can	97.4%	2.6%	92.7%	7.3%	98.1%	1.9%	95.8%	4.2%
Tape	99.4%	0.6%	93.7%	6.3%	99.5%	0.5%	93.8%	6.2%
AVG	97.5%	2.5%	94.9%	5.2%	98.3%	1.8%	97.4%	2.9%

Functional Questionnaires:

Capabilities of Upper Extremity (CUE) Instrument

The CUE ranges in total score from 32-244 and percent of normal function score can be calculated as well. The trained (non-dominant) limb showed a small increase in total score and normality, from 104 to 109, and from 37.5% to 40.1%, respectively after the 8 weeks of training. A small decrease was seen in the control (dominant) limb, which went from a total CUE score of 110 (40.6% normality) at pre-testing, to a total CUE score of 108 (39.6% normality) at post-testing.

Functional Independence Measure (FIM)

Only the self-care portion of the FIM was used for the purpose of the study, 42 being the highest possible score achievable. Also, questions were answered based on the participant's ability to use both hands together, not individually. Participant 1 showed no change before and after the 8-week program for the self-care portion of the FIM, scoring a 42 on both tests.

Haptic Wrist Device:

Tracking

For this task participants completed 2 rounds of 2 laps of the figure-8 track. Tracking error and figural error were calculated for each of the 2 rounds and an average was taken. Tracking error measures the displacement between the target and the participant over the course of the trial, whereas figural error assesses accuracy, measuring the participant's ability to recreate the target path/shape during the trial. For both of these measures, error values closer to zero demonstrated greater accuracy of the participant's tracking abilities. The table below displays the averages and standard deviations at pre- and post-testing for the trained (non-dominant) and control (dominant) limb.

For the trained limb a decline in performance was seen in the tracking task as demonstrated by an increased tracking error by 0.38 and figural error by 0.09 from pre to post-testing. A similar decline was also present in the control limb, tracking error increased by 0.5 and figural error by 0.28 from pre to post-testing.

Table 2.1 *Tracking task error values*

	Trained				**Control**			
	Pre-testing		**Post-testing**		**Pre-testing**		**Post-testing**	
	Tracking	**Figural**	**Tracking**	**Figural**	**Tracking**	**Figural**	**Tracking**	**Figural**
Avg(°)	1.26	0.63	1.64	0.72	1.26	0.71	1.76	0.99
SD	0.23	0.003	0.04	0.06	0.1	0.1	0.01	0.002

Proprioception

The proprioception task involved 12 continual attempts to replicate various wrist angles produced by the haptic wrist robot. The table below displays the two types of error used to measure performance in this task. For both types of error, zero shows perfect performance, a positive number shows error towards the right and a negative number shows error towards the left. Due to the increase in values across both error types in extension and flexion we can conclude that no improvement was seen pre- and post-testing in either the trained or control limb.

Table 2.2 *Proprioception task error values*

	Trained				Control			
	Pre-testing		**Post-testing**		**Pre-testing**		**Post-testing**	
	Matching	**Error Bias**	**Matching**	**Error Bias**	**Matching**	**Error Bias**	**Matching**	**Error Bias**
Extension	3.48	-2.42	4.84	4.84	4.64	-3.70	5.05	-4.06
Flexion	3.84	0.74	6.12	4.17	6.77	-4.78	4.89	0.03

Participant 2

Participant 2 completed the full 10 weeks of training with the Xcite, 30 sessions in total.

Strength Tests:

Grip Strength

Palmer grasp and tip pinch were measured pre and post training for both the trained (non-dominant) and control (dominant) hands. Participant 2 showed improvement in grip strength for the palmer grasp in both hands. The trained hand showed an improvement from 5.1kg at pre-testing to 7.3kg after the 10 weeks of training, while the control hand showed an increase from 14.2kg at pre-testing to 15.6kg at post-testing. Tip pinch strength also increased in both hands. The trained hand improved from 1.7kg at pre-testing to 2.1kg after the 10-week FES program, and the control hand increased from 3.9kg at pre-testing to 5.5kg at post-testing.

Functional Tests:

Sollermans Hand Function Test (SHFT)

Participant 2 showed a two-point improvement on the SHFT (from 11/80 to 13/80) following the 10-week training program in the trained limb, with only a one-point change in the control limb (from 47/80 to 48/80).

Grasp and Release Test

The following table shows the number of successes and the number of failures for each of the six tasks at pre- and post-testing for both the trained (non-dominant) and control (dominant) hands. Number of successes increased, and the number of fails decreased in all six tasks, showing an improvement in the trained hand. In the control hand, there was a decline in the number of successes in four of the six tasks, and a small improvement in two tasks most of which were not meaningful changes. There was an improvement in number of fails in two objects and no change in the other four items. This holds true when assessing the successes and fails as a percent of the total number of grasps.

Table 3.0a *Grasp and Release Data*

	Trained				**Control**			
	Pre-testing		**Post-testing**		**Pre-testing**		**Post-testing**	
	Successes	**Failures**	**Successes**	**Failures**	**Successes**	**Failures**	**Successes**	**Failures**
Peg	0	1	2.5	0	6	1	8	0.5
Weight	0	1	1	0	8.5	0	11.5	0
Fork	1.5	1	6	0	6	0	5	0
Block	0.5	1	0.5	0	9	0	6.5	0
Can	0	1	0.5	0.5	7	1.5	5	0
Tape	0	1	0.5	0.5	8.5	1.5	7.5	0.5
AVG	0.3	1	1.8	0.2	7.5	0.7	7.3	0.2

Table 3.0b *Grasp and Release Data as a Percent*

	Trained				Control			
	Pre-testing		Post-testing		Pre-testing		Post-testing	
	Successes	Failures	Successes	Failures	Successes	Failures	Successes	Failures
Peg	0%	100%	100%	0%	85.7%	14.3%	94.1%	5.9%
Weight	0%	100%	100%	0%	100%	0%	100%	0%
Fork	60%	40%	100%	0%	100%	0%	100%	0%
Block	33.3%	66.7%	100%	0%	100%	0%	100%	0%
Can	0%	100%	50%	50%	82.4%	17.6%	100%	0%
Tape	0%	100%	50%	50%	85%	15%	93.8%	6.2%
AVG	15.5%	84.5%	83.3%	16.7%	92.2%	7.8%	98%	2%

Functional Questionnaires:

Capabilities of Upper Extremity (CUE) Instrument

The CUE ranges in total score from 32-244 and percent of normal function score can be calculated as well. The trained (non-dominant) limb showed virtually no change in total score and normality, from 33 to 31, and from 37.5% to 40.1%, respectively after the 10 weeks of training. A similar lack of effect was also seen in the control (dominant) limb, which went from a total CUE score of 81 (25.5% normality) at pre-testing, to a total CUE score of 78 (23.9% normality) at post-testing.

Functional Independence Measure (FIM)

Only the self-care portion of the FIM was used for the purpose of the study, 42 being the highest possible score achievable. Also, questions were answered based on the participant's ability to use both hands together, not individually. Participant 2 demonstrated a two-point change after the 10-week program, scoring 17 on the pre-test then 19 on the post-test.

Haptic Wrist Device:

Tracking

Participant 2 experienced great difficulty in completing the tracking task with the trained limb as demonstrated by the great tracking and figural error value however, there was improvement seen. Figural error improved by 2.31 from pre- and post-testing. Tracking error improved by 4.6 but this is not a meaningful change due to the high intra-individual variability recorded. The control limb demonstrated a decline in performance from pre to post-testing in tracking error (with a difference of 1.66) and virtually no change in figural error (with a difference of 0.34).

Table 3.1 *Tracking task error values*

	Trained				Control			
	Pre-testing		Post-testing		Pre-testing		Post-testing	
	Tracking	Figural	Tracking	Figural	Tracking	Figural	Tracking	Figural
Avg(°)	22.97	5.28	18.27	2.97	6.33	1.71	7.99	2.05
SD	8.21	1.38	1.54	0.11	0.93	0.09	1.36	0.07

Proprioception

The proprioception task involved 12 continual attempts to replicate various wrist angles produced by the haptic wrist robot. Table 3.2 displays the two types of error used to measure performance in this task. For both types of error, zero shows perfect performance, a positive number shows error towards the right and a negative number shows error towards the left. There was a small decline seen in matching error and error bias in the extension trials of the trained limb, changing from 12.17 to 13.92 and -12.17 and -13.92 respectively. In the flexion trials of the task there was a small improvement in matching error from 8.50 to 7.77 in the trained limb, however, this was not a meaningful change. For the control limb, small improvements were seen in matching error from 5.73 to 5.21 and error bias -5.42 to -4.91 in the extension trials but were not meaningful. As for the flexion trails in the control limb, there were small declines in matching error from 4.80 to 5.30 and in error bias from -4.80 to -5.30.

Table 3.2 *Proprioception task error values*

	Trained				**Control**			
	Pre-testing		**Post-testing**		**Pre-testing**		**Post-testing**	
	Matching	**Error Bias**	**Matching**	**Error Bias**	**Matching**	**Error Bias**	**Matching**	**Error Bias**
Extension	12.17	-12.17	13.92	-13.92	5.73	-5.42	5.21	-4.91
Flexion	8.50	-8.50	7.77	-7.77	4.80	-4.80	5.30	-5.30

Participant 3

Participant 3 completed the full 10 weeks of training with the Xcite, 30 sessions in total.

Strength Tests:

Grip Strength

Palmer grasp and tip pinch were measured pre and post training for both the trained (non-dominant) and control (dominant) hands. Participant 3 showed a small increase in grip strength for the palmer grasp in both hands. The trained hand showed an improvement from 20kg at pre-testing to 22.1kg and the control hand showed an increase from 24.7kg at pre-testing to 25.5kg at post-testing after 10-weeks of training. In contrast, tip pinch strength decreased in both hands; the trained hand from 8.9kg at pre-testing to 8.5kg, and in the control hand from 8.9kg at pre-testing to 7.9kg at post-testing after the 10-week FES program.

Functional Tests:

Sollermans Hand Function Test (SHFT)

Participant 3 showed virtually no change in the trained limb on the SHFT (from 74/80 to 75/80) following the 10-week training program, as well as in the control limb (from 75/80 to 76/80), with only a one point change in both.

Grasp and Release Test

The following table shows the number of successes and the number of failures for each of the six tasks at pre- and post-testing for both the trained (non-dominant) and control (dominant) hands. In the trained hand, the number of successes increased in three of the six tasks, decreased in the other three tasks and the number of fails decreased or showed no change. When this data is expressed as a percent of the total number of grasps, an increase in successes is seen in all six items as well as decreases in failures in all items. When successes and failures are averaged across the six items, a small improvement is seen in the trained hand. In the control hand, there was an improvement in the number of successes in two tasks and a decline in the other four of the six tasks along with an increase or no change in the number of fails. Small decreases in successes and increases in failures are seen in the first three items when the data is expressed as a percent in the control hand. The last three items showed no change in successes or failures in the control hand. When successes and failures are averaged across the six items, a small improvement is seen in successes and a reduction in failures of the control hand.

Table 4.0a *Grasp and Release Data*

	Trained				Control			
	Pre-testing		Post-testing		Pre-testing		Post-testing	
	Successes	Failures	Successes	Failures	Successes	Failures	Successes	Failures
Peg	26.5	0.5	35	0	27	0	33.5	0.5
Weight	29	0.5	34.5	0	29.5	0	34.5	0.5
Fork	13.5	0.5	15.5	0	15.5	0	15	0.5
Block	45	0.5	38.5	0	44	0	39.5	0
Can	44	0	41	0	44	0	39.5	0
Tape	41.5	0	42	0	42.5	0	42.5	0
AVG	33.3	0.3	34.4	0	33.8	0	34.1	0.3

Table 4.0b *Grasp and Release Data as a Percent*

	Trained				Control			
	Pre-testing		Post-testing		Pre-testing		Post-testing	
	Successes	Failures	Successes	Failures	Successes	Failures	Successes	Failures
Peg	98.1%	1.9%	100%	0%	100%	0%	98.5%	1.5%
Weight	98.3%	1.7%	100%	0%	100%	0%	98.6%	1.4%
Fork	96.4%	3.6%	100%	0%	100%	0%	96.8%	3.2%
Block	98.9%	1.1%	100%	0%	100%	0%	100%	0%
Can	100%	0%	100%	0%	100%	0%	100%	0%
Tape	100%	0%	100%	0%	100%	0%	100%	0%
AVG	98.6%	1.4%	100%	0%	100%	0%	99%	1%

Functional Questionnaires:

Capabilities of Upper Extremity (CUE) Instrument

The CUE ranges in total score from 32-244 and percent of normal function score can be calculated as well. The trained (non-dominant) limb showed an increase in total score and normality, from 108 to 113, and from 39.6% to 42.2%, respectively after the 10 weeks of training. A small decrease was seen in the control (dominant) limb, with a score of 107 (39.1% normality) at pre-testing, to 105 (38% normality) at post-testing.

Functional Independence Measure (FIM)

Only the self-care portion of the FIM was used for the purpose of the study, 42 being the highest possible score achievable. Also, questions were answered based on the participant's ability to use both hands together, not individually. Participant 3 showed a two-point improvement, with a pre-testing score of 37 to 39 after the 10-week program for the self-care portion of the FIM.

Haptic Wrist Device:

Tracking

Participant 3 demonstrated a small decline in performance in the trained limb with an increased tracking error value of 0.28, and figural error value of 0.25. The control limb demonstrated virtually no change in the tracking error and in figural error, with decrease of only 0.06 and 0.09 from pre to post-testing measures, respectively.

Table 4.1 *Tracking task error values*

	Trained				**Control**			
	Pre-testing		**Post-testing**		**Pre-testing**		**Post-testing**	
	Tracking	**Figural**	**Tracking**	**Figural**	**Tracking**	**Figural**	**Tracking**	**Figural**
Avg(°)	1.08	0.48	1.36	0.73	1.43	0.72	1.49	0.75
SD	0.02	0.04	0.12	0.05	0.11	0.12	0.16	0.16

Proprioception

The proprioception task involved 12 continual attempts to replicate various wrist angles produced by the haptic wrist robot. The table below displays the two types of error used to measure performance in this task. For both types of error, zero shows perfect performance, a positive number shows error towards the right and a negative number shows error towards the left. There was an increase in all values across both error types in extension and flexion showing that no improvement was seen pre- and post-testing in the trained limb. A decline was seen in the extension trials of the control limb in both matching error and error bias, 4.18 to 6.72 and -4.17 to -6.72 respectively. However, there was an improvement seen in matching error from 5.46 to 3.72 and error bias from -5.56 to -2.97 in the flexion trials of the control limb.

Table 4.2 *Proprioception task error values*

	Trained				Control			
	Pre-testing		Post-testing		Pre-testing		Post-testing	
	Matching	Error Bias	Matching	Error Bias	Matching	Error Bias	Matching	Error Bias
Extension	4.66	-4.66	5.89	-5.89	4.18	-4.17	6.72	-6.72
Flexion	2.65	-0.61	5.42	-5.42	5.46	-5.56	3.72	-2.97

Participant 4

Participant 4 completed 8 weeks of training with the Xcite, 23 sessions in total.

Strength Tests:

Grip Strength

Palmer grasp and tip pinch were measured pre and post training for both the trained (non-dominant) and control (dominant) hands. Participant 4 showed virtually no change in grip strength for the palmer grasp in the trained hand, which tested at 25.7kg at pre-testing and 25.8kg at post-testing, while the control hand showed a small improvement from 29.9kg at pre-testing to 32.7kg at post-testing. In tip pinch strength, an improvement was seen in the trained hand from 8.9kg at pre-testing to 11.4kg after 8-weeks of FES training, while tip pinch strength in the control hand decreased from 10.5kg at pre-testing to 9.6kg at post-testing.

Functional Tests:

Sollermans Hand Function Test (SHFT)

Participant 4 showed a three-point change on the SHFT (from 69/80 to 72/80) following the 8-week training program in the trained limb, with no change in the control limb (70/80).

Grasp and Release Test

The following table shows the number of successes and the number of failures for each of the six tasks at pre and post-testing for both the trained (non-dominant) and control (dominant) hands. Number of successes increased across all six tasks in both hands. In the trained hand, the number of failures did not change and in the control hand, no change was seen in three items, but a small reduction was present in the other three items. When expressed as a percent, one item showed improvement in successes and failure, the others showed no change in the control hand. In the control hand, three items showed improvement and three items showed no change in the successes or failures. When successes and failures are averaged across the six items, virtually no change is seen in either hand when expressed as a percent.

Table 5.0a *Grasp and Release Data*

	Trained				**Control**			
	Pre-testing		**Post-testing**		**Pre-testing**		**Post-testing**	
	Successes	**Failures**	**Successes**	**Failures**	**Successes**	**Failures**	**Successes**	**Failures**
Peg	20.5	2	26.5	2	28.5	2.5	46	0.5
Weight	29.5	0	56.5	0	31.5	0	57.5	0
Fork	13	0	21	0	13	0	21.5	0
Block	40.5	0	65	0	44	1	65.5	0
Can	40.5	0	64.5	0	45	0.5	62	0
Tape	43	0	69	0	48	0	73	0
AVG	31.2	0.3	50.4	0.3	35	0.7	54.3	0.1

Table 5.0b *Grasp and Release Data as a Percent*

	Trained				**Control**			
	Pre-testing		**Post-testing**		**Pre-testing**		**Post-testing**	
	Successes	**Failures**	**Successes**	**Failures**	**Successes**	**Failures**	**Successes**	**Failures**
Peg	91.1%	8.9%	93%	7%	91.9%	8.1%	98.9%	1.1%
Weight	100%	0%	100%	0%	100%	0%	100%	0%
Fork	100%	0%	100%	0%	100%	0%	100%	0%
Block	100%	0%	100%	0%	97.8%	2.2%	100%	0%
Can	100%	0%	100%	0%	98.9%	1.1%	100%	0%
Tape	100%	0%	100%	0%	100%	0%	100%	0%
AVG	98.5%	1.5%	98.8%	1.2%	98.1%	1.9%	99.8%	0.3%

Functional Questionnaires:

Capabilities of Upper Extremity (CUE) Instrument

The CUE ranges in total score from 32-244 and percent of normal function score can be calculated as well. Participant 4 showed virtually no change, with only a 4-point reduction in the both the trained (non-dominant) and the control (dominant) limb in total CUE score from 80 to 76, and from 25% to 22.9% normality after the 8 weeks of training.

Functional Independence Measure (FIM)

Only the self-care portion of the FIM was used for the purpose of the study, 42 being the highest possible score achievable. Also, questions were answered based on the participant's ability to use both hands together, not individually. Participant 4 showed no change before and after their 8 weeks of training for the self-care portion of the FIM, scoring a 36 on both tests.

Haptic Wrist Device:

Tracking

Participant 4 experienced a decline in performance in both limbs. The trained limb showed an increased tracking error by 4.2 and figural error by 0.39 from pre to post-testing. A greater decline was present in the control limb, as the tracking error increased by 5.5, with virtually no change in figural error which increased by 0.05 from pre to post-testing.

Table 5.1 *Tracking task error values*

	Trained				**Control**			
	Pre-testing		**Post-testing**		**Pre-testing**		**Post-testing**	
	Tracking	**Figural**	**Tracking**	**Figural**	**Tracking**	**Figural**	**Tracking**	**Figural**
Avg(°)	1.69	0.78	5.89	1.17	2.09	1.08	7.59	1.13
SD	0.05	0.1	1.18	0.07	0.59	0.2	0.79	0.03

Proprioception

The proprioception task involved 12 continual attempts to replicate various wrist angles produced by the haptic wrist robot. The table below displays the two types of error used to measure performance in this task. For both types of error, zero shows perfect performance, a positive number shows error towards the right and a negative number shows error towards the left. A decline in performance was seen with increased values of 4.17 to 5.95 in matching error and 2.89 to 5.95 in error bias in the extension trials in the trained limb. However, in the flexion trials of the trained limb, an improvement is seen in both types of error, from 6.16 to 2.60 in matching error and from 5.10 to 0.80 in error bias. Due to the decrease in values across both error types in extension and flexion we can conclude that some improvement was seen pre- and post-testing in the control limb.

Table 5.2 *Proprioception task error values*

	Trained				**Control**			
	Pre-testing		**Post-testing**		**Pre-testing**		**Post-testing**	
	Matching	**Error Bias**	**Matching**	**Error Bias**	**Matching**	**Error Bias**	**Matching**	**Error Bias**
Extension	4.17	2.89	5.95	5.95	8.48	8.48	5.52	3.85
Flexion	6.16	5.10	2.60	0.80	6.22	6.22	3.76	0.59

Table 6.0 *Absolute Changes Pre-Post in trained limb/control limb*

		Participant 1	Participant 2	Participant 3	Participant 4
Grip Strength: Palmar (kg)		4.05/4.3	2.25/1.4	2.05/+0.8	+0.15/2.75
Grip Strength: Tip (kg)		+0.25/1.55	0.4/1.5	1/0.75	2.5/0.95
Sollerman		1/0	2/1	1/1	3/0
Grasp and Release (successes)	**Peg**	32.5/26	2.5/+2	8.5/6.5	6/17.5
	Weight	2/5	1/+3	5.5/5	27/26
	Fork	9.5/10.5	4.5/-1	2/-0.5	8/8.5
	Block	49.5/37.5	0/2.5	6.5/4.5	24.5/21.5
	Can	29/33.5	0.5/2	3/4.5	24/17
	Tape	30.5/28	0.5/1	0.5/0	26/25
FIM		0	2	2	0
CUE		5/-2	-2/-3	5/-2	-4/-4
Tracking (Error)	**Tracking**	-0.38/0.5	+4.6/1.66	0.28/0.06	4.2/5.5
	Figural	0.09/0.28	2.31/0.34	0.25/-0.09	0.39/-0.05
Proprioception: Extension	**Matching**	1.36/-0.41	1.75/+1.48	1.23/2.54	1.78/2.96
	Error Bias	7.26/-0.36	1.75/+0.51	1.23/2.55	3.06/4.63
Proprioception: Flexion	**Matching**	2.28/1.88	+0.73/0.5	2.77/1.74	3.56/2.46
	Error Bias	3.41/4.81	+0.73/0.5	4.81/2.59	4.3/5.63

Green indicates likely improvement, red indicates likely worsening, black indicates no change. Likely changes are based on MCIDs or clinical thresholds (Grip strength and CUE) or percent change beyond that in baseline testing (GRT, Tracking) or greater than 10% change from pre to post testing (Proprioception).

Testimonials

Participant 1

Overall, this participant noticed functional improvement in daily activities involving her trained limb even though her training program was cut short due to some negative effects she experienced outside of the Xcite sessions. She was able to share her experiences in a post-study interview.

"I did notice after about week 2 or 3 that holding the steering wheel was much easier with my left hand (non-dominant/trained hand) than it was before… I opened 2 jars the other day without my assistive device."

When asked if she noticed a difference when performing any of the functional tests, she shared this experience regarding the haptic wrist device pre- and post-testing.

"It was frustrating, it was hard to do and I wanted to get up out of the chair to move it (pre-testing) and instantly from doing it yesterday there was a difference (post-testing). I couldn't believe how much it (wrist movement/control) flowed and how much of an ease there was, it kind of blew me away like how different it was, it was insane, it just felt smoother like it wasn't tight, it wasn't difficult, I wasn't struggling, I wasn't pushing to make it go."

Participant 2

Although this participant reported improvements in daily life, not much of those improvements were experienced in the hand or arm directly. A greater feeling of confidence in attempting tasks was noted.

> "Getting off the commode (an assistive device for toileting) seems easier… and I am warmer, I am always freezing and now I don't always have to have a blanket around my shoulders… holding my bladder better, hardly ever an accident."

She also noted an improvement in sleep and overall energy throughout the day as increased. This participant planned to continue training with the Xcite in hopes of eliciting greater improvements, specifically in the hand.

Participant 3

A positive outcome and experience with the Xcite were also reported from Participant 3 and she was able to elaborate in the post-study interview.

"I can hold things up longer, like a coffee pot… um… I can squeeze it better with my left hand and hold it up… when I am putting on earrings I am using my left hand more… the ropes (battle ropes exercise) this arm is holding it easier."

"I can take things and not worry so much about dropping it because this hand (left-trained hand) is not going to let go of it."

> "I didn't have any trouble moving around while tying hair up in a pony tail, I know you have to use both hands for that, both arms actually went up and did it (with ease), sometimes I can't do that as well."

She also noted improved fatigue and planned to continue training on the Xcite to further her gains and improve her other limb. This participant finished off the interview with this statement:

"I think it if it could continue it would make a much bigger difference because I have noticed that strength in that arm (left). But it has got to be longer, I could have done more of the grasping repetitions."

Participant 4

Participant 4 had mixed reviews in regard to the outcomes and process of the study. He shared how although he felt improvements in hand function it was not consistent.

"I tried early on with my barometer, which was chopsticks and sometimes it would be easier, sometimes it's not, it differed. So, it had become too difficult for me to use chopsticks, now it depends sometimes it's not too bad, sometimes it was just as bad, it's hard to tell."

Due to hypersensitivity, his training sessions with the Xcite were uncomfortable at times and he hoped the outcome would be sizable to outweigh the discomfort.

"…On the whole, it's a type of therapy that I would want to make sure that I really could tell there was a marked improvement if I were to pursue it."

Discussion

Main Findings

To our knowledge this is the first study using the Xcite iFES Clinical Station as a mode of rehabilitation/exercise, specifically in the hand and arm in persons with MS. This case study has shown that some functional improvement may be evoked from a 10-week Xcite FES training protocol. When grip strength was tested in the trained hand, 3 of the 4 participants improved their palmar grasp ranging from 0.2kg to 2.3kg and 3 participants improved their tip pinch between 0.3kg to 2.5kg. Similar results were seen in the control hand, 3 participants showed small improvements in palmer grasp varying from 0.8kg to 2.75kg with 1 participant decreasing by 4.3kg. The reverse was seen in tip pinch, 3 participants showed small declines in grip strength ranging from 0.75kg to 1.55kg and 1 showed a small increase of 1.5kg. A study assessing day-to-day variability in both hands of right-dominant healthy male and female adults (ages 20-45) and found that variability was 4.99% for the right hand and 3.04% for the left [Trossman et. al., 1990]. Knowing this information, 3 of the 4 changes (2 improvements, 1 decline) seen in the palmar grasp and tip pinch of the trained hand are true changes. For the control hand, all but one participant showed true changes (2 improvements, 1 decline) in the palmar grasp and all participants showed true change in tip pinch (1 improvement, 3 declines). The lack of improvement seen in the tip pinch grip strength, was not an expected result of the study, especially considering finger dexterity was incorporated in the Xcite exercises.

In the Sollermans hand function test, all 4 participants showed very small increases in their scores from pre to post-testing; 1 point, 4 points, 1 point and 3 points in the trained limb all of which are likely not meaningful. As for the control limb, 2 participants improved their scores by 1-point pre to post-testing and the other 2 participants showed no change. Unfortunately, the Sollermans hand function test currently does not have an established minimal clinical important difference (MCID) or minimal detectable change (MCD) in neurological patients but there is a MCD for burn victims that ranges from 6.7-6.9 [SCIRE Project, 2020, Weng et. al., 2010]. The changes reported in the present study were quite a bit smaller than this and thus, we can assume they are not clinically significant.

As for the grasp and release test, all 4 participants improved in number of successes using the peg, the weight and the fork with a range of 1 to 32.5 with an average improvement of 9.1 in the trained hand. An improvement was also seen in the trained hand in 2 participants using the block by 49.5 and 24.5 with one participant showing no change and one with a decline of 6.5. Lastly, 3 of the 4 participants improved in using the can by 0.5, 24, 29 and the tape by 0.5, 26, 30.5 with participant 3 failing to improve with 2 objects in the trained hand. In the control limb, all 4 participants improved number of successes with the peg and weight with increases ranging from 2 to 25, averaging 11.4. Two participants improved their successes with the fork, block, can and tape while the other 2 participants performed less successes compared to pre-testing. The improvements ranged from 8.5 to 37.5 and the worsening ranging from 0.5 to 4.5. The outcome for number of fails in the control limb varied for each participant in each for the six objects. Since the grasp and release test does not have a MCID or MCD established, the percent change between trials at baseline were calculated and then compared to the percent change pre and post-testing. If the pre- post testing change was greater than the intra-individual variability it was considered a meaningful change.

The results from the questionnaires showed a split response with 2 of the 4 participants improving by 2 points each on the FIM and 2 participants improving on the CUE by 5 points each. The FIM does not have an MCID established and seeing as the improvements were so small for a questionnaire scoring out of 42, the changes were not seen as meaningful. One study reported the CUE having a MCID of 6.1-6.3 but this is still higher than the change seen in this study [Marino et. al., 2018].

Overall, the 3 participants did not improve on the haptic wrist device tracking task and 1 participant showed a reduced tracking error by 4.6 points and figural error by 2.31 points in the trained limb. Similar results were seen in the control limb, all 4 participants displayed poorer performance with both error types increasing. In the wrist extension/flexion matching activity on the haptic wrist device 2 participants showed greater error post-testing in both directions and 2 participants only showed improvement (less error) in flexion of the trained limb. However, there were a range of improvements in at least one direction in the control limb, 1 participant showing improvement in both directions. Majority of the changes recorder were decreases in performance and the cases where improvement was seen it was often too small to be considered meaningful. For the tracking task, the percent change between trials at baseline were calculated and compared to the percent change pre and post-testing. If the pre- post testing change was greater than the intra-individual variability it was considered a meaningful change. Since the proprioception task was only one trial, changes that were greater than 10% pre- to post-testing were considered meaningful.

As previously mentioned, some participants experienced improvement in the control limb which may be due to a phenomenon referred to as 'cross-education'. This describes a strength gain or improvement in performance in the untrained limb following a unilateral training intervention [Lee & Carroll, 2007, Fimland et, al,. 2009]. Cross-education can occur with training accomplished by voluntary muscle activation or unvoluntary muscle activation as seen in FES. Research suggests that alterations in neural control such as neural drive or increased circulation are responsible for this effect since no change appears in cross-sectional surface area, muscle enzyme activities or fibre types in the untrained limb [Lee & Carroll, 2007, Fimland et, al,. 2009]. Although the improvements seen in this study were small to moderate in magnitude, this form of rehabilitation does show promise as a means to improve hand function in those with MS.

Participants enjoyed their experience with the Xcite iFES clinical station with some feeling improvement, and some not noticing much change over the training program. Most participants were interested in continuing training to maintain and achieve greater improvement.

Clinical Significance

As previously mentioned, research examining FES on the hand and arms of people with MS is limited however, there has been positive outcomes. In a 10-week study that used FES and passive robot support to complete a reaching task, there was a substantial improvement in tracking of 12.8% and 23.6% for the elbow and shoulder, respectively [Sampson et al., 2015].

Other studies involving FES training in the MS population were applied to the lower body to determine if improvements in cardiovascular fitness and strength performance as well as overall walking ability were possible. These studies ranged from 8 to 24 weeks in duration, either in a cycling or muscle-isolated format all of which yield clinically significant improvement [Edwards et al., 2018, Chang et al., 2011, Street et al., 2015]. The 8-week study conducted by Chang and colleagues focused on stimulating the quadriceps which improved knee extension and reduce general fatigue [2011]. Another study in 2015 applied FES over the peroneal nerve at the fibular head and over the tibialis anterior during walking to determine the effects on foot drop, and over the 20-week intervention clinically significant improvement was seen in the 10m walk test by 27% [Street et al., 2015]. Edwards and colleagues utilized FES cycling for a 24-week period, to determine the effects in many walking tests, including walking speed as determined by the T25FW, and walking endurance as determined by the 2-minute walk test, and both increased by 22.9% and 11.7% respectively. There were also increases in VO_{2peak} (13.8%) and WR_{peak} (15.3%) as well as knee extensor strength (22.7%) [Edwards et al., 2018]. The improvements seen in the abovementioned FES studies seem to be notably greater than the improvements seen in the present study that used the Xcite iFES clinical station. When improvements were detected in our participants most were small across the many tests. Many studies involving FES were more than double the length of the present study, which likely contributes a large part of the substantial difference in results seen between this study and the literature. Although there is potential for the Xcite to be an effective mode of rehabilitative exercise, there will be limitations of its effectiveness as well. To gain considerable functional improvements, Xcite training may need to be limited to people with MS who experience mild to moderate levels of hand dysfunction. There may be a point at which functional movement may not be able to be returned through FES training. When assessing the participants used in other FES literature the EDSS scores commonly ranged within the lowest severity or the mid-range, either 1.0 to 4.0 or 3.0 to 6.5 [Chang et al., 2011, Edwards et al., 2018, Street et al., 2015]. Street and colleagues stated that FES is generally used for people with SPMS or PPMS whose EDSS level is between 4.0-6.5 leads to successful mitigation of foot drop [Street 2017]. As EDSS scores worsen (even at 5.0), less improvement is seen, and often only muscle strength maintenance is achieved to aid in standing or transfers [Street 2017]. Note that the participants in this study ranged from a 3.0 to a 7.0, putting our group on the cusp of where literature has witnessed the most gains. However, EDSS scores pertain primarily to walking function which has little to no relevance to our hand and arm-focused Xcite training. When assessing each participants' change pre- and post-testing in the Grasp and Release Test there was a pattern; the participant with the lowest EDSS score of 3.0 showed the greatest improvements and the participant with the highest EDSS score of 7.0 experienced the least amount of improvement. The other participants whose scores were 6.0 and 6.5 showed moderate improvements in number of successes. This correlates with the idea that persons with a greater level of disability will not show as great as improvements as others with a lesser degree of disability. However, when assessing the Sollermans Hand Function Test, the improvements across the participants were more similar regardless of their EDSS score. Perhaps, this is due to the robustness of the activities involved in the test battery and much change is not expected to be seen based on time to complete the task.

This range also supports the reason for seeing varying effects between each participant and perhaps between the tests in the same individual, with some test requiring more or less dexterity or overall strength. Participant 1 is a great example, an (s)he worsened in palmar grasp strength starting at 22.2kg and ending at 18.2kg in the trained hand. However, (s)he improved in tip pinch strength, from 8.8kg to 9.05kg in the trained hand and made large developments in successful grasps and releases in the GRT across all six objects.

There is more to uncover regarding FES as treatment for MS that is outside the scope of this study, mainly the mechanisms involved. Although the underlying mechanisms of the function of FES and how it interacts with able-bodied, SCI and Stroke patients are somewhat understood, there is not the same level of understanding of the mechanisms at work with MS.

In this study, it is possible there were both neural adaptations as well as peripheral, strength adaptations present. Participant 1 demonstrated improvement in the functional tests, Sollermans and GRT but did not show improvement in grip strength which alludes to neural adaptations rather than peripheral being the source of change. Their ability to perform tasks improved without showing signs of increased strength. Participants 2, 3 and 4 all improved grip strength with mostly positive changes in other functional tasks and haptic wrist device testing, and thus, functional improvements may have been be due to peripheral and neural adaptation over the duration of the program. Since there were signs of increased strength as well as some increase in ability to perform various functional tasks, both mechanisms may be involved in these cases.

Limitations

There were a few limitations present in this study. First, the study was limited to a small sample size due to the specific, special population under investigation and the relatively small recruiting pool due to other on-going research in the same facility. Recruitment was also hindered by the considerable time commitment that the study demanded; 50-minute sessions, 3 times per week, for 10 weeks which was not feasible for many interested parties.

Second, the size and duration of the study was also directly affected by the outbreak of COVID-19. One participants' training was cut short and 2 additional participants were forced to drop out due to the inability to compete the minimal amount of Xcite training sessions.

Third, due to the great novelty that the haptic wrist device presents more time may have been needed to appropriately familiarize the participants with the system. This would have led to a more accurate testing measure as the learning effect would have been addressed prior to testing and reduce the variability between trials.

Another limitation of the study is that there may have been some inconsistency with electrode placement over the 23-30 sessions among the participants. Small differences in placement may have been present between the individuals assisting with the study. Some adjustments were also required to satisfy the participants comfort over the course of the intervention.

Lastly, since many of the testing measures do not have established MCDs/MCIDs, thresholds based on inter-trial variability were determined to help distinguish if changes were meaningful. Even with these thresholds it is difficult to confidently concluded the significance of the results.

Future Directions

This study shows that FES training of the hand and arm with the Xcite iFES clinical station has the potential to evoke selected functional upper limb improvements in those with moderate severity MS. However, further research needs to be conducted with bigger sample size to better understand the duration and volume of the training required to evoke more prominent changes. As mentioned in the testimonials, some of the participants felt that if the study were longer more changes would be present. Studies that assess the impact of FES on special populations range in length, but many are upwards of 20 weeks, with sessions running from 3 to 5 times per week [Chang et al., 2011, Edwards et al., 2018].

Future research should also explore the mechanisms behind functional improvement that are achieved with Xcite training in those with MS. Although there is extensive information on the mechanisms that attribute to the positive outcomes of FES, most findings are based on healthy, abled-bodied individuals or those with a SCI or stroke. We have assumed that these FES mechanisms translate across many neurological conditions such as MS, but there is not definitive research stating that it does. Research should also investigate what types and severities of MS respond best to FES in terms of strength gains and functional improvements, and to what degree hypersensitivity or dulled sensation may impact this therapy.

Another avenue that this research can explore is coupling this Xcite training with other forms of exercise such as resistance training, yoga or traditional physiotherapy. There are similar studies that pair various forms of exercise together that would support this idea [Oken et al., 2004, Zaenker et al., 2016]. Perhaps with more intensive training involving props related to the Xcite task and/or adding resistance training would evoke more substantial improvements.

Conclusion

The present study is the first to utilize the Xcite iFES clinical station as a mode of exercise rehabilitation and assess its effect on hand and arm function of persons with MS. The effectiveness of thrice-weekly training for 8-10 weeks is equivocal as participants showed a range of adaptations with some measures indicating meaningful improvement, some worsening and some showing no change. When assessing each participant individually, three showed notable improvement in both grip strength and functional tests suggesting they experienced both an increase in muscular strength and function. The other participant demonstrated minor improvement in some of the functional tests but worsened or did not improve in grip strength which may indicate that functional improvement was due to some neural adaptations. However, as this was a case series and the changes were small it is difficult to draw conclusions on the impact this study holds within this field of research. Future research in this topic could greatly benefit the MS population and help to find modes of exercise to improve independence and quality of life through upper body FES training.

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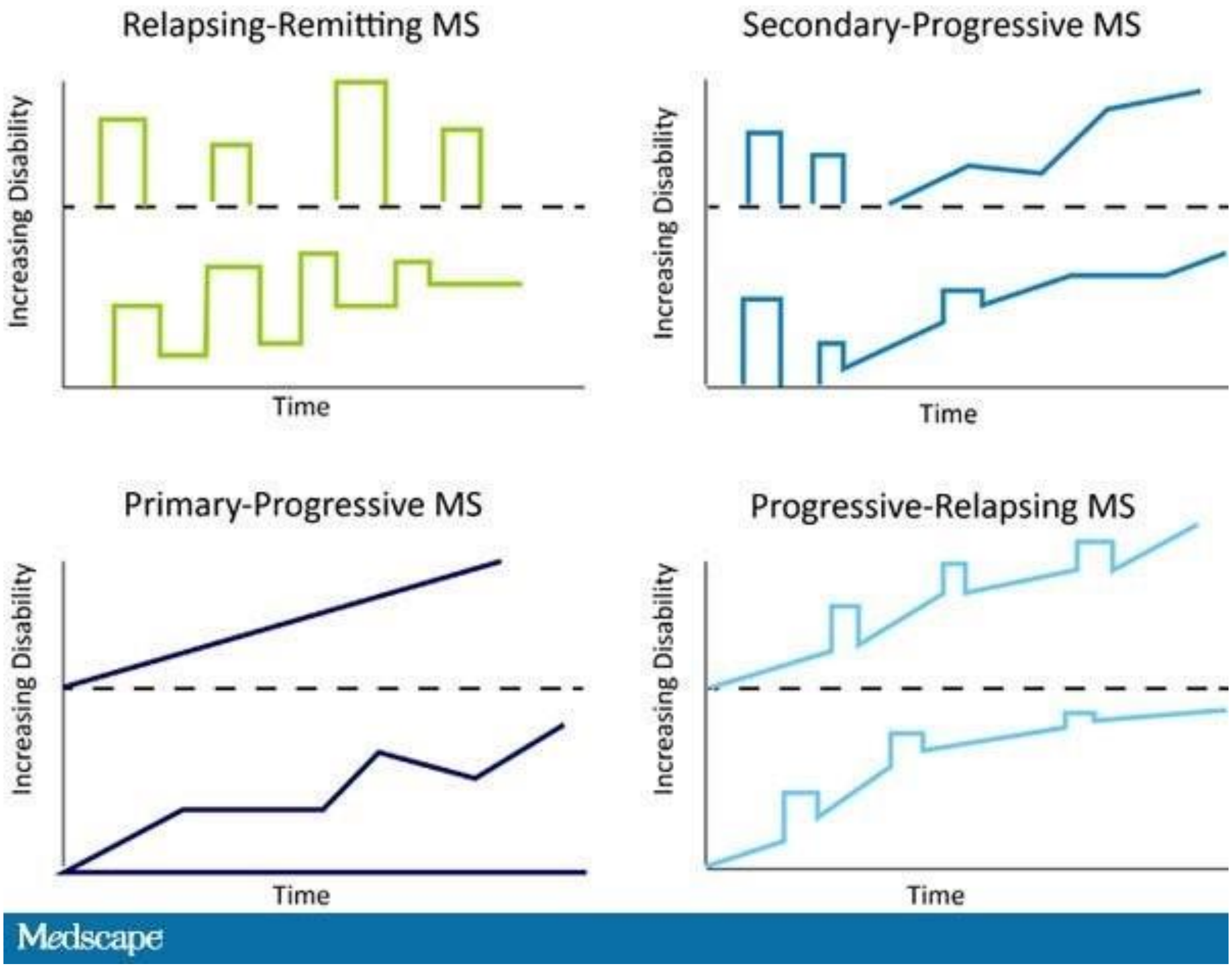
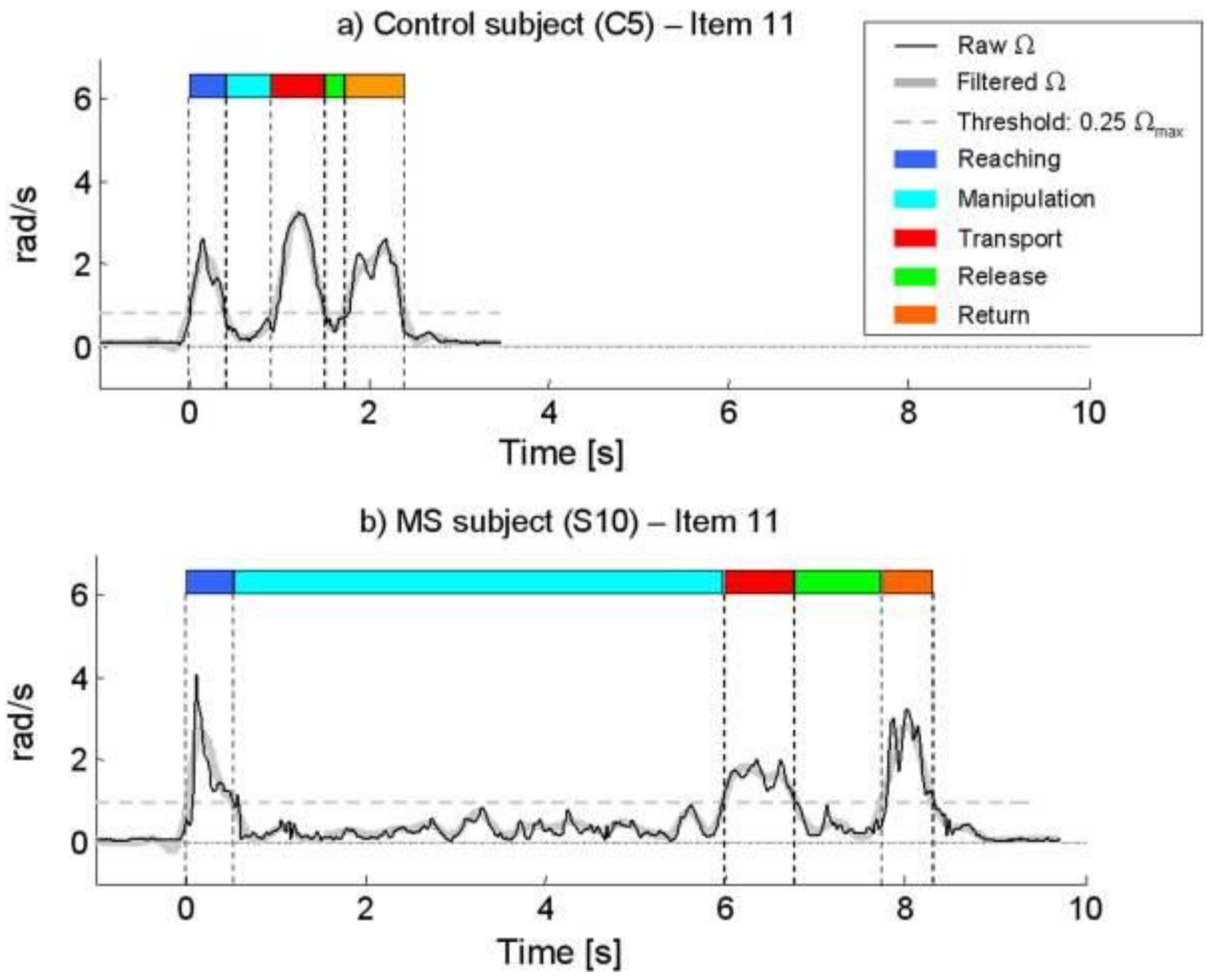
Appendix A

Figure 1. *Types of MS*



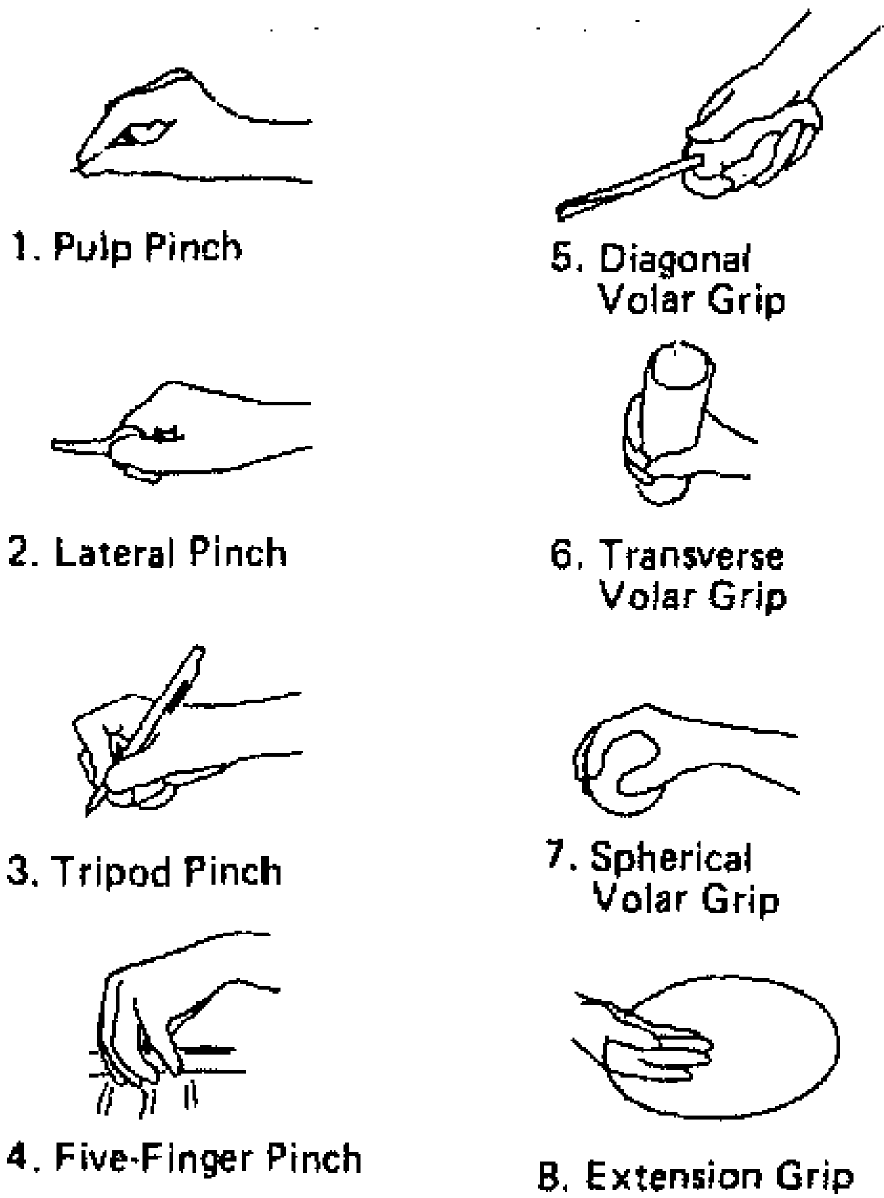
Appendix B

Figure 2. *Carpinella study: The time required for MS subject to manipulate & release the object*



Appendix C

Figure 3. *Types of Grips used in GRT*



Appendix D

Figure 4. *Starting position on Haptic Wrist Device* **(***neutral grip)*

Appendix E

Figure 5. *Depiction of Sollerman Hand Function Test kit*

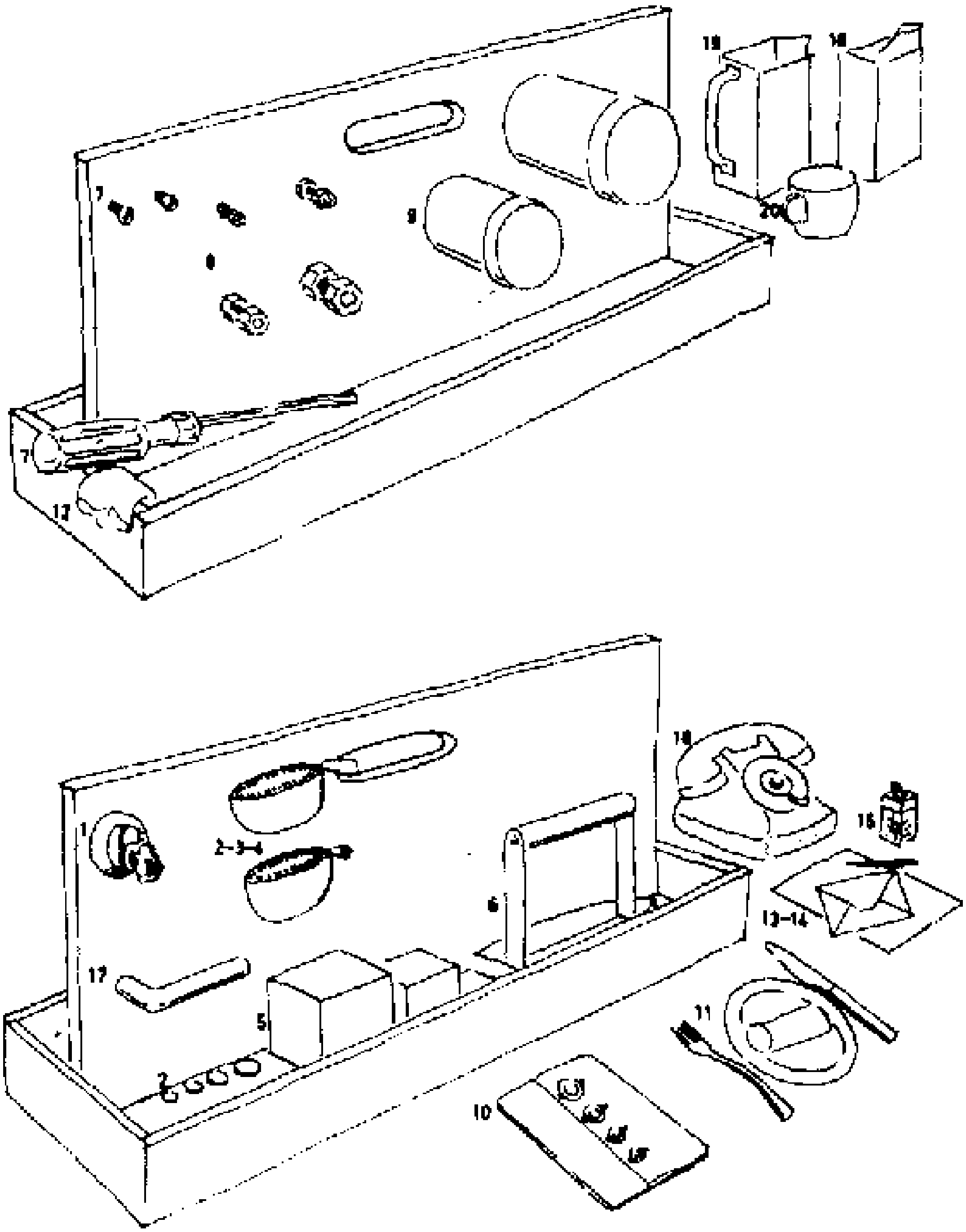


Figure 6. *Sollerman Hand Function Test Order of Subtests*

Table III. *The 20 subtests comprising the Sollerman grip function test*

1. Put key into Yale lock, turn 90°
2. Pick coins up from flat surface, put into purses mounted on wall
3. Open/close zip
4. Pick up coins from purses
5. Lift wooden cubes over edge 5 cm in height
6. Lift iron over edge 5 cm in height
7. Turn screw with screwdriver
8. Pick up nuts
9. Unscrew lid of jars
10. Do up buttons
11. Cut Play-Doh with knife and fork
12. Put on Tubigrip stocking on the other hand.
13. Write with pen
14. Fold paper, put into envelope
15. Put paper-clip on envelope
16. Lift telephone receiver, put to ear
17. Turn door-handle 30°
18. Pour water from Pure-pak
19. Pour water from jug
20. Pour water from cup

Table 1. *Sollerman Hand Function Test scoring guidelines*

Sollerman hand function test in tetraplegia 169

Table II. *Guidelines for scoring of subtests*

	Score
The task is completed without any difficulty within 20 seconds and with the prescribed hand-grip of normal quality	4
The task is completed, but with slight difficulty, or the task is not completed within 20 seconds, but within 40 seconds, or the task is completed with the prescribed hand-grip with slight divergence from normal	3
The task is completed, but with great difficulty, or the task is not completed within 40 seconds, but within 60 seconds, or the task is not performed with the prescribed hand-grip	2
The task is only partially performed within 60 seconds	1
The task cannot be performed at all	0

Appendix F

Figure 7. *Electrode placement for feeding task*

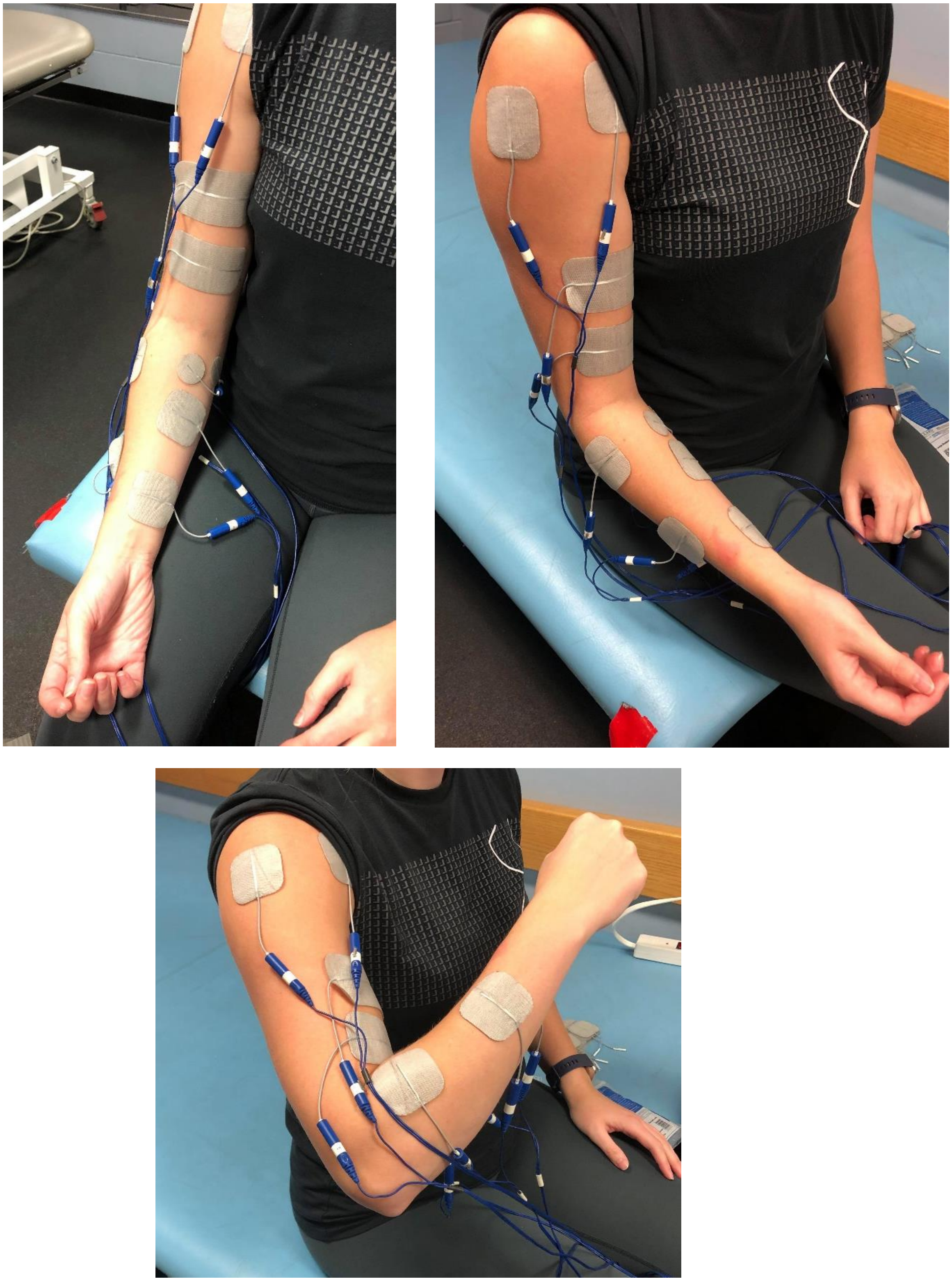


Figure 8. *Electrode placement for forward reach and grasp task*

Figure 9. *Electrode placement for opposition task*

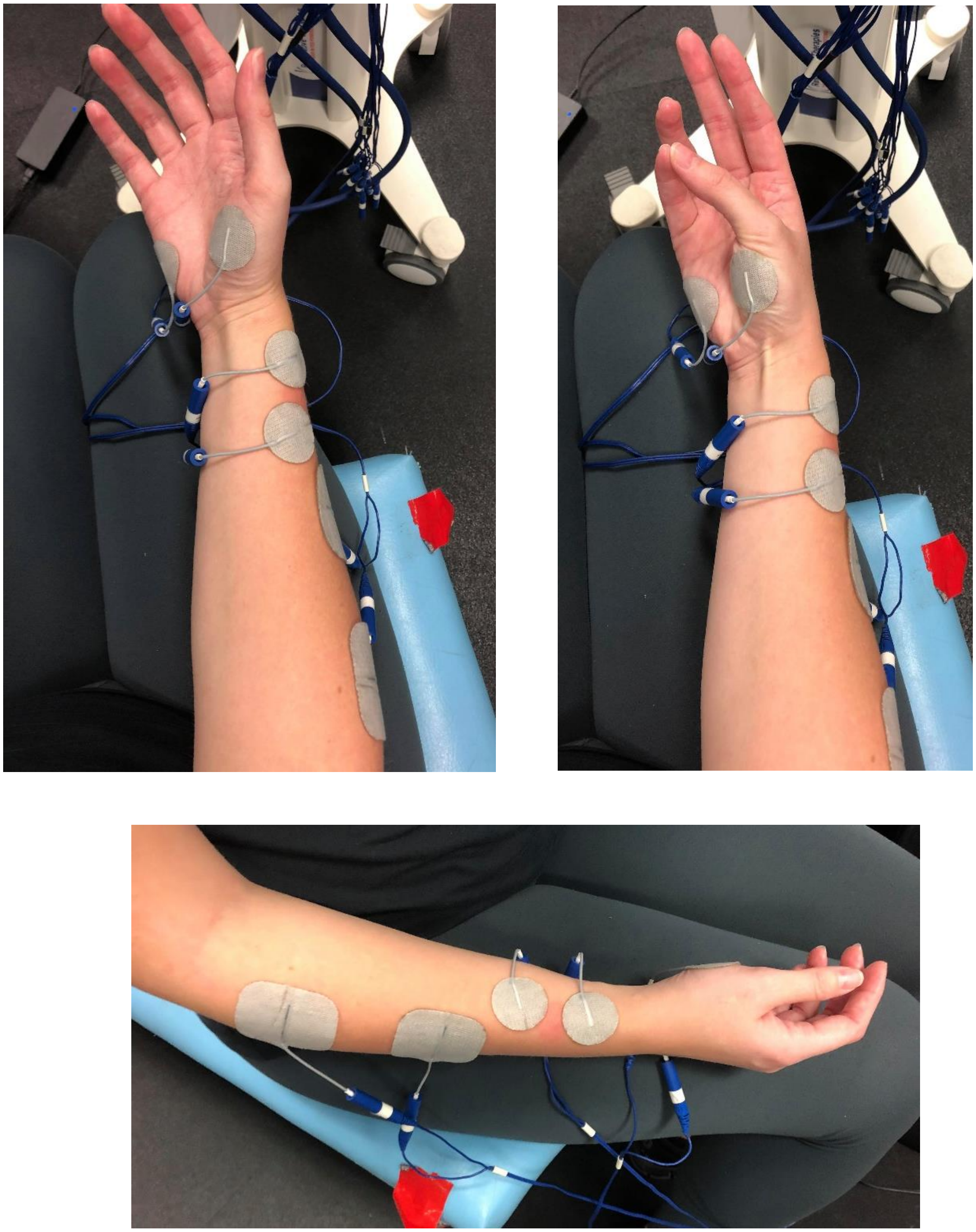
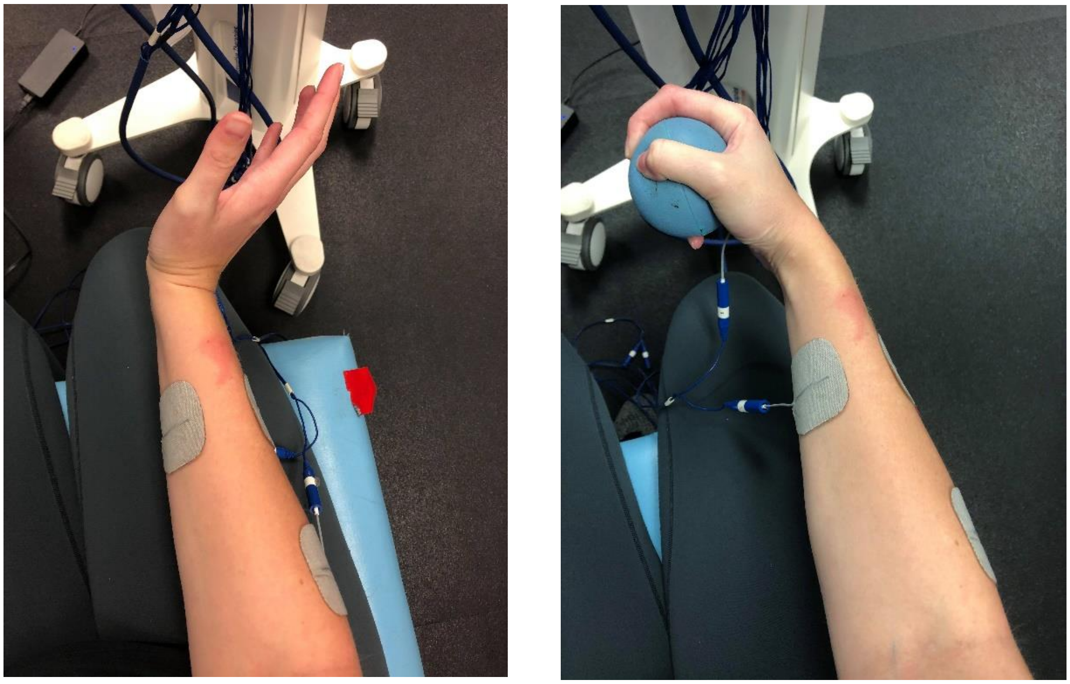


Figure 10. *Electrode placement for lumbrical grasp task*



Appendix G

Figure 11. *Xcite iFES Clinical Station*

Figure 12. *Electrodes used during Xcite exercises*